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BRIEF COMMUNICATION

Chronic Covert Brain Infarctions and White Matter Hyperintensities in Patients With Stroke, Transient Ischemic Attack, and Stroke Mimic

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BACKGROUND: This study was conducted to compare frequencies of chronic brain infarctions (CBIs) and white matter hyperintensities (WMHs) as well as their associations with established early recurrence risk scores in patients with transient ischemic attack (TIA) and stroke mimics compared with ischemic stroke.

METHODS AND RESULTS: Single-center cohort study including consecutive patients with TIA, stroke mimics, and acute ischemic stroke, with available magnetic resonance imaging from January 2015 to December 2017. Blinded raters adjudicated WMH (age-related white matter changes score) and CBI according to established definitions. A total of 2112 patients (median [Q1–Q3] age 71 [59–80] years, 43% women, National Institutes of Health Stroke Scale score of 2 [1–7], 80% ischemic stroke, 18% TIA, 2% stroke mimics) were included. While CBIs were present in only 10% of patients with stroke mimic, they were detected in 28% of TIAs and 38% of ischemic strokes ($P<0.001$). WMHs were less pronounced (0, 0–1) in patients with stroke mimic, but there was no difference between TIA (1, 1–2) and ischemic stroke (0, 1–2) patients. CBIs (adjusted odds ratio, 0.3; 95% CI, 0.1–0.9) were associated with a lower rate of stroke mimic as the final diagnosis, while WMHs were not (adjusted odds ratio per point, 1.3; 95% CI, 0.7–2.2). WMH (β per point, 0.4; 95% CI, 0.3–0.6) and presence of CBI (β, 0.6; 95% CI, 0.3–0.9) were associated with a higher cardiovascular risk profile according to the ABCD3-I score. The accuracy of prediction was good for high-risk TIA (cross-validated area under the receiver operating characteristic curve, 0.89; 95% CI, 0.79–0.93) on the basis of brain imaging, age, and sex.

CONCLUSIONS: CBI and WMH differ between patients with stroke mimic and patients with TIA/ischemic stroke and are closely associated with established recurrence risk scores. Prospective studies need to clarify whether including brain frailty markers may contribute to the refinement of current management algorithms and risk stratifications.

Key Words: covert brain infarction ■ ischemic stroke ■ stroke mimic ■ transient ischemic attack ■ white matter hyperintensities

In refining the prognostic models for predicting stroke recurrence and hospitalization,[1] diffusion weighted imaging lesions proving acute ischemia and ipsilateral carotid stenosis were identified as important imaging predictors of recurrent events.[2] Chronic covert brain infarctions (CBIs) and white matter hyperintensities (WMHs) are known surrogate markers for cardiovascular risk,[3] but evidence regarding risk stratification is inconclusive.[4–8]

In the emergency setting, it can be difficult or impossible to obtain a correct medical history, especially

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because of increasing rates of demented, aphasic, or confused patients.[9] Unfortunately, little is known about the phenotypes of CBI in patients with transient ischemic attack (TIA), although they might help to assess the cardiovascular risk profile and recurrence risk. Furthermore, imaging biomarkers might be useful in differentiating true vascular TIA from stroke mimics.

Using data of a comprehensive registry with state-of-the-art neuroimaging from a center with high rates of magnetic resonance imaging (MRI) usage, we aimed to describe the frequency and phenotypes of CBI and WMH according to established imaging definitions in patients with TIA and stroke mimics and compare them with patients with acute ischemic stroke. Second, we analyzed associations of established risk scores for early stroke recurrence (ABCD3-I score[10]) with the mentioned biomarkers.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. Details on this cohort and ethics approval have been published previously; briefly, it was approved by an independent ethics committee, and requirement for informed consent was waived according to Swiss law.[11] Overall, 81% of patients had MRI either on admission or during the acute hospitalization with details on the MRI methodology available elsewhere.[11]

We included all consecutive hospitalized patients at our university stroke center (admission list) in a prospective registry collecting standardized, prespecified variables. For this analysis, we analyzed all patients with a final diagnosis of ischemic stroke, TIA, or stroke mimic admitted between January 1, 2015, and December 31, 2017. Ischemic stroke was defined according to the tissue-based definition as imaging-proven acute ischemia regardless of symptom duration or symptom duration of >24 hours without imaging evidence of cerebral ischemia. TIA was defined as symptoms lasting <24 hours without imaging-proven cerebral ischemia. Patients were classified as a stroke mimic if they were admitted for stroke/TIA but discharge diagnosis was not as such. For differentiation of ischemic stroke and TIA, the updated definition incorporating imaging information was used.[12] Patients with diagnoses potentially leading to brain lesions that could mimic CBI (Figure S1) were excluded. We also excluded patients who had only computed tomographic imaging until discharge (lower predictive likelihood of TIA and stroke mimics; Table S1).

