Diagnostic Accuracy of a Simple Clinical Score to Screen for Vascular Abnormalities in Patients with Intracerebral Hemorrhage

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Background: Patients with intracerebral hemorrhage may have vascular abnormalities. There is no consensus about which patients should be studied with angiographic methods. Our aim was to derive a simple clinical score to screen for vascular abnormalities in intracerebral hemorrhage (ICH) and test its accuracy. *Methods:* The data were extracted from 2 different registries of patients with ICH. Variables associated with a vascular abnormality were studied in the derivation cohort. We derived a scale by assigning scores to the degree of association. We applied the score to the validation cohort and calculated sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios (LRs), receiver operating curves (ROC) and area under the curve (AUC). *Results:* The performance of the scale in the derivation cohort showed the maximum operating point (MOP) at ≥5 (sensitivity .77, specificity .5). In the validation cohort, the MOP was a cutoff point of ≥5 (sensitivity .76, specificity .467). The positive and negative LRs were 2.1 and .6, respectively. The ROC showed similar AUC for both cohorts: .7. The probability of a vascular malformation was 23% with scores ≤5 and 83% with scores ≥9 in the validation cohort. *Conclusions:* This simple clinical score can be used immediately on diagnosing an ICH to decide accurately whether to perform an angiographic study or not. Further studies using this simple score should be used to validate it in larger prospective unselected cohorts and consecutive patients. **Key Words:** Intracerebral hemorrhage—vascular abnormality—angiography—diagnostic criteria.

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Intracerebral hemorrhage (ICH) causes 10% to 20% of the first-ever strokes worldwide. In a meta-analysis of population-based studies, the overall incidence of ICH was 24.6 per 100,000 person-years (95% confidence interval [CI] 19.7-30.7)[1] and has increased significantly by 22% (5-30) in low middle income countries in the last 22 years according to the Global Burden of Disease Project.[2] Most ICHs are spontaneous; hypertension, amyloid angiopathy, coagulation disorders including oral anticoagulation treatment, and increasing age being the major associated risk factors.[3] Nevertheless, a small proportion of ICHs are secondary to vascular abnormalities, mostly arteriovenous malformations (AVMs), aneurysm that rupture into the parenchyma, dural fistula, cerebral venous sinus thrombosis, cavernomas, vasculitis, and other

vasculopathies.[4] These have higher rates of rebleeding and have specific preventive treatments. Digital subtraction angiography (DSA) is the gold standard diagnostic method to detect secondary vascular etiologies of ICH but it has risks, is expensive, and has limited accessibility in nonspecialized tertiary care settings.[5]

Previous studies show that vascular malformations are more common in younger patients in the absence of hypertension or anticoagulant use, in lobar ICH and in those with intraventricular hemorrhage (IVH).[6-8] Noninvasive imaging modalities such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), or magnetic resonance imaging (MRI), can be accurate in the detection of underlying vascular lesions compared with conventional catheter angiography and are being increasingly used in the acute setting of an ICH.[9,10] Unfortunately, current clinical guidelines have low or intermediate levels of evidence in their recommendations about imaging modalities in acute ICH[11,12] and thus there is no consensus about which patients should be studied with DSA or other noninvasive vascular imaging method (MRA or CTA) in the acute setting and which do not need any other vascular imaging study.[13]

Clinicians must determine the risk that a patient with ICH has of harboring an underlying vascular abnormality with the purpose-making decision about ordering an invasive or noninvasive angiographic diagnostic method, but there is a paucity of risk-stratification systems aiding in this decision.[14] Recently a practical clinical based scoring system was proposed, which stratifies patients according to their risk of an underlying vascular lesion, but it includes a noncontrast computed tomography (NCCT) scoring system of the presence or not of vascular abnormalities in the vicinity of the ICH that could make more complicated to use in many health settings.[15]

Our aim was to test the accuracy of an even simpler clinical score to screen patients with acute ICH to perform vascular imaging in patients, to be used in any health care setting.

