Article published online: 2023-06-13

https://doi.org/10.1590/0004-282X20200008

ARTICLE

Predictors of hemorrhagic transformation after acute ischemic stroke based on the experts' opinion

Preditores de transformação hemorrágica após acidente vascular cerebral isquêmico agudo a partir da opinião de especialistas

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ABSTRACT

Background: Hemorrhagic transformation (HT) is a common complication after ischemic stroke. It may be associated to poor outcomes. Some predictors of HT have been previously identified, but there remain controversies. **Objective:** To describe the risk factors for HT more frequently reported by a panel of experts surveyed for this project. **Methods:** We sent a standard questionnaire by e-mail to specialists in Vascular Neurology from 2014 to 2018. Forty-five specialists were contacted and 20 of them responded to the invitation. Predictors cited by three or more specialists were included in a table and ranked by the frequency in which they appeared. A review of the literature looking for published predictive scores of HT was performed, comparing to the answers received. **Results:** The 20 responding specialists cited 23 different risk factors for HT. The most frequent factors in the order of citation were the volume of ischemia, previous use of antithrombotic medication, neurological severity, age, hyperglycemia at presentation, hypertension on admission, and cardioembolism. Most variables were also found in previously published predictive scores, but they were reported by the authors with divergences of frequency. **Conclusion:** Although many studies have evaluated HT in patients with acute ischemic stroke, the published risk factors were neither uniform nor in agreement with those cited by the stroke specialists. These findings may be helpful to build a score that can be tested with the goal of improving the prediction of HT.

Keywords: acute ischemic stroke; hemorrhagic transformation; neurological complication.

RESUMO

Introdução: A transformação hemorrágica (TH) é uma complicação comum após a isquemia cerebral e pode estar associada a desfechos desfavoráveis. Alguns fatores de risco para TH têm sido identificados, mas ainda há controvérsias. **Objetivo:** Descrever os fatores de risco para TH mais frequentemente reportados por um painel de especialistas consultados para esse projeto. **Métodos:** Enviamos um questionário padronizado por e-mail para 45 especialistas em Neurologia Vascular no período de 2014 a 2018. Vinte dos 45 especialistas responderam ao convite. Preditores citados por três ou mais especialistas foram incluídos em uma tabela e classificados pela frequência em que foram reportados. Uma revisão de literatura foi realizada em busca de escores preditivos de TH publicados anteriormente, comparando-os com as respostas recebidas. **Resultados:** Os 20 especialistas citaram 23 diferentes fatores de risco para TH. Os fatores mais frequentemente citados foram, pela ordem, volume da isquemia, uso prévio de medicação antitrombótica, gravidade neurológica, idade, hiperglicemia na apresentação, hipertensão na admissão e cardioembolismo. A maioria das variáveis também foi incluída em escores preditivos de TH já publicados, mas sem a mesma frequência e com divergências entre os especialistas consultados. **Conclusão:** Embora muitos estudos tenham avaliado a TH em pacientes com isquemia cerebral, os fatores de risco já publicados não foram uniformes na concordância com aqueles reportados pelos neurologistas vasculares consultados. Esses achados podem ser úteis para elaborar um escore que possa ser testado para aperfeiçoar a predição de transformação hemorrágica.

Palavras-chave: acidente vascular cerebral isquêmico agudo; transformação hemorrágica; complicação neurológica.

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Conflict of interest: There is no conflict of interest to declare.

Support: This study was partly financed by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) — Finance Code 001.

Received on September 19, 2019; Received in its final form on December 16, 2019; Accepted on January 10, 2020.

Hemorrhagic transformation (HT) is a well-known risk in the natural course of acute ischemic stroke (AIS). This complication may lead to short and long-term worse functional outcomes even in patients either treated or not with reperfusion therapies[1,2,3,4].

Overall, less than 5 to 20% of all stroke patients are considered eligible for treatment with intravenous recombinant tissue plasminogen activator (rtPA)[1,4]. This low percentage of treated patients reflects, in part, the concerns for HT. Around 15% of the patients with AIS not treated with reperfusion therapies will have HT within the first 7–14 days[1,4].