Details on the neuroimaging protocol, assessment of agreement, and phenotypes of CBI have been published before.[11] WMHs were assessed according to the age-related white matter changes rating scale.[13] As described by Vynckier et al, CBI phenotypes were classified as lacunes, combined gray and white matter lesions, isolated gray matter lesions, and large subcortical (noncavitating) infarcts (Figure S2).[11] The rationale to choose those imaging biomarkers was that since they reflect postischemic lesions, they might have the strongest association with established risk scores for early recurrence of ischemic stroke as compared with other features of small-vessel disease and brain frailty.

The main outcomes for this analysis were (1) overall frequency of CBIs; (2) phenotypes of CBI, and (3) association of CBI frequency and phentotypes with ABCD2 and ABCD3-I score.[10] A secondary outcome was the discrimination of the final diagnosis of stroke mimic using models with basic clinical information (age and sex) in addition to neuroimaging as compared with models using all available clinical information. The rationale was that such a basic model could be used also if obtaining a more detailed medical history is impossible, for example, in patients who are aphasic or demented.

Statistical Analysis

We used medians (25th percentile, 75th percentile [Q1–Q3]) and percentages (95% CI) to present the distribution of continuous, ordinal, and categorical variables. Baseline characteristics were compared using the Pearson χ^2 test for categorical variables and Wilcoxon rank-sum or Kruskal-Wallis test for continuous and ordinal variables. STATA 16 including the *table1_mc*, *idi* (calculating the integrated discrimination improvement as a measure to compare the discrimination ability between 2 logistic regression prediction models) and *cvauroc* (implementing k-fold internal cross-validation for the under the receiver operating characteristic curve of the logistic regression models to correct for optimism bias) package was used to analyze the predictive performance (under the receiver operating characteristic curve) of logistic regression models for the prediction of high-risk TIA (ABCD2 score >4 and ABCD3-I score >7) and stroke mimics. The predictive performance of models for discrimination of stroke mimics was compared using the *roccomp* command and plotted as receiver operating characteristic curves. Least absolute shrinkage and selection operator was used for model selection in addition to pathophysiologically plausible and established predictors from the literature. Complete case analysis was done without imputation.

RESULTS

A total of 2112 patients were included in the study, of which 43% were female. The median age was 71 years [Q1–Q3, 59–80]; the median score on the National Institutes of Health Stroke Scale was 2 points [1–7].

Patient characteristic and imaging biomarkers according to the neurological event are shown in Table 1 and Table S2. Patients with a final diagnosis of stroke mimic were significantly younger than patients with an acute ischemic stroke/TIA and showed a lower cardiovascular risk profile.

Chronic CBIs were more frequently found in patients with ischemic stroke (38%; 95% CI, 36%–41%) and patients with TIA (28%; 95% CI, 23%–32%) compared with patients who suffered from stroke mimics (10%; 95% CI, 3%–23%). None of the patients with stroke mimic had multiple CBIs, although only 4 patients had any CBIs, but the proportion of patients with stroke mimic with multiple CBIs was not significantly different from that in the other 2 groups. WMH score was lower in patients with stroke mimic, but there was no significant difference between patients with TIA and patients with ischemic stroke (P=0.093, Table 1). On linear regression, the presence of any CBI (β, 0.69; 95% CI, 0.38–1.01) and WMH (β per point on age-related white matter changes scale, 0.42; 95% CI, 0.27–0.58) was associated with ABCD2 scores in patients with TIA. The accuracy of prediction was good for high-risk TIA (cross-validated area under the receiver operating characteristic curve [cvAUC] 0.89; 95% CI, 0.79–0.93) and fair for low-risk TIA (cvAUC, 0.76; 95% CI, 0.59–0.77) on the basis of brain imaging and basic clinical information (age and sex) alone. The discrimination for the prediction of stroke mimic between models incorporating only age and sex in addition to imaging biomarkers as compared with more sophisticated models incorporating clinical information was not statistically significant (P=0.18; Figure S3).