Materials and Methods

Derivation Cohort

We retrospectively obtained data from an imaging database of patients with nontraumatic ICH examined at the Instituto de Neurocirugía Asenjo, a tertiary care public hospital in Santiago, Chile, who underwent diagnostic cerebral angiography between August 2003 and December 2005. The initial database included a total of 1840 patients. We included only those patients with an acute ICH (less than 72 hours), diagnosed by CT scan, older than 15 years, and who had no contraindication for DSA. Patients were excluded if they had any cisternal subarachnoid hemorrhage, known brain tumor, a nondiagnostic DSA, or incomplete data. All the data were extracted from the registry of diagnostic angiography and patients' clinical records by trained vascular neurologists (V.O. and J.L.).

Validation Cohort

Patients were recruited from the Clínica Alemana de Santiago Stroke Registry (RECCA), a prospective registry of all patients with stroke admitted to Clínica Alemana, a nonprofit private academic medical center in Santiago, Chile. The initial database consisted of 296 patients with nontraumatic ICH admitted consecutively to our institution, from 1997 to 2011. Patients were included if they were admitted with symptoms of an acute stroke, had an NCCT or MRI performed within 1 hour of being admitted, which was diagnostic of nontraumatic ICH, and had at least 1 vascular neuroimaging procedure (CTA, MRI/MRA, or DSA) performed during their hospitalization. Patients were excluded if they had any cisternal subarachnoid hemorrhage, a brain tumor, a cavernous angioma, a hemorrhagic transformation of a cerebral infarction, or a previously known brain vascular malformation.

Variables and Procedures

Intracerebral or intraparenchymal hemorrhage was defined as an acute stroke syndrome in which a computed tomography (CT) of the brain showed an area of high attenuation in a region compatible with the clinical signs and symptoms. Hypertension was diagnosed if the patients had a known history of or if on treatment with antihypertensive drugs. Lobar ICH was defined as a bleeding in the supratentorial lobes, and nonlobar ICH if in the basal ganglia, thalamus, brainstem, or cerebellum. Cases with IVH could be either lobar or nonlobar. The site of bleeding was adjudicated by a neuroradiologist masked to the results of angiography. In both the derivation and the validation cohort, we considered a positive angiographic finding when it was diagnostic of a vascular abnormality, which according to the neuroradiologist's standard report was the cause of the ICH, such as AVM, dural AVM, cerebral aneurysm, Moyamoya disease, cerebral vasculitis, or cerebral venous sinus thrombosis. We excluded cases in which vascular abnormalities were seen on plain CT.

Analysis

To determine the variables associated with positive or negative findings on angiographic studies, univariate analysis was performed. Chi-square or Fisher exact test was used to compare discrete variables and Student *t* test for continuous variables, when appropriate. We then constructed a logistic regression model to investigate the strength of the association of the variables associated with a positive DSA in the univariate analysis. We derived a scoring system for the variables by assigning differential scores according to the degree of association in the derivation cohort. We then applied the scoring system to the validation cohort and calculated sensitivity, specificity, positive and negative predictive values, and

Table 1. *Distribution of study variables in derivation and validation cohorts, stratified according to angiographic findings*

Variables (%)	Derivation cohort, N = 160			Validation cohort, N = 106		
	Positive angiographic findings, n = 82	Negative angiographic findings, n = 78	*P* value	Positive angiographic findings, n = 34	Negative angiographic findings, n = 72	*P* value
Mean age (SD)	37.4 (14.1)	45.5 (14.4)	.004	47.6 (16.8)	61.0 (18.0)	.01
Age groups (y)						
15-50	65 (57.9)	48 (42.5)	.01	18 (58.1)	19 (26.4)	.03
≥51	17 (36.1)	30 (63.8)	.01	16 (33.4)	53 (73.6)	.03
Female sex, n (%)	45 (54.9)	40 (51.3)	.60	14 (42.4)	32 (44.4)	.70
Hypertension, n (%)	16 (19.8)	34 (46.6)	.001	9 (27.3)	29 (40.3)	.02
Location, n (%)						
Lobar	63 (76.8)	55 (70.5)	.30	19 (57.6)	48 (66.6)	.30
Deep	19 (23.2)	23 (29.5)	.40	15 (42.4)	24 (33.3)	.30
IVH, n (%)	24 (29.3)	19 (24.4)	.50	17 (50)	23 (31.9)	.20
Use of oral anticoagulants, n (%)	0	5 (6.4)	-	1 (2.9)	2 (2.8)	.70
Drug or vasoactive medication use, n (%)	2 (2.4)	0	-	3 (8.8)	4 (5.6)	.70