There are many divergences in the literature about the imaging and clinical classification of HT[1,5]. This scenario explains some of the controversies about predicting HT. Moreover, the occurrence and the severity of HT have been unclear[1]. Therefore, an accurate prediction of HT could anticipate and reduce the risk of HT from cerebral infarction. A comparison between the opinion from experts in Vascular Neurology and reported findings in the literature may be helpful to understand this complex phenomenon, particularly in patients not treated with rtPA.

Although some predictors of HT have been identified, there are still some controversies regarding the strength of the association between HT. Understanding the risk factors for its occurrence in patients not treated with reperfusion could impact management plans for those eligible for interventions[4].

The goal of the present study is to describe the risk factors associated to HT cited by a panel of experienced vascular neurologists, and to compare them with the reported data from published predictive scores of HT.

METHODS

Opinion from vascular neurologist specialists

From October 2014 to October 2018, 45 established neurologists with notable knowledge of stroke and/or neurocritical care (selected based on previous publications in the field), from eight countries, were emailed a questionnaire to share their opinion about variables associated to the risk of HT. These neurologists were selected based on their publications over the last 15 years about hemorrhagic transformation, acute-stage treatment in AIS and neuroprotection.

A standard question was sent in English: In your opinion, what factors are related to spontaneous hemorrhagic transformation in patients with AIS?

Twenty out of the 45 invited neurologists replied to the invitation.

The variables mentioned by each specialist were listed according to the order in which they appeared in the answers (Table 1). However, we did not ask the specialists to arrange the answers by relevance. The published predictive scores

Table 1. Opinion by specialists listed in the sequence in which they were first cited.

3	Country	Answer	Specialist	Country	Answer
A	India	Neurological severity Volume of ischemia Cardioembolism	B	United States	Volume of ischemia Treatment with IV recombinant tissue plasminogen activator (rtPA) Probably, previous use of antithrombotic medicines
C	United States	Previous use of antithrombotic medicines (specially the combined therapy with clopidogrel) Treatment with IV rtPA Arterial Hypertension on admission Hyperglycemia on admission	D	United States	Volume of ischemia Time interval between Stroke and hospital arrival Cardioembolism Reperfusion of the ischemic area Arterial Hypertension on admission Previous use of antithrombotic medicines Ischemia at anterior circulation Dose of rtPA
E	Portugal	Volume of ischemia Neurological severity Atrial fibrillation Treatment with heparin Uncontrolled arterial hypertension	F	Egypt	Neurological Severity Age Elevated INR Volume of ischemia/ASPECTS on admission
G	United States	Previous use of antithrombotic (specially the combined therapy with clopidogrel) Arterial Hypertension Diabetes Mellitus Volume of ischemia Previous Stroke Leukoaraiosis and/or microbleeds Cardioembolism Aging	H	United States	Neurological severity Volume of ischemia Etiology of Stroke Age Previous use of antithrombotic medicines Arterial Hypertension

Continue...

Table 1. Continuation.