The distribution of CBI phenotypes was different in TIA risk stratification groups; compared with patients with severe WMHs without CBIs, multiple CBI phenotypes were more frequent in high-risk patients with TIA (see Table 2 for details).

Multivariable logistic regression showed an independent association of CBIs (adjusted odds ratio [OR], 0.3; 95% CI, 0.1–0.9; full model in Table S3), but not WMHs with the final diagnosis of a stroke mimic (less likely if CBI was present). Addition of CBI to clinical variables alone had a small but significant incremental value for the prediction of stroke mimic (integrated discrimination improvement, 0.01; P<0.001). Receiver operating characteristic analysis comparing different predictive performance models for the identification of stroke mimics showed a similar performance for those incorporating clinical information alone (cvAUC, 0.85; 95% CI, 0.70–0.86), the combination of clinical information and neuroimaging biomarkers (cvAUC, 0.85; 95% CI, 0.68–0.86) as well as models incorporating only neuroimaging biomarkers (cvAUC, 0.76; 95% CI, 0.72–0.87) with minimal clinical information (only age and sex; Figure S3) for identification of stroke mimics.

In patients with TIA, neither CBI (OR, 1.6; 95% CI, 1.3–2.0) nor cortical CBI (OR, 1.8; 95% CI, 1.3–2.4) were associated with atrial fibrillation after adjustment for age and hypertension (adjusted OR, 0.94; 95% CI, 0.5–1.9; adjusted OR, 0.91; 95% CI, 0.3–2.8).

Table 1. Basic Information and Neuroimaging Biomarkers of Patients According to Final Diagnosis

	Ischemic stroke	TIA	Stroke/TIA mimic	*P* value
Clinical characteristics	n=1693	n=377	n=42	
Age, y	71.4 (59.6–80.5)	70.3 (59.1–79.4)	48.65 (37.4–57.5)	<0.001
Female sex	689 (40.7)	187 (49.6)	27 (64.3)	<0.001
NIHSS admission	3 (1–8)	0 (0–1)	0 (0–2)	<0.001
Neuroimaging biomarkers				
Any CBI	641 (37.9)	102 (27.1)	4 (9.5)	<0.001
Multiple CBI (if at least 1)	296 (17.7)	44 (12.5)	0 (0.0)	<0.001
CBI phenotypes				<0.001
Lacune	196 (11.6)	56 (14.9)	3 (7.1)	
Large noncavitating subcortical	32 (1.9)	2 (0.5)	0 (0.0)	
Isolated cortical CBI	58 (3.4)	10 (2.7)	1 (2.4)	
Combined gray and white matter	109 (6.4)	10 (2.7)	0 (0.0)	
Multiple CBI phenotypes	247 (14.6)	27 (7.2)	0 (0.0)	
Any cortical CBI	221 (13.1%)	31 (8.2%)	1 (2.4%)	0.005
Age-related white matter changes scale	1 (0–2)	1 (1–2)	0 (0–1)	<0.001*

Data presented as median (Q1–Q3) and n (%). CBI indicates covert brain infarction; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*P=0.093 for comparison of ischemic stroke and TIA when excluding patients with stroke/TIA mimic.

Table 2. ABCD3-I Risk Category and WMH/CBI Phenotypes

ABCD3-I risk category		WMH rating scale					Any CBI	CBI phenotypes					
		0.020					0.088	0.026					
P value	N	0	1	2	3			Lacune	Large non-cavitating subcortical	Isolated Cortical	Combined gray and white matter	Multiple CBI types	Severe white matter hyperintensities without additional CBI
Low risk (0–3 points), n (%)	57	20 (35.1)	30 (52.6)	4 (7.0)	3 (5.3)		9 (15.8)	6 (10.5)	0 (0.0%)	1 (1.8)	1 (1.8)	1 (1.8)	3 (5.3)
Intermediate risk (4–7 points), n (%)	260	51 (19.9)	121 (47.3)	55 (21.5)	29 (11.3)		78 (30.0)	44 (16.9)	1 (0.4)	9 (3.5)	7 (2.7)	20 (7.7)	39 (15.0)
High risk (8–13 points), n (%)	43	7 (16.3)	19 (44.2)	9 (20.9)	8 (18.6)		13 (30.2)	4 (9.3)	1 (2.3)	0 (0.0)	2 (4.7)	6 (14.0)	9 (20.9)

Seventeen patients with TIA had missing information for correct ABCD3-I classification. CBI indicates covert brain infarction; TIA, transient ischemic attack; and WMH, white matter hyperintensity.