Abbreviations: IVH, intraventricular hemorrhage; SD, standard deviation; y, years.
Numbers in parenthesis are % unless otherwise stated.

positive and negative likelihood ratios (LRs) with their respective 95% CIs for each cutoff point. We constructed receiver operator curves to determine areas under the curve (AUC) and maximum operating points (MOP) for each individual cohort. All tests were 2-tailed and considered significant if $P < .05$. Statistical analyses were performed with Epi Info 3.5.1 (Epi Info [TM] software is in the public domain and freely available for use, copying, translation and distribution. EPI Info is a trademark of the Centers for Disease Control and Prevention [CDC]) and Epidat 3.1. (Servizo de Epidemioloxía de la Dirección Xeral de Innovación e Xestión da Saúde Pública de la Consellería de Sanidade [Xunta de Galicia], Organización Panamericana de la Salud [OPS-OMS]).

Ethics

The project has been approved by the institutional review board and the ethics committee of our institution.

The article is reported according to the STAndards for the Reporting of Diagnostic accuracy where appropriate. [16]

Results

Derivation Cohort

The sample consisted of 160 cases of spontaneous ICH, mean age 41.4 (standard deviation 14.8), 85 women (53.1%). Eighty-two patients (51.3%) had positive angiographic findings. Demographic and clinical characteristics of patients with or without angiographic findings in the derivation cohort are shown in Table 1. Most cases of positive angiograms were AVMs as shown in Table 2.

Logistic regression analysis showed that younger age (≤50 years) and no history of hypertension were independent factors strongly associated with a positive angiography. IVH, lobar ICH, and oral anticoagulant use were found to be less strongly associated and not significantly. With these results the scoring depicted in Table 3 was derived. The minimum score was 0 and the maximum was 10.

Validation Cohort

The sample consisted of 106 patients with ICH who underwent DSA, MRA, or CTA in our Institution. The mean age was 56.7 (standard deviation 18.6) and 46 (43.4%) were women. The frequency of vascular neuroimaging was 45 DSA (56.9%), 51 CTA (64.5%), and 19 MRA (24%). Of the patients who underwent CTA, 23 (29.1%) had DSA also, and of the patients who underwent MRA, 10 (12.6%) had DSA also. Another 4 patients (5%) had both MRA and CTA. Thus 12 (15.1%) had DSA only, 24 (30%) had CTA only, and 5 (6%) had MRA only.

Table 2. *Vascular abnormalities identified by digital subtraction angiography, computed tomography angiography, or magnetic resonance angiography in both the derivation and validation cohorts*

Etiology (%)	Derivation cohort, N = 82	Validation cohort, N = 34
Arteriovenous malformation	62 (75.6)	22 (64.7)
Aneurysm	13 (15.8)	6 (17.6)
Dural fistula	4 (4.8)	4 (11.7)
Dural vein sinus thrombosis	1 (1.2)	2 (5.8)
Moyamoya	2 (2.4)	0

Table 3. *Risk-stratification score of cerebral vascular abnormalities in intracerebral hemorrhage*

Variables	Groups	Assigned score
Age, y	≤50	3
	>50	0
Hypertension	No	3
	Yes	0
Site of intracerebral hemorrhage	Lobar	1
	Deep	0
Intraventricular hemorrhage	Yes	2
	No	0
Oral anticoagulant use	No	1
	Yes	0

The simple ICH score is calculated by adding the total number of points for a given patient.