3	Country	Answer	Specialist	Country	Answer
I	United States	Volume of ischemia Grade of arterial collaterals Elevated INR Previous use of antithrombotic medicines Reperfusion of the ischemic area Probably, microbleeds	J	United States	Volume of ischemia Treatment with IV rtPA Late reperfusion of the ischemic area Hyperglycemia on admission Microbleeds are unclear
L	United States	Aging Volume of ischemia Probably: Arterial hypertension on admission Hyperglycemia on admission	K	United States	Neurological severity Volume of ischemia Localization of the ischemia (cortical/ subcortical/brainstem cerebellum) Hyperglycemia on admission Arterial hypertension on admission and for next 3 days Previous use of antithrombotic medicines Age Renal failure Elevated INR Platelets account Previous Stroke Arterial Hypertension Diabetes Mellitus Heart failure Microbleeds
M	United States	Reperfusion of the ischemic area Volume of ischemia Localization of the ischemia	N	United States	Cardioembolism
O	Italy	Cardioembolism Neurological severity Volume of ischemia Arterial hypertension on admission Hyperglycemia on admission Leukoaraiosis	P	Germany	Arterial hypertension Volume of ischemia Aging is unclear
Q	Canada	Age Neurological severity Cardioembolism Renal failure Heart failure Hyperglycemia on admission Gender (male)	R	United States	Age Renal failure Volume of ischemia
S	United States	Arterial hypertension Blood pressure variability Volume of ischemia Neurological severity Diabetes Hyperglycemia on admission Anticoagulation Treatment with IV rtPA	T	Australia	Depth and duration of CBF reduction Time interval between Stroke and hospital arrival Volume of ischemia Reperfusion of the ischemic area Blood pressure Previous use of antithrombotic medicines (antiplatelet or anticoagulant)

ASPECTS: Alberta Stroke Program Early CT Score; INR: International Normalized Ratio; CBF: Cerebral blood flow; IV: Intravascular; rtPA: Intravenous recombinant tissue plasminogen activator.

of hemorrhagic transformation are summarized in Table 2. Predictors cited by three or more specialists were assembled in Table 3. Specialists were described by letters and displayed in alphabetical order according to the first to respond. A chart with the opinion from specialists was created.

Review of the literature

We individually reviewed all the papers seeking scales or scores to predict the risk of HT. PubMed was searched using the terms: "hemorrhagic transformation", "stroke" and "prediction" in the titles. We found nine articles written in English as of October 2019. We limited our search to the last 15 years, excluding papers of predictive scores, which included only patients submitted to mechanical thrombectomy or intra-arterial thrombolysis.

RESULTS

The top-ranked variables described by the specialists interviewed as the first risk factors for HT were: volume of ischemia (5 specialists), neurological severity (4), and age (3)

(Table 1). At least two specialists graded other variables as the first risk factor for HT, including previous use of antithrombotic medicines, cardioembolism and arterial hypertension.

The single most frequently cited risk factor for HT was volume of ischemia, which was alluded to by 80% of the specialists (n=16). This variable has been included in three out of nine published scores to predict the risk of HT (Table 2).

The mostly frequently cited variables by the existing scores were neurological severity and age — which were ranked by specialists as the third and fourth risk factors in order of relevance, respectively. In the published scores, neurological severity was measured with the National Institutes of Health Stoke Scale (NIHSS) or the Canadian Neurological Scale[6].

A total of seven (35%) specialists rated cardioembolism as a risk factor for HT. Overall, it was the fourth risk factor most cited by the stroke neurologists interviewed. To the best of our knowledge, 22 publications described cardioembolism as an independent risk factor for HT. However, it was included in only two of the existing predictive scores[6,7].

Table 2. Published predictive scores of hemorrhagic transformations.

Scores	Variables
HTI[4]	ASPECTS, Atrial Fibrillation on ECG, NIHSS and hyperdense middle cerebral artery sign
iSCORE[6]	Age, Atrial Fibrillation on ECG, chronic heart failure, NIHSS/Canadian Neurological Scale, preadmission disability, renal dialysis, male, clinical Stroke subtype (lacunar or non-lacunar) and blood glucose on admission (≥135 mg/dL)
HAT[7]	Diabetes Mellitus, NIHSS, presence of easy visible hypodensity on initial CT scan and blood glucose on admission
HeRS[8]	Age, infarct volume and glomerular filtration rate
SEDAN[9]	Age, NIHSS, early infarct signs on admission CT, hyperdense middle cerebral artery sign and blood glucose on admission
SITS-SICH[10]	Age (≥72), antiplatelet (aspirin alone or aspirin+clopidogrel), history of arterial hypertension, NIHSS, stroke onset to treatment time (≥180 min), SBP (≥146 mmHg), weight (≥95 kg) and blood glucose on admission (≥180 mg/dL)
GRASPS[11]	Age, ethnicity, male, NIHSS, SBP and blood glucose on admission
MSS[12]	Age (≥60), NIHSS (≥10), blood glucose (>150 mg/dL) and platelets account less than 150.000/mm^3
SPAN-100[13]	Age and NIHSS on admission