DISCUSSION

This study shows that imaging biomarkers indicating prior brain ischemia differ between patients with stroke mimics, TIAs and acute ischemic stroke. The presence of CBIs and WMHs closely correlated with established risk scores for early stroke recurrence. Our analysis suggest that biomarkers might be a promising surrogate to correctly identify high-risk patients with TIA if obtaining a reliable medical history is impossible. Nevertheless, given the limitations of this study, we strongly recommend obtaining a reliable medical history—if necessary, by proxies. WMHs[5,7] and overall CBIs[14] have been shown to predict recurrence after TIA, and our results strengthen this observation. Additionally, our studies provide the frequencies of different small-vessel and non–small-vessel phenotypes of CBI within the population of patients with TIA. Further prospective studies should analyze whether specific phenotypes of CBI can further refine risk stratification since basic parameters such as WMHs failed to improve recurrence prediction.[8]

Previous studies found a higher WMH volume in TIA/minor strokes compared with stroke mimics.[15] Similarly, other studies found an association of WMHs with stroke recurrence[3,5] and long-term risk of mortality.[3] Our study confirms those findings and also shows that CBIs are less frequent, with multiple CBIs being nonexistent in patients with stroke mimic.

Additionally, our analysis showed very similar measures of discrimination for the prediction of stroke mimics between models incorporating only minimal clinical information in addition to the biomarkers compared with more sophisticated models incorporating profound clinical information. Given the small but significant discrimination improvement, further studies need to examine whether including brain frailty markers may contribute to the refinement of current identification[15,16] algorithms.

Limitations

Because of the limited sample size and low frequency of outcome events, we could not analyze the association of those biomarkers with recurrent stroke or death. Also, the number of stroke mimics was very small, leading to wide CIs for adjusted ORs and a lack of statistical power to detect differences. Prospective studies need to show whether incorporating neuroimaging brain frailty markers might replace or even outperform current management algorithms. Additionally, we do not know how many patients were unable to provide a history in the emergency department, since the data in the registry also uses information ascertained after admission from family friends, doctors, pharmacies, or skilled living facilities. Additionally, the exclusion of patients with other diagnoses potentially causing brain

lesions similar to CBI and patients with only computed tomographic imaging will have introduced selection bias, and our findings should not be extrapolated to those patients.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S3

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Supplemental Material

Table S1. Comparison of event types between patients receiving MRI and CT

	Ischemic stroke	TIA	Mimic	P <0.001
CT	91%	8%	1.4%	
MRI	84%	14%	1.9%	

Table S2. Baseline characteristics of patients according to final diagnosis

	Ischemic stroke	**TIA**	**Stroke/TIA mimic**	p-value
Clinical Characteristics	N=1,693	N=377	N=42	
Age, years	71.4 (59.6-80.5)	70.3 (59.1-79.4)	48.65 (37.4-57.5)	<0.001
Female Sex	689 (40.7%)	187 (49.6%)	27 (64.3%)	<0.001
NIHSS admission	3 (1-8)	0 (0-1)	0 (0-2)	<0.001
Living at home before event	1,611 (95.5%)	359 (95.2%)	40 (95.2%)	0.97
1st systolic blood pressure, mmHg	160 (139-180)	157.5 (140-177)	138 (126-160)	<0.001
Hypertension	1,138 (67.3%)	233 (61.8%)	8 (19.0%)	<0.001
Diabetes	299 (17.7%)	52 (13.8%)	2 (4.8%)	0.021
Hyperlipidemia	980 (58.0%)	152 (40.3%)	16 (38.1%)	<0.001
Smoking	407 (24.5%)	76 (20.2%)	13 (31.0%)	0.11
Atrial Fibrillation	363 (21.5%)	42 (11.1%)	3 (7.1%)	<0.001
Coronary heart disease	259 (15.3%)	58 (15.4%)	5 (11.9%)	0.83
Peripheral artery disease	67 (4.0%)	22 (5.8%)	1 (2.4%)	0.22
Active cancer	68 (4.0%)	10 (2.7%)	0 (0.0%)	0.19
1st glucose, mmol/L	6.4 (5.6-7.7)	8.3 (8.3-8.3)	NA	0.27
1st creatinine, umol/L	80 (67-94)	78 (66-92)	69 (57-83)	<0.001