A positive angiographic study was found in 34 (43%) of cases. As in the derivation cohort, most cases of positive angiograms were AVMs (Table 2). Univariate analysis in this cohort also showed that patients with positive angiograms were younger with no history of hypertension and more frequently had IVH.

Performance of the Simple ICH Score

The accuracy at different cutoff points of the scoring system in the derivation and validation cohort is shown in Tables 4 and 5. In the derivation cohort, the MOP was a cutoff point of ≥5, which had a sensitivity of .8 (95% CI .6-.8) and a specificity of .5 (.4-.6). The positive and negative LRs were 1.5 (1.2-2.0) and .5 (.3-.7), respectively. In the validation cohort, the MOP was a cutoff point of ≥5, which had a sensitivity of .8 (95% CI .6-.9) and a specificity of .5 (95% CI .3-.6). The positive and negative LRs were 2.1 (1.2-3.7) and .6 (.4-.9), respectively. The receiver operator curves showed similar AUC for both cohorts: .65 (95% CI .56-.73) for the derivation cohort and .67 (95% CI .55-.79) for the validation cohort (Fig 1). Figure 2 shows that in the validation cohort, patients with scores of 0-5 had a low probability of vascular malformation, patients with scores of 6-8 had an intermediate probability, and scores of 9-10 a very high probability of finding a vascular malformation after vascular imaging. The specificity using a cutoff point of 9 is 90% with a positive LR of 9 (Table 5).

Discussion

Our results demonstrate that this simple scoring scale can be used at the bedside of patients with ICH diagnosed using NCCT to decide if they should undergo further vascular imaging. The probability of an underlying vascular malformation is very high if the score is over 8. Increasing scores over 5 will have increasing LRs of changing the pretest probabilities to detect a vascular malformation as the underlying cause if CTA, MRA, or DSA is performed. These LRs range from small to high shifts in the pre- to post-test probability.

This score uses all the demographic and clinical variables found to be associated with a higher yield of finding an AVM or an aneurysm in patients with ICH reported in previous studies.[7,17-20] It also agrees with the usual response of the panel of experts in France, United Kingdom, and the Netherlands managing patients with ICH.[13] Many previous studies have investigated the best imaging strategy for these patients (CTA, MRA or DSA) but few have investigated about developing clinical strategies to make such decisions.[13] The recently published spontaneous ICH score is valid and has higher AUCs than ours, but it is somewhat more difficult to use as it needs coagulation laboratory results to not be impaired defined as admission international normalized ratio > 3, a prothrombin time > 80 seconds, platelet count < 50,000, and NCCT to be scored also according to the presence of "enlarged vessels or calcifications along the margins of the ICH and or hyper attenuation within a dural venous sinus or cortical vein along the presumed venous drainage path of the ICH", which may have more errors and be less reliable than ours, which

Table 4. *Performance of scoring at different cutoff points in derivation cohort*

Scores	Sensitivity	Specificity	PPV	NPP	LR+	LR−
1	.99 (.94-.99)	.07 (.03-.15)	.53 (.45-.61)	.92 (.52-.99)	1.07 (1.00-1.14)	.09 (.01-1.54)
2	.93 (.85-.97)	.19 (.12-.29)	.55 (.46-.63)	.71 (.5-.87)	1.15 (1.01-1.3)	.4 (.16-.93)
3	.91 (.83-.96)	.23 (.17-.37)	.57 (.48-.64)	.74 (.55-.87)	1.23 (1.06-1.42)	.33 (.15-.74)
4	.89 (.80-.94)	.33 (.24-.44)	.58 (.49-.67)	.74 (.58-.86)	1.34 (1.12-1.59)	.33 (.16-.66)
5	.78 (.68-.86)	.46 (.35-.57)	.60 (.50-.67)	.67 (.53-.78)	1.45 (1.14-1.83)	.48 (.3-.76)
6	.76 (.65-.84)	.51 (.40-.62)	.62 (.52-.71)	.67 (.54-.77)	1.55 (1.2-2.01)	.5 (.31-.74)
7	.54 (.43-.6)	.63 (.52-.73)	.60 (.49-.71)	.56 (.46-.66)	1.44 (1.02-2.05)	.74 (.55-.98)
8	.17 (.11-.27)	.92 (.84-.96)	.7 (.48-.85)	.51 (.43-.6)	2.22 (.9-5.48)	.0 (.8-1.01)
9	.11 (.03-.15)	.973 (.907-.993)	.714 (.359-.918)	.514 (.432-.596)	2.534 (.508-12.648)	.957 (.89-1.03)
10	.068 (.059-.196)	.975 (.937-.99)	.692 (.424-.873)	.681 (.618-.738)	4.39 (1.394-13.828)	.913 (.843-.989)