HTI: Hemorrhagic Transformation Index Score; ASPECTS: Alberta Stroke Program Early CT Score; ECG: Electrocardiogram; iScore: Ischemic Stroke Predictive Risk Score; HAT: hemorrhage after thrombolysis; HeRS: Hemorrhage Risk Stratification Score; SEDAN: Blood Sugar [glucose] on admission, Early infarct signs and [hyper] Dense cerebral artery sign on admission computed tomography [CT] head scan, Age, and NIHSS; SITS-SICH: Safe Implementation of Treatments in Stroke (SITS) Symptomatic Intracerebral Hemorrhage Risk Score; SBP: Systolic Blood Pressure; GRASPS: Get With The Guidelines–Stroke symptomatic intracerebral hemorrhage risk; MSS: Multicenter rt-PA Stroke Survey Group Score; SPAN-100: Stroke Prognostication using Age and NIH Stroke Scale. Modified from Kalinin[4].

Renal impairment was cited by three specialists, and has been addressed by two predictive models[6,8].

Hyperglycemia and arterial hypertension on admission are also well-established risk factors for HT and are included in several predictive scores[7,9,10,11,12]. Interestingly reperfusion of the ischemic area was not reported by any predictive scale. Five specialists surveyed cited this variable as a risk factor for HT (Table 3).

Previous use of antithrombotic medicines was the second most common risk factor cited by specialists. This variable has been included in only one predictive score of HT[10]. Although a history of arterial hypertension and diabetes are established risk factors for HT in some series, both were included in just one of the scores of HT prediction[10].

Table 3. Summary of predictors of hemorrhagic transformation.

Variables	Scores [References]	Specialists
Volume of ischemia	HTI [4]; HAT [7]; HeRS [8];	A, B, D, E, F, G, H, I, J, L, K, M, O, P, R, T
Previous use of antithrombotic medicines	SITS-SICH [10]	B, C, D, G, H, I, K, S, T
Neurological severity	HTI [4]; iSCORE [6]; SEDAN [9]; SITS-SICH [10]; GRASPS [11]; MSS [12]; SPAN-100 [13]	A, E, F, H, K, O, Q, S
Age	iSCORE [6]; HeRS [8]; SEDAN [9]; SITS-SICH [10]; GRASPS [11]; MSS [12]; SPAN-100 [13]	F, G, H, L, K, Q, R
Hyperglycemia on admission	HAT [7]; SEDAN [9]; GRASPS [11]; MSS [12]	C, J, L, K, O, Q, S
Hypertension on admission	SITS-SICH [10]; GRASPS [11]	C, D, E, L, K, O, S
Cardioembolism	iSCORE [6]; HTI [4]	A, D, E, G, N, O, Q
Reperfusion of ischemic area	-	D, I, J, M, T
Treatment with rtPA	-	B, C, D, J, S
Microbleeds and/or leukoaraiosis	-	G, I, K, O
History of Arterial Hypertension	SITS-SICH [10]	G, H, K, P
Prothrombin time on admission	HTI [4]	F, I, K
History of Diabetes Mellitus	HAT [7]	G, K, S
Renal impairment	iSCORE [6]; HeRS [8]	K, Q, R

GRASPS: Get With The Guidelines–Stroke symptomatic intracerebral hemorrhage risk; HTI: Hemorrhagic Transformation Index Score; iScore: Ischemic Stroke Predictive Risk Score; MSS: Multicenter rt-PA Stroke Survey Group Score; SEDAN: Blood Sugar [glucose] on admission, Early infarct signs and [hyper] Dense cerebral artery sign on admission computed tomography [CT] head scan, Age, and NIHSS; SITS-SICH: Safe Implementation of Treatments in Stroke (SITS) Symptomatic Intracerebral Hemorrhage Risk Score; SPAN-100: Stroke Prognostication using Age and NIH Stroke Scale; HeRS: Hemorrhage Risk Stratification Score.