NIHSS: National Institute of Health Stroke Severity Scale.

Table S3. Full model for prediction of stroke mimic

Variable	Odds Ratio	Standard error	Z	P>|z	Lower 95% confidence interval	Upper 95% confidence interval
Age, years	.9546463	.0125021	-3.54	0.000	.9304545	.979467
Female sex	3.205605	1.146679	3.26	0.001	1.590106	6.462401
1st systolic blood pressure after admission, mmHg	.9983998	.0068523	-0.23	0.816	.9850595	1.011921
Medical history of arterial hypertension	.2478853	.1222059	-2.83	0.005	.0943222	.6514599
Medical history of prior transient ischemic attack	.9408665	.7083861	-0.08	0.935	.2151054	4.115329
Medical history of diabetes mellitus	.5585549	.4500273	-0.72	0.470	.1151472	2.709433
Medical history of atrial fibrillation	.9448546	.63339	-0.08	0.933	.2539545	3.515394
1st creatinine level after admission, umol/L	1.010199	.0031162	3.29	0.001	1.00411	1.016325
Age related white-matter hyperintensities severity score, ordinal ranging from 0-3	1.328679	.3698693	1.02	0.307	.76996	2.292832
Chronic covert brain infarction	.2619454	.1661211	-2.11	0.035	.0755777	.9078784

Full model showing association of CBI (SBIany) with lower probability of a final diagnosis of stroke mimic with adjustment for covariates identified using lasso regression.
Number of observations 2061, Likelihood ratio (chi^2): 80.59, P<0.001, Pseudo-R^2 0.2042, Log likelihood = -156.99672