Abbreviations: LR, likelihood ratio; NPP, negative predictive value; PPV, positive predictive value.

Table 5. *Performance of scoring at different cutoff points in validation cohort*

Scores	Sensitivity	Specificity	PPV	NPP	LR+	LR−
1	.88 (.73-.95)	.07 (.02-.18)	.41 (.31-.53)	.43 (.16-.75)	.95 (.82-1.1)	1.76 (.42-7.37)
2	.82 (.66-.917)	.23 (.16-.41)	.46 (.34-.58)	.67 (.44-.84)	1.12 (.89-1.42)	.66 (.28-1.58)
3	.76 (.6-.88)	.36 (.23-.50)	.47 (.35-.60)	.67 (.5-.8)	1.19 (.89-1.58)	.66 (.32-1.36)
4	.76 (.6-.88)	.47 (.33-.61)	.52 (.38-.65)	.72 (.54-.85)	1.43 (1.03-2.0)	.50 (.25-1.0)
5	.62 (.45-.76)	.6 (.45-.73)	.54 (.37-.69)	.67 (.52-.8)	1.54 (.99-2.41)	.64 (.39-1.04)
6	.6 (.4-.71)	.73 (.59-.84)	.61 (.44-.76)	.69 (.55-.80)	2.1 (1.19-3.70)	.60 (.4-.91)
7	.5 (.31-.63)	.87 (.74-.94)	.73 (.52-.87)	.69 (.55-.79)	3.53 (1.54-8.06)	.61 (.44-.86)
8	.26 (.15-.43)	.96 (.87-.99)	.82 (.52-.95)	.66 (.55-.76)	6.75 (1.55-29.3)	.76 (.62-.94)
9	.176 (.083-.335)	.991 (.948-.998)	.75 (.301-.954)	.772 (.695-.835)	9.353 (1.006-86.978)	.92 (.828-1.024)
10	.088 (.03-.23)	.991 (.948-.998)	.857 (.487-.974)	.789 (.713-.85)	18.706 (2.334-149.949)	.831 (.711-.972)

Abbreviations: LR, likelihood ratio; NPP, negative predictive value; PPV, positive predictive value.

only scores the location of ICH.[15] The spontaneous ICH score was validated in a cohort in the United States but did not perform well in a cohort of patients with ICH in the Netherlands.[21,22] In the latter, the inter-rater agreement was only .64 (.55-.73) and the discriminative ability (c statistics) was moderate .73 (95% CI .65-.80) and not significantly greater than our score.

The strengths of this investigation are that we were able to derive the score in a large sample of patients undergoing DSA and validate it in a different sample of patients with ICH undergoing mostly DSA or CTA as vascular neuroimaging diagnostic method.

There are several limitations in this study, which could influence our results. It is a retrospective study and patients in both cohorts were not consecutive patients with ICH but selected in some way. For instance, we do not know how many patients had an MRI after the CT and before DSA were performed in both cohorts. This selection bias could influence the yield of the scoring system. The high rate of vascular abnormalities in the derivation cohort is a manifestation of this, because patients with ICH were selected for angiography based on clinical suspicion of vascular abnormality as in everyday clinical practice in a tertiary care center. Another limitation is that patients in the validation cohort were diagnosed with a vascular malformation based on 3 different vascular imaging studies: DSA, CTA, and MRA, which could also decrease the yield of the score in this cohort. Most patients had a diagnostic DSA (57%), and although both MRA and CTA have been shown to have a high performance in detecting vascular malformations in the setting of an acute ICH, these methods do not have the same diagnostic accuracy as DSA and could have misclassified patients as false negative to vascular abnormalities.[23-25] We included these patients in the validation cohort to have a less selected sample and so validate the score on a more usual clinical setting.