Prothrombin time on admission was cited by three specialists and has been previously described by few authors[4].

Some of the already described risk factors in predictive scores of HT were not cited by three or more of our consulted specialists, like ethnicity[11], gender[6], weight[10], and platelets count[12].

Eight risk factors were cited by up to two specialists and have not been included in Table 3. Time interval between stroke onset and hospital arrival, ischemia of the anterior circulation, grade of collaterals, localization of the ischemia, platelet count, heart failure, gender (male) and impaired flow on cerebral perfusion scan. Each of these factors has not been described by predictive score, except for gender[6], heart failure[6] and platelets count[12].

Use of anticoagulation (either with heparin or not) was cited by two specialists. One scale[8] specifically addresses the risk of HT in patients using anticoagulation in the acute phase.

Age was the third most cited risk factor of HT. Many authors addressed this factor in their predictive models[6-13]. Aging is associated to some underlying conditions, such as heart failure, atrial fibrillation, diabetes mellitus and arterial hypertension[6-13].

As shown in Tables 1 and 3, neither of the 20 experts nor the literature showed a uniform ranking for their estimates of risk factors for HT.

DISCUSSION

Our findings suggest that although many studies have evaluated HT in patients with AIS, the described risk factors are not uniform. Moreover, stroke specialists tended to value the results of specific factors differently. This finding might reflect personal experiences or distinct interpretation of inferences drawn from the literature.

Most consulted specialists considered large lesions and a severe neurological deficit at presentation as variables indicating increased risk of HT. Large ischemic lesions, especially if they are located in the cortex, present a high chance of direct or retrograde reperfusion, which can lead to a secondary injury[14]. The integrity of the blood brain barrier (BBB) in such territories seems to be closely related to the risk of HT. A failure in the BBB could also be potentiated by other factors described by the specialist in our series, as well as by the existing literature like hyperglycemia, renal failure, prothrombin time on admission and platelets count. Severe neurological deficits on admission also increase the risk of HT[11,14]. The most common scale used to describe the neurological severity at presentation is the NIHSS. In general, scores under 5 indicate small lesions on the middle cerebral artery territory or deep lesions, representing lacunar syndromes[15]. Usually, severity of the stroke symptoms measured by a scale is a surrogate marker for lesion volume, therefore collinearity between those two variables is highly anticipated.

The survey by specialists considered a previous use of antithrombotic medicines as a risk factor for HT. In the literature, antiplatelet use is indeed associated to a higher risk of HT, especially in patients undergoing thrombolysis with rtPA[10,16,17,18,19].

Age seems to be a risk factor for HT as pointed out by many specialists; in a systematic review of the literature, which included 55 papers, age was indeed associated to HT[5]. Patients of older age are more likely to have severe medical conditions, large ischemic lesions and a greater frequency of with cardioembolic etiology[20]. However, some other authors do not consider age as an independent risk factor for HT, but as a surrogate marker for other conditions that increase the chances of HT[4,21]. Moreover, older patients also have a high prevalence of cardiac diseases, uncontrolled hypertension and decompensated heart failure[22]. Thus, during the hospitalization for AIS, they are more likely to develop pneumonia — which promotes an inflammatory state and can increase the risk of HT, probably by influencing the dynamics of BBB permeability[2,21,23].

