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Facteurs prédictifs de transformation hémorragique symptomatique après thrombolyse intraveineuse pour ischémie cérébrale.

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AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

LISTE DES ABREVIATIONS

ACA	anterior cerebral artery
AChA	anterior choroidal artery
ADC	apparent diffusion coefficient
adjOR	adjusted odds ratio
AUC	area under the curve
BA	basilar artery
BMB	brain microbleed
CBV	cerebral blood volume
CCPPRB	Comité consultatif de protection des personnes dans la recherche biomédicale
CI	confidence interval
cSS	cortical superficial siderosis
CT	computed tomographic
DWI	diffusion-weighted imaging
ECASS2	European co-operative acute stroke study-II
ESO	European stroke organisation
FLAIR	fluid attenuation inversion recovery
FVH	fluid attenuation inversion recovery vascular hyperintensity
HI	hemorrhagic infarction
HT	hemorrhagic transformation
IC	intervalle de confiance
ICA	internal carotid artery
ICH	intracerebral hemorrhage
IQR	interquartile ranges
IRM	imagerie par résonance magnétique
IV	intravenous
MCA	middle cerebral artery
MRI	magnetic resonance imaging
mRS	modified Rankin scale
MT	mechanical thrombectomy
NIHSS	national institutes of health stroke scale
PCA	posterior cerebral artery
PH	parenchymal hemorrhage
ROC	receiver operating characteristic
rt-PA	recombinant tissue-plasminogen activator
s-HT	symptomatic hemorrhagic transformation
s-TH	transformation hémorragique symptomatique
TH	transformation hémorragique
TIA	transient ischemic attack
TOAST	Trials of Org 10172 in Acute Stroke Treatment
TOF-MRA	time-of-flight magnetic resonance angiography
WMH	white matter hyperintensities

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RESUME :

TITRE : Facteurs prédictifs de transformation hémorragique symptomatique après thrombolyse intraveineuse pour ischémie cérébrale.

CONTEXTE : Le *recombinant tissue-plasminogen activator* (rt-PA), administré par voie intraveineuse à la phase aigüe d'une ischémie cérébrale, améliore le pronostic fonctionnel sans augmenter la mortalité, malgré le risque d'hémorragie intracérébrale dont la plupart sont des transformations hémorragiques (TH) au sein de la région infarcie. Notre objectif était de déterminer les facteurs prédictifs de TH symptomatique (s-TH) chez des patients consécutifs traités par rt-PA par voie intraveineuse (IV) et sélectionnés en imagerie par résonance magnétique.

METHODE : Nous avons définis les s-TH comme des TH remplissant les critères cliniques selon la définition de l'étude ECASS 2 et nous avons étudié les s-TH de classes 1 et 2 selon la classification d'Heidelberg. Nous avons évalué les facteurs prédictifs de s-TH avec les courbes *receiver operating characteristic* en considérant une valeur d'aire sous la courbe (AUC) de 0,70 ou plus comme l'indicateur d'une discrimination acceptable.

RESULTATS : Parmi les 944 patients inclus, 261 (27,6%) ont présenté une TH de classe 1 ou 2, dont 49 s-TH. Les facteurs indépendamment associés à la survenue d'une s-TH étaient l'âge (odds ratio ajusté [adjOR] 1.028 for pour une augmentation d'un an; intervalle de confiance [IC] à 95% 1.004-1.052), la consommation excessive d'alcool (adjOR 3.129; IC à 95% 1.320-7.415), un accident ischémique transitoire récent (adjOR 2.877; IC à 95% 1.042-7.947) et le national institutes of health stroke scale à l'admission (adjOR 1.057 pour une augmentation d'un point; IC à 95% 1.020-1.095) dans le modèle clinique et l'existence de flux lents (adjOR 3.887; IC à 95% 1.499-10.082), la présence d'un infarctus ancien (adjOR 2.010; IC à 95% 1.105-3.654) et le volume des anomalies en séquence de diffusion (adjOR 1.018 pour une augmentation d'un cm^3; IC à 95% 1.007-1.029) dans le modèle radiologique. La seule variable permettant de prédire de manière acceptable le risque de s-TH était le volume des anomalies en séquence de diffusion (0,719 IC à 95% 0,644-0,793), une valeur de 4 cm^3 permettant de prédire une s-TH avec une sensibilité de 78,3% et une spécificité de 58.0%.