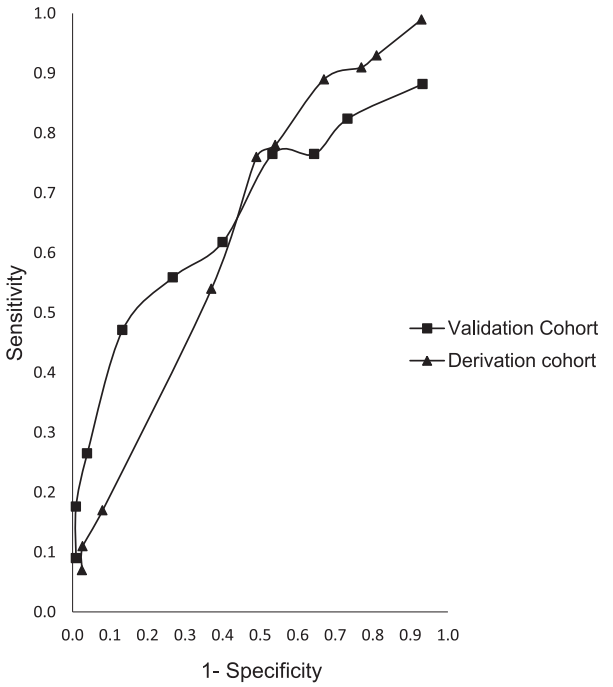

Figure 1. *Derivation and validation cohort receiver operator curves (ROC). Derivation cohort maximum operating point (MOP) ≥ 5, area under the curve (AUC) = .65 (95% CI .56-.73). Validation cohort MOP ≥ 5, AUC = .67 (95% CI .55-.79).*

This study is the second to propose and validate a simple clinical score to screen patients with ICH for vascular malformations after an NCCT scan has been performed. Although the overall diagnostic accuracy of this score is intermediate as depicted by the AUCs, we believe it is clinically useful as it is simple and is able to select patients with very low probability and those with intermediate or high probability of a vascular malformation at the bedside in any clinical setting with NCCT. This score could be used to not order any further vascular imaging (≤5), use a noninvasive method such as MRA or CTA if the scores are 6-8, and perform a DSA if it is 9-10. Busy clinicians caring for patients with ICH through out the world and especially in middle and low income countries or other poor resource settings, have now 2 scoring systems that can be used at the patient's bedside before ordering further neuroimaging, thus increasing the

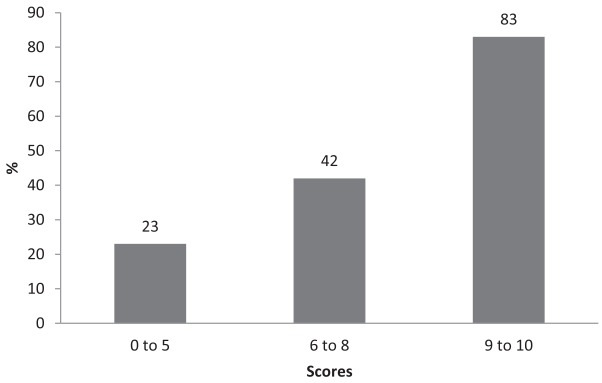

Figure 2. *Rate of vascular malformation findings according to score results in the validation cohort.*

likelihood of detecting an underlying vascular malformation at a low risk and cost.

Further studies using this simple score should be used to validate it in larger prospective unselected cohorts and consecutive patients with ICH hopefully undergoing DSA. Because how and when to undertake further diagnostic investigations in ICH is an issue of ongoing research and debate, this data could be used in developing clinical decision trees to define standard diagnostic algorithms and cost-effective strategies for investigating patients with ICH especially at older ages and in poor resource settings as has been stated previously.[14]

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