Hyperglycemia on admission was cited by 30% of the interviewed neurologists as a risk factor for HT and is also described in several series of the literature to be associated to HT in patients with AIS (Table 2). Hyperglycemia may be associated to undiagnosed vascular disease and can lead to endothelial dysfunction[24]. In several series of patients treated with intravenous thrombolysis, hyperglycemia was not only associated to HT, but also with increased mortality and a non-favorable outcome at three months[17,25,26]. In addition to the direct endothelial dysfunction of hyperglycemia, hyperglycemia appears to reduce platelet count and aggregation, and increases the expression of neutrophils, which are responsible for part of the signaling that perpetuates BBB permeability and increases the inflammatory activity at the site of ischemia, facilitating the progression of the ischemic area and increasing cerebral edema[27]. Moreover, hyperglycemia increases brain lactate levels and the expression of reactive oxygen species. Such cascade increases endothelial damage and the influx of calcium into the neuron, leading to hypoxia and malnutrition of the vessel walls[28,29].

Although arterial hypertension is present in many series as a predictor of HT, only two scores[10,11] takes it into account. From the specialists surveyed, seven cited either arterial hypertension or blood pressure on stroke admission as a risk factor for HT. Extremes values of blood pressure at admission may be a consequence of a severe neurological presentation[30], meaning an adrenergic reaction, regardless of age and other underlying medical conditions. A recently published study[31] did not show differences in the risk of o HT or clinical outcomes of patients treated to lower blood pressure targets (Systolic Blood Pressure<140 mmHg) and standard therapy (Systolic Blood Pressure<180 mmHg) after treatment with intravenous thrombolysis.

Seven of the specialists surveyed herein and three of the scores[4,6] evaluated in this manuscript included cardio-aortic

etiology as a risk factor for HT. HT has been reported in up to 71% of cardioembolic infarcts[32]. Patients with cardioembolic strokes more frequently have proximal arterial occlusions leading, thus, to extensive ischemic lesions. With greater frequency, cardiac embolus is rich in red blood cells and fibrin. Such thrombi are more likely to be destroyed, leading to a consequent reperfusion of the large ischemic area[32,33]. Also, proximal occlusion of large vessels can lead to a vascular spasm[33]. The occurrence of vasospasm, even if it is floating, together with thrombus fragmentation, might allow the thrombus to migrate distally, increasing ischemia to other areas and damaging vessel walls and capillaries with an intermittent injury reperfusion. Arterial dissection at the occlusion site has also been postulated as mechanism of HT in patents with cardioembolic strokes[32]. Cardioembolism has also been associated to older age and delayed recanalization both factors that can increase the risk of HT[32]. An abrupt onset with poor collateral circulation leading to severe hypoperfusion, and then a large ischemic area, can also explain a higher risk of HT in patients with cardioembolic strokes[1,32,33].

Most available medical data about HT after AIS is built from classical Statistics, which, although useful and necessary to define limits, has been limited for not considering subjectivity. Bayesian Statistics, on the other hand, may provide tools for designing trials more effectively using subjectivity. Subjectivity can be a powerful tool in helping to identify bias and to select the best models to predict or explain an event[34]. In fact, the opinion by specialists is an example of subjectivity. Specialists have specific skills and, indeed, the clinical decision-making process may be Bayesian[35], particularly in the face of unclear clinical phenomena.

This paper has some limitations. First, out of 45 specialist who were contacted, only 20 of them responded; the remaining 25 specialists have not provided us with their responses. None of them discriminated between symptomatic and asymptomatic HT in their answers. On the other hand, we considered both symptomatic and asymptomatic cases of HT in the literature review. Second, we did not ask the specialists about biomarkers and advanced neuroimaging techniques, which have recently been reported as predictive factors of HT[36]. Third, we listed the variables mentioned by each specialist according to the order in which they appeared in the answers. Nonetheless, we did not ask formally the specialists to arrange the answers by relevance. Fourth, despite our focus on patients not treated with rtPA, five specialists included treatment and/or dose of rtPA as risk factors of HT in their answers. And finally, we surveyed specialists from 2014 to 2018 — interval time which may have made the latest answers more aligned with the current literature than earlier responses.

HT after AIS remains a controversial topic. Predicting HT is crucial in order to understand the natural history of this condition. Conciliating evidence-based information with the opinion from a panel of specialists may be an invaluable resource.

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