CONCLUSION : Déterminer le volume des anomalies en séquence de diffusion à l'admission peut permettre d'identifier des patients à risque de s-TH après administration de rt-PA par voie IV, un volume de 4cm^3 ou plus étant le meilleur facteur prédictif de s-TH.

INTRODUCTION GENERALE

Les accidents vasculaires cérébraux (AVC) représentent un problème majeur de santé publique. En effet, en France, ils sont la première cause de mortalité chez les femmes (18.343 décès en 2013) et la troisième cause de mortalité chez les hommes.[1] Ils représentent également la première source de handicap acquis de l'adulte et la seconde cause de troubles cognitifs majeurs après la maladie d'Alzheimer. En 2014, 110.438 AVC ont été notifiés en France parmi lesquels 82.912 étaient des AVC ischémiques.[1] Malgré des politiques d'information du public et de prévention primaire centrées respectivement, sur le diagnostic précoce et le traitement des facteurs de risque modifiables, l'incidence des AVC ischémiques chez les sujets de moins de 65 ans a connu une hausse significative (+14,3%) en France entre 2008 et 2014 alors qu'elle a légèrement diminué chez les sujets de 65 ans et plus (-1,5%).[1]

PRISE EN CHARGE DES AVC ISCHEMIQUES

A l'heure actuelle, 5 traitements ont été validés, par des essais thérapeutiques randomisés, dans la prise en charge en phase aigüe des AVC ischémiques:

1. Chronologiquement, le premier traitement validé a été la prise en charge en unité de soins intensifs neurovasculaires (USINV) qui a montré une réduction de la mortalité de 28% dans les 4 premiers mois comparativement à une prise en charge dans des services de médecine.[2]
2. Secondairement, l'administration précoce d'aspirine, en l'absence d'hémorragie cérébrale associée, a montré des réductions significatives de

0,7% du risque de récidive d'AVC ischémique et de 0,4% du risque de décès sans AVC ischémique. La posologie recommandée est de 160 à 300mg.[3]

3. La fibrinolyse intra-veineuse (IV) par *recombinant-tissue plasminogen activator* (rt-PA) a également montré son efficacité sur l'amélioration du pronostic fonctionnel chez les patients présentant un AVC ischémique dans les 3 heures[4,5] avec une extension de la fenêtre thérapeutique suite aux résultats de l'étude ECASS 3.[6] L'Agence Européenne du Médicament approuve son utilisation depuis 2003.
4. Le traitement chirurgical par hémicraniectomie décompressive est réservé à la prise en charge des infarctus étendus du territoire de l'artère cérébrale moyenne, à risque de devenir malins, chez des patients jeunes, et a montré une augmentation de la proportion de patients survivants avec un handicap modéré.[7]
5. Depuis 2015, 6 essais randomisés ont montré l'efficacité du traitement intra-artériel par thrombectomie mécanique chez les patients présentant une ischémie cérébrale associée à une occlusion proximale en circulation antérieure, avec une augmentation de la proportion de patients indépendants.[8,9] Deux nouveaux essais ont montré un bénéfice de la thrombectomie au-delà de 6 heures en cas de mismatch clinico-radiologique[10] ou purement radiologique, sur les données de l'imagerie de perfusion.[11]

PRINCIPES DU TRAITEMENT FIBRINOLYTIQUE

En Europe, la posologie du rt-PA (Altéplase) est de 0.9mg/kg sans dépasser 90mg, 10% étant injecté en bolus, le reste étant injecté à la seringue électrique sur 1h. Outre son utilisation dans l'ischémie cérébrale en phase aigüe, le rt-PA bénéficie également d'une indication à la phase aigüe des infarctus du myocarde et de

l'embolie pulmonaire massive. Cette molécule présente de multiples contre-indications générales, notamment des situations à haut risque hémorragique, notamment post-opératoires, mais également des situations spécifiques aux ischémies cérébrales.

EFFETS INDESIRABLES DE LA FIBRINOLYSE IV

Le risque d'hémorragie extra-cérébrale grave reste faible en cas de respect des contre-indications du rt-PA. Le principal risque non hémorragique du rt-PA est la survenue d'un œdème aigu angioneurotique dans environ 2% des cas.[12] L'hémorragie intracrânienne, symptomatique ou asymptomatique, représente le principal effet indésirable de la fibrinolyse IV.

La fréquence des hémorragies intracrâniennes symptomatiques varie de 2 à 8% selon les études et selon les définitions[4–6] mais la survenue d'une hémorragie intracrânienne, qu'elle soit symptomatique ou asymptomatique, est très fréquente et peut, selon les études, avoisiner les 50%.[13]

CLASSIFICATION DES HEMORRAGIES INTRACRANIENNES POST-THROMBOLYSE

Plusieurs classifications ont été proposées pour les hémorragies intracrâniennes compliquant une thrombolyse IV pour ischémie cérébrale. La plus récemment proposée est la classification d'Heidelberg[14] qui reprend les définitions de la classification ECASS 2[6] concernant les hémorragies parenchymateuses survenant au sein de la région infarcie (transformation hémorragique (TH)), en y ajoutant les hémorragies parenchymateuses survenant à distance du corps ischémique (remote hemorrhage) ainsi que les hémorragies intracrâniennes extra-parenchymateuses

(hémorragie intraventriculaire, hémorragie sous-arachnoïdienne et hémorragie sous-durale). On distingue ainsi, au sein des hémorragies parenchymateuses au sein du corps ischémique, 4 aspects morphologiques différents et mutuellement exclusifs : l'infarctus hémorragique de type 1 (HI1) (pétéchies éparses, absence d'effet de masse), l'infarctus hémorragique de type 2 (HI2) (pétéchies confluentes, absence d'effet de masse), l'hémorragie parenchymateuse de type 1 (PH1) (hématome au sein du tissu infarci, occupant moins de 30% du volume de l'infarctus, sans effet de masse significatif), l'hémorragie parenchymateuse de type 2 (PH2) (hématome occupant au moins 30% du tissu infarci, avec effet de masse évident). Si l'influence pronostique des PH1 et 2 semble établie,[15] celle des HI 1 et 2, majoritairement asymptomatiques en phase aigüe, reste incertaine à moyen terme et une étude récente a montré qu'ils étaient associés à une réduction de la proportion de patients avec un excellent pronostic à 3 mois.[16]

FACTEURS PREDICITFS DES TRANSFORMATIONS HEMORRAGIQUES POST-THROMBOLYSE

De multiples facteurs prédictifs (clinique, radiologique ou biologique) de la survenue d'une TH après thrombolyse IV pour ischémie cérébrale ont été évalués. Les facteurs les plus souvent associés à la survenue d'une TH sont un score NIHSS élevé, un âge plus avancé, un traitement antiagrégant plaquettaire lors de la survenue de l'infarctus cérébral ou encore le volume du corps ischémique.[17–20] Néanmoins, le rôle de certains facteurs prédictifs radiologiques reste incertain voir inconnu. Le rôle des microsaignements chroniques cérébraux (*microbleeds*) reste discuté avec des résultats discordants dans la littérature[17,21] et le rôle de l'existence d'une séquelle hémorragique n'a jamais été évalué. L'influence de la sidérose superficielle sur le risque de TH n'a été évaluée que dans une étude avec un effectif faible[22] et

l'existence de lésions chroniques de substance blanche a été avancée comme étant un facteur prédictif de remaniement hémorragique mais uniquement dans des études l'ayant évalué en tomodensitométrie.[17,23] Enfin, l'essentiel des études ayant évalué ces facteurs prédictifs ont utilisé la tomodensitométrie comme modalité d'imagerie, qui apparaît moins sensible que l'imagerie par résonnance magnétique pour les dépister et les caractériser.

SYNTHESE ET OBJECTIF

Une meilleure connaissance des facteurs prédictifs de remaniement hémorragique, notamment radiologiques, paraît importante pour une prise de décision optimale sur l'organisation de la prise en charge en phase aigüe des patients présentant une ischémie cérébrale qui est en constante évolution depuis l'avènement de la thrombectomie mécanique en 2014.

Ainsi, notre travail a pour objectif principal de déterminer les facteurs prédictifs de TH symptomatique au sein d'une large cohorte de patients sélectionnés par IRM cérébrale et traités par thrombolyse intraveineuse.

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Predictors of symptomatic hemorrhagic transformation after IV thrombolysis for cerebral ischemia

Running title: hemorrhagic transformation after thrombolysis

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Abstract

Objective: to evaluate predictors of symptomatic hemorrhagic transformation (s-HT) in consecutive patients treated with IV recombinant tissue-plasminogen activator (rt-PA) who underwent MRI-scans at baseline.

Method: We defined s-HT according to the ECASS2 criteria and analyzed s-HT of subgroups 1 and 2 of the Heidelberg classification. We evaluated predictors of s-HT with receiver operating characteristic curves considering an area under the curve (AUC) value of 0.70 or higher as indicating an acceptable discrimination.

Results: of 944 patients, 261 (27.6%) had hemorrhagic transformation (HT) class 1 or 2, including 49 with s-HT. Factors independently associated with s-HT in the clinical model were age (adjusted odds ratio [adjOR] 1.028 for 1 year increase; 95% confidence interval [CI] 1.004-1.052), excessive alcohol consumption (adjOR 3.129; 95% CI 1.320-7.415), recent transient ischemic attack (adjOR 2.877; 95% CI 1.042-7.947) and baseline national institutes of health stroke scale (adjOR 1.057 for 1 point increase; 95% CI 1.020-1.095), and in the radiological model, vascular hyperintensities (adjOR 3.887; 95% CI 1.499-10.082), old infarcts (adjOR 2.010; 95% CI 1.105-3.654) and volume of diffusion-weighted imaging (DWI) abnormality (adjOR 1.018 for 1 cm^3 increase; 95% CI 1.007-1.029). The only variable with an acceptable discrimination was volume of DWI abnormality (AUC 0.719; 95% CI 0.644-0.793), a value of 4 cm^3 at baseline predicting s-HT with a 78.3% sensitivity and a 58.0% specificity.

Conclusion: determining the baseline volume of DWI abnormality, can help identifying patients at risk for s-HT after IV rt-PA, a volume of 4 cm3 or more being the best predictor of s-HT.

Introduction

In patients with cerebral ischemia, IV recombinant tissue-plasminogen activator (rt-PA), increases the proportion of survivors with a modified Rankin scale (mRS)[1] score of 0-1, or 0-2 after 3 months, without significant effect on mortality.[2–4] The increased risk of intracranial bleedings does not outweigh the benefit.[2–4] Intracranial bleedings after rt-PA are divided in the Heidelberg bleeding classification[5] into (i) type 1: hemorrhagic transformation (HT) of infarcted brain tissue; (ii) type 2: intracerebral hemorrhage within and beyond infarcted brain tissue; and (iii) type 3: intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage. Many of these bleedings remain apparently asymptomatic but some are associated with a clinical worsening, and are called symptomatic hemorrhagic transformations (s-HT).[2–4]

Risk factors for s-HT have been studied in randomized controlled trials[2,3,6–10] and in large multicenter registries,[11–14] in patients who underwent computed tomographic (CT)-scans. MRI provides more information, especially on brain microbleeds (BMBs),[15] cortical superficial siderosis (cSS),[16] fluid attenuated inversion recovery (FLAIR) vascular hyperintensity (FVH),[17] volume of diffusion abnormality and apparent diffusion coefficient (ADC).[18] MRI is also more sensitive than CT to identify old infarcts[19] or hemorrhages[20] and white matter changes.[21]

The aim of this study was to evaluate predictors of s-HT in a cohort of consecutive patients treated with IV rt-PA after a baseline MRI-scan.

Method

Setting

We performed this retrospective study with data prospectively collected in a registry of consecutive patients treated with IV rt-PA for cerebral ischemia at the Lille University Hospital between September 27th 2009 and June 13th 2018. The 375 patients recruited between October 2009 and May 2014 were included in a previously published multicenter study on BMBs.[22] The organization of stroke care in this hospital has been previously reported.[23] Mechanical thrombectomies became part of routine care for patients with large-vessel occlusion after evidence of efficacy.[24]

Eligibility criteria for thrombolysis.

The eligibility criteria for thrombolysis were those of the ECASS 2 trial[7] with an extension of the time-window at 4.5 hours,[3] eligibility of patients aged 80 years or more,[25] and eligibility of patients with unknown onset time if they had no or minor abnormalities on FLAIR sequences.[19] We considered as eligible for this study all consecutive patients who received rt-PA as first line therapy, alone or in association with mechanical thrombectomy and gave consent for the follow-up.

Exclusion criteria

We excluded from the study patients treated with IV rt-PA during the study period who (i) were 18 years of age or less; (ii) did not consent for the follow-up, (iii) underwent a CT-scan at baseline; (iv) did not undergo a 2nd brain imaging (usually because of early death); or (v) whose baseline MRI was not considered appropriate for analysis.

Imaging

According to the national recommendations for the management of acute stroke,[26] all patients underwent at admission a MRI-scan on a 1.5T machine. The imaging protocol included diffusion weighted imaging (DWI) (b-values = 0 and 1000 s.mm^2) with ADC mapping, FLAIR sequences, gradient-echo T2*, and time-of-flight (TOF) magnetic resonance angiography (MRA) sequences. All patients underwent another MRI-scan 22 to 36 hours after treatment, or earlier in case of clinical worsening.

Treatment administration

We administered IV rt-PA according to the recommendations of the European Stroke Organisation (ESO)[25] *i.e*. 0.9 mg/kg body weight, maximum 90 mg, 10% of the dose as a bolus, followed by a 60-min infusion.

Clinical assessment

We assessed the baseline stroke severity with the National Institutes of Health Stroke Scale (NIHSS),[27] and the presumed cause of ischemic stroke with the Trials of Org 10172 in Acute Stroke Treatment (TOAST) criteria[28] in which we added the possibility of stroke mimics as a diagnostic category. We evaluated the pre-existing functional status according to the mRS,[1] after an interview with the patient, a close relative or the family physician. We evaluated also the outcome at 3 months with the mRS[29] either during a face-to-face visit or by a telephone interview with the patient, the family, or the general practitioner. The telephone interview has been shown to have a good agreement with face-to-face evaluation.[30] The definitions of variables used in the analysis were detailed in a previous study from our group.[23]

Radiological assessment

We determined the infarct territory on admission DWI sequences. We calculated the volume of diffusion abnormality on ADC maps using an automated threshold method (ADC<600×10^{-6} mm^2/s)[31] with OleaSphere 3.0 software (Olea Medical SAS, La Ciotat, France)[32]. We also computed mean ADC values within the infarct core. We evaluated presence and site of vascular occlusion on TOF-MRA, presence of FVH and old infarcts (territorial vs. lacunar) on FLAIR sequences and BMBs on gradient echo T2* sequences. We also used semi-quantitative scales to assess radiological markers: (i) white matter hyperintensities using the Fazekas' scale[33] (evaluation from 0 to 3 of deep white matter lesions) on FLAIR sequences, (ii) BMBs using a semi-quantitative scale (none, one, two to four and five or more) on gradient echo T2* sequences, and (iii) cSS using the multifocality score[16] on gradient echo T2* sequences.

A board-certified senior neuroradiologist (GK) blinded to the clinical outcome analyzed the volume of diffusion abnormality and the mean ADC of all patients. Four authors (FC, GK, AD, DL) made a complete assessment of 50 randomly selected MRI. We assessed the interrater reliability for the variables other than volume of diffusion abnormality and mean ADC, using the Kappa statistics. We found an excellent reliability for all criteria with Kappa values higher than 0.8, with the exception of the evaluation of FVH for 2 raters (AD and DL). Taking into account the excellent interrater reliability, all the MRI were analyzed by a single observer (FC) for all variables except volume of diffusion abnormality and mean ADCs.

Criteria for hemorrhagic transformation

The presence of any intracranial bleeding was assessed on the 2nd imaging performed 22 to 36 hours after thrombolysis or earlier in case of clinical worsening. MRI was the standard of care

for the 2nd imaging but unstable patients were evaluated by CT-scans. Patients whose second imaging was a CT scan were not excluded. We used the Heidelberg bleeding classification based on CT-scans,[5] and analyzed for the purpose of this study only the subgroups of the class 1 and class 2 bleedings. HT were divided into 4 categories[5]: (i) hemorrhagic infarction (HI) type 1 ("scattered small petechiae, no mass effect"); (ii) HI type 2 ("confluent petechiae, no mass effect"); (iii) parenchymal hemorrhage (PH) type 1 ("hematoma within infarcted tissue, occupying less than 30%, no substantive mass effect") and (iv) PH type 2 ("hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect").

Outcomes

All patients were followed up at 3 months. We defined excellent outcome as a mRS score 0-1 or similar to the pre-stroke mRS, good outcome as a mRS 0-2 or similar to the pre-stroke mRS, we defined s-HT as a HT meeting the ECASS 2 definition[7] for being symptomatic.

Statistics

We performed statistical analyses with the SPSS 22.0 package for windows. We used median values, interquartile ranges (IQR), and percentages. We compared groups for categorical variables, with the Chi Square test with Yates' correction or Fisher exact test when appropriate, and for continuous variables with the Mann-Whitney U test, or Kruskal-Wallis H test. P values lower than 0.05 were considered significant. We compared baseline characteristics between patients included and those excluded. In the group of patients included in the study, we compared baseline characteristics and outcomes between those with s-HT and those without. We calculated adjusted odds ratios ($_{adj}$OR) and 95 % confidence interval (CI) by logistic regression analyses,[34] with s-HT as dependent variable, independent variables being selected from a bivariate analysis, with a 0.20 level as a screening criterion for

the selection of candidate variables.[35] For the logistic regression analyses we dichotomized the Fazekas' rating scale between scores 0-1 vs. 2-3, the number of old infarcts between 0 vs. 1 or more, and the number of microbleeds between 0 to 4 vs. 5 or more. We used 2 models, one with clinical variables and the other with radiological variables. Correlations between variables were checked for possible colinearity, defined as $r > 0.6$. The bivariate part of analysis was repeated between patients without HT and the 4 different types of HT.

We used receiver operating characteristic (ROC) curves to determine the predictive values for s-HT of the area under the curve (AUC) and 95% CI, for quantitative variables independently associated with s-HT. We considered an area under the curve value of 0.70 or higher as indicating an acceptable discrimination.[36] We determined the cut-off point that better distinguish patients with and without s-HT for variables with an acceptable discrimination. We considered the point at which the sum of specificity and sensitivity was the highest.

Ethics

The registry was approved by the ethical committee of Lille in 2003 and the study classified as observational (CCPPRB, *Comité consultatif de protection des personnes dans la recherche biomédicale*). After 2010, all patients were prospectively included in the OPHELIE observational registry (ClinicalTrials.gov Identifier n° NCT01614080) that needed a new approval by French health authorities and relevant ethical committee (*Comité de Protection des Personnes Nord Ouest IV Lille, France*, March 9th 2010, registration number 10.677). Patients were managed according to local rules without any investigation or treatment specifically performed for the study. Patients gave consent themselves or via a close relative for the follow-up.

Data availability

Following publication, any data not published within this article will be anonymized and shared by request from any qualified investigator.

Results

General features and main characteristics of the study population.

Between September 27th 2009 and June 13th 2018, we treated 1,135 patients with IV rt-PA in the stroke unit of the Lille University Hospital. One hundred and ninety one of them (16.8%) were not included in this study for reasons detailed in figure 1. The comparison of baseline characteristics between patients included and non-included are detailed in table 1. Patients who were not included were more likely to have atrial fibrillation, and to be under antiplatelet agent at admission. They were less likely to have had a recent transient ischemic attack (TIA), to have undergone mechanical thrombectomy (MT), and to have small-vessel occlusion. They also had significantly lower platelet counts, and higher baseline NIHSS scores. Imaging characteristics at baseline and at 22-36 hours, and outcomes at 7 days and 3 months are reported in table 2. Of 944 patients, 261 (27.6%) had HT class 1 or class 2 on the 2nd imaging, that was MRI in 244 patients (93.5%).

Characteristics of patients with s-HT.

The baseline characteristics of the 49 patients with s-HT are detailed in table 3. They accounted for 5.2% (95% CI: 3.8-6.6) of the study population. If we considered that all patients who died before the 2nd imaging and were therefore excluded from the study, had a s-HT, this prevalence would have been of 59 out of 954 (6.2%, 95%CI 4.7-7.7). The logistic regression analysis with the clinical model (overall p value <0.0001; r^2 =0.082) found as

independent predictors of s-HT increasing age, excessive alcohol consumption, TIA within 7 days and increasing NIHSS at baseline (table 3). The other variable selected for the model (arterial hypertension) was not independently associated with s-HT. The logistic regression analysis with the radiological model (overall p value <0.0001; r^2 =0.092) found as independent predictors of s-HT (i) volume of diffusion abnormality at baseline, (ii) at least 1 old infarct, and (iii) FVH (table 3). The other variables selected for the model (presence of an old intracerebral hemorrhage [ICH] and 5 or more BMBs) were not independently associated with s-HT. We could not include mean ADC in the same radiological model because of collinearity with the volume of diffusion abnormality. The replacement of volume of diffusion abnormality by mean ADC in the model did not change the main results except that presence of an old ICH became associated, while mean ADC was inversely associated.

Several baseline characteristics differed according to the subtypes of HT, especially a higher severity in patients with PH2 and a higher frequency of diabetes mellitus (table 4). The outcome was worse in patients with HT, the major difference being between no HT or HI1 vs. the other categories (figure 2).

Predictive values for s-HT of the AUC for quantitative variables independently associated with s-HT.

We performed the ROC curves with the 4 quantitative variables independently associated with s-HT (age, baseline NIHSS, volume of DWI abnormalities, mean ADC) (figure 3). The only variable that reached an acceptable discrimination was the volume of DWI abnormalities (AUC 0.719; 95% CI 0.644-0.793), a value of 4 cm^3 being a predictor of s-HT (sensitivity 78.3% and specificity 58.0%). A volume of DWI abnormalities of 105 cm^3 or more was at 100% predictor of s-HT. Other values of AUC were 0.585 for age, 0.661 for baseline NIHSS, and 0.359 for the mean ADC.

Discussion

Our study has shown that: (i) 1 patient out of 4 had an HT of any type and severity; (ii) 1 patient out of 19 met ECASS2 criteria for s-HT; (iii) predictors of s-HT were increasing age, excessive alcohol consumption, TIA in the previous 7 days, NIHSS at baseline, presence of an old infarct, of FVH and increasing volume of diffusion abnormality, and (iv) the best discrimination for the occurrence of s-HT was obtained with the volume of diffusion abnormality.

Our study is the largest study evaluating predictors of s-HT in patients treated with IV rt-PA for cerebral ischemia that used MRI at baseline. More than 90% of these patients underwent MRI as second imaging resulting in a high sensitivity to detect HT. Another strength is the evaluation of several radiological markers potentially associated with HT, with a centralized reading leading to a good homogeneity of assessments, and the use of previously validated scales. The absence of patients lost to follow-up at 3 months, the small number of missing data and the homogeneity of the management over the study period, are other strengths.

Our study has also limitations. The single center design of the study leads to uncertainty about the generalizability of the results. The exclusion of 1 patient out of 6 for reasons related to the feasibility of MRI may be associated with selection bias, as most of these patients were excluded because of their clinical status at baseline. We cannot exclude that patients who were not eligible had significant differences in volumes of diffusion abnormalities. We did not evaluate the impact of the severity of hypoperfusion because multimodal imaging was not part of our routine protocol. We did not assess the influence of early recanalization although it is associated with HT[37] because we wanted to evaluate predictors of HT available at baseline before the decision to give rt-PA.

The most important finding in our study is the independent association between the volume of DWI abnormalities and the risk of s-HT, greater volumes being associated with higher risks. This association is in line with the results of a study conducted in a smaller group of patients using the DWI-ASPECTS score to evaluate the volume.[38] A volume of 4 cm^3 or greater had the best compromise between a good sensitivity to predict s-HT and an acceptable specificity. There is also an association between the baseline NIHSS score and the risk of s-HT, but this association is probably related with the volume. The ROC curves (figure 2) suggest that the superiority of the volume over the NIHSS to predict s-HT is more important for patients with smaller volumes of DWI abnormalities and lower NIHSS scores. In more severe patients with higher volumes the two curves are quite similar.

The association between white matter changes and HT found in several studies using CT scans[39,40] was not confirmed in our study. This finding could be explained by the lower sensitivity of CT-scan to detect these changes, leading to the detection of severe changes only, i.e. the most likely to be associated with HT.

Our study found an association between a previous ICH and the risk of s-HT in the model with mean ADC and a strong tendency in the other with DWI volume of abnormalities. This finding has never been reported before and needs confirmation in other cohorts. The association between old ICH and the risk of s-HT could be explained by an underlying vasculopathy responsible for the previous ICH and that could indicate a higher risk of bleeding in the infarcted area related to brain-blood-barrier disruption because of the brain tissue damage associated with the chronic underlying vasculopathy.

cSS is associated with spontaneous cerebral hemorrhages[16,41,42] but its influence on the risk of HT after rt-PA has been previously evaluated only in a single cohort where only 3 patients had cSS.[43] Although our study was performed in a larger sample of 31 patients with cSS, we

did not find any association with s-HT. The likely explanation is a probable self-limitation of neurologists to give rt-PA in patients with severe cSS.

Our study also adds new data on the association of FVH and s-HT. This new finding is in line with the independent association of intracranial arterial occlusions with the risk of HT that has been reported in patients treated by MT.[44,45] Because of colinearity between variables, arterial occlusions could not be included in the model in our study.

The influence of FVH on the risk of s-HT is probably associated with the volume and the severity of hypoperfusion, these parameters being linked with the proximal site of occlusion. Hypoperfusion severity, evaluated on the basis on the reduction of the cerebral blood volume (CBV) was associated with the risk of PH in a previous study.[46] Other studies found an association between the risk of HT and post-ischemic hyperperfusion evaluated on arterial spin labeling sequences at different time-points after thrombolysis, mechanical thrombectomy or combination of both.[47,48] These results suggest the potential harm of reperfusion in a severe hypoperfused tissue. Reperfusion within the area with the deepest perfusion impairment has already been demonstrated as an independent predictor of HT.[49]

We found increasing age as an independent predictor of s-HT. The impact of age has been shown in several studies[39] and is probably associated with a higher proportion of patients with microangiopathies. We also found an influence of excessive alcohol consumption on the risk of s-HT which is a new finding.[39] Contrary to the available literature on HT, we did not find atrial fibrillation as a predictor of s-HT.[39,50] This could be explained by the exclusion of many patients with atrial fibrillation because they could not receive rt-PA in case of oral anticoagulation, or they underwent more frequently CT-scans at baseline because of a pacemaker or a more severe clinical status.

Besides age and stroke severity, baseline MRI characteristics can help identifying patients at risk for s-HT after IV rt-PA. This finding may be of interest for the selection of patients in trials exploring other strategies in patients at increased risk for s-HT, such as trials testing lower doses of rt-PA, and trials testing IV rt-PA in patients who need mechanical thrombectomy.

Appendix

Name	Location	Role	Contribution
François Caparros	University of Lille. Inserm U 1171 CHU Lille.	Author	Analyzed the data; drafted the manuscript for intellectual content.
Gregory Kuchcinski	University of Lille. Inserm U 1171 CHU Lille.	Author	Analyzed the data; revised the manuscript for intellectual content.
Agathe Drelon	University of Lille. CHU Lille.	Author	Interpreted the data. Revised the manuscript for intellectual content.
Barbara Casolla	University of Lille. Inserm U 1171 CHU Lille.	Author	Interpreted the data. Revised the manuscript for intellectual content.
Solène Moulin	University of Lille. Inserm U 1171 CHU Lille.	Author	Interpreted the data. Revised the manuscript for intellectual content.
Nelly Dequatre-Ponchelle	CHU Lille.	Author	Interpreted the data. Revised the manuscript for intellectual content.
Hilde Hénon	Inserm U