Fig S1. Flow Chart of Patient In/Exclusion

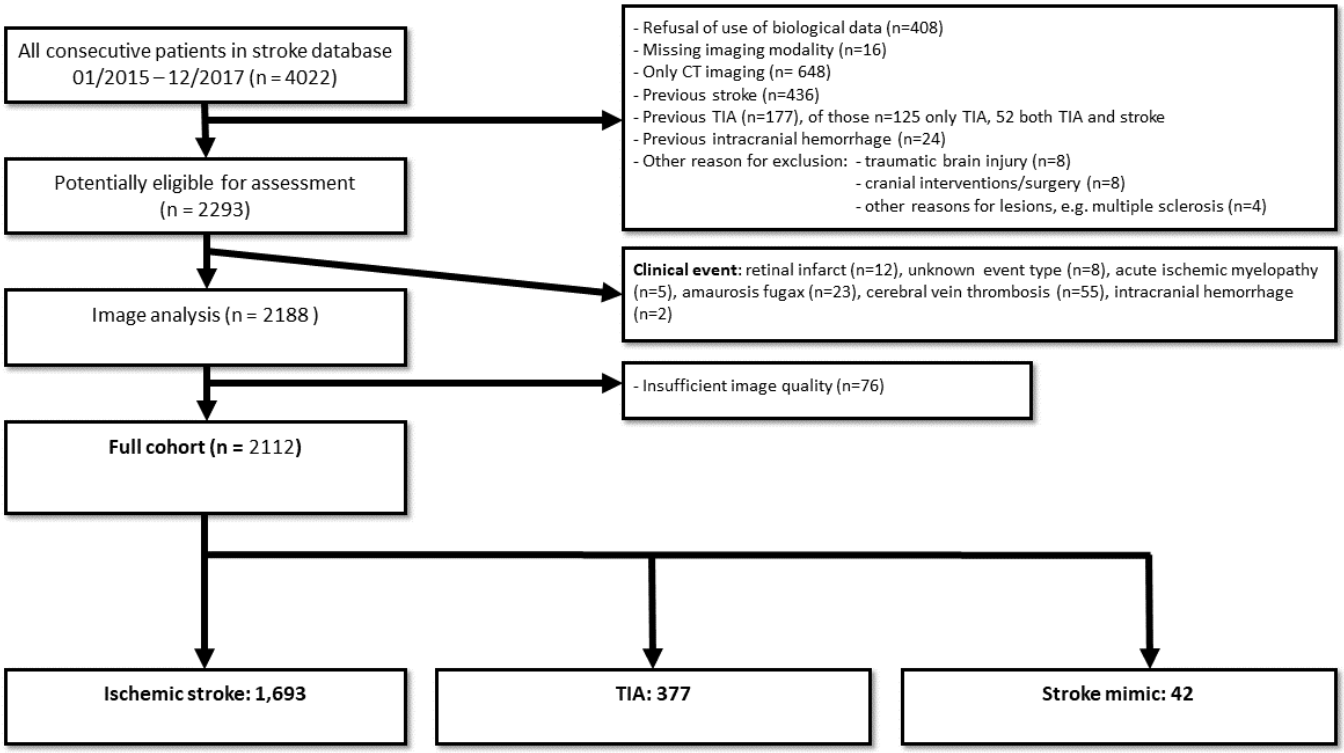

Figure S2. Examples of phenotypes of covert brain infarction

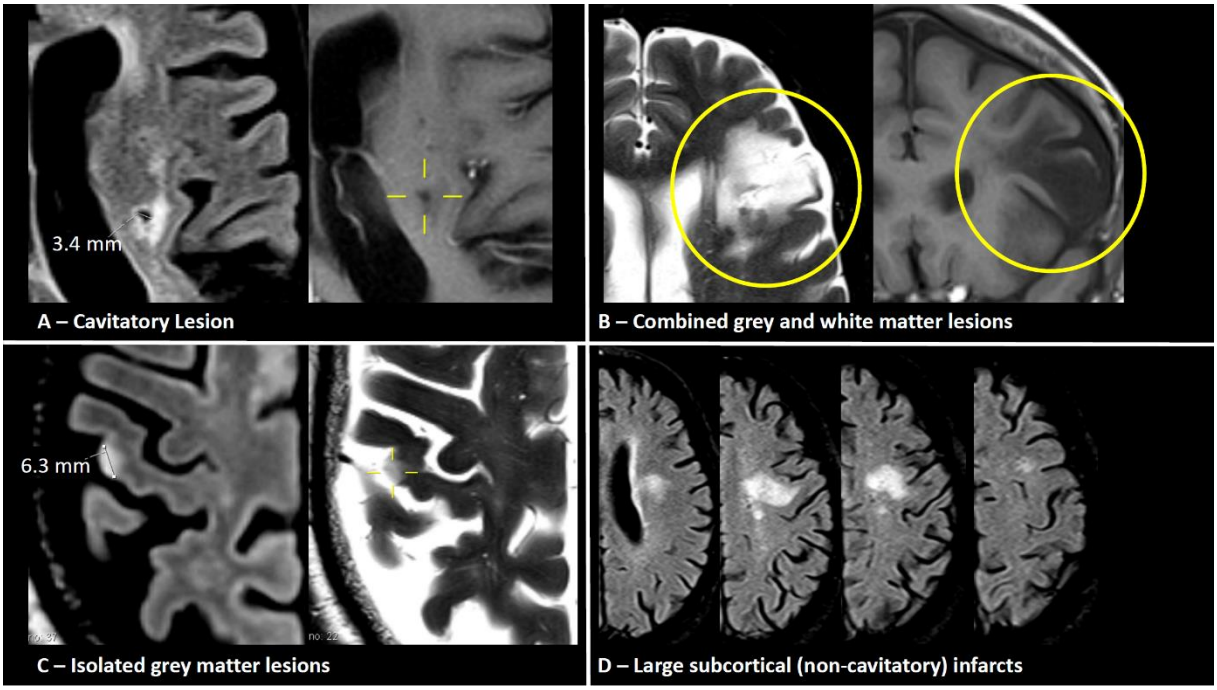

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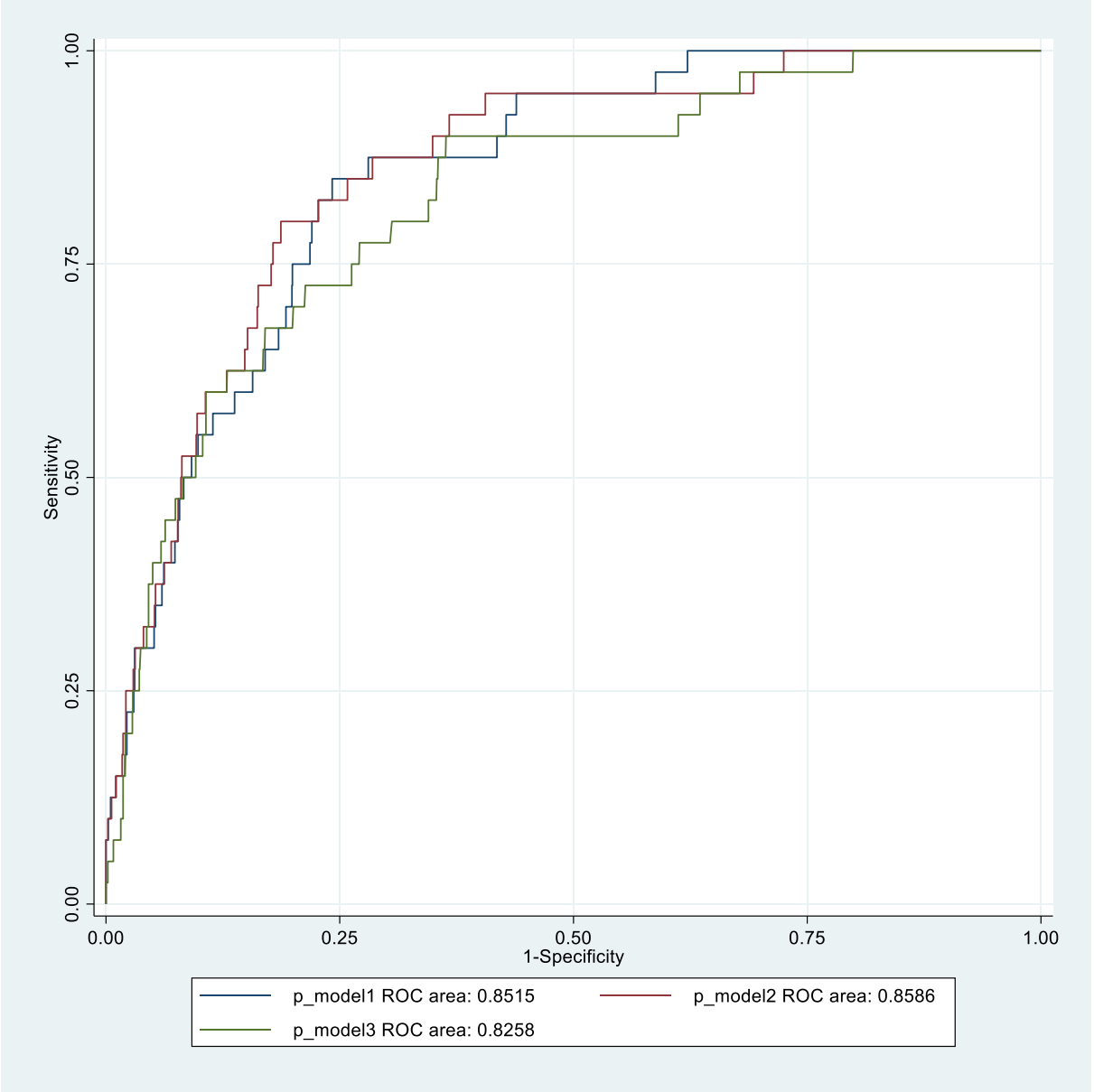
Figure S3. Predictive Performance to identify stroke mimics



p_model1 (blue) only clinical variables (Age, sex, systolic blood pressure, history of hypertension, TIA, diabetes, atrial fibrillation and creatinine), model 2 (red) clinical AND neuroimaging (presence of any CBI and WMH severity), model 3 (green) only age, sex and neuroimaging (presence of any CBI and WMH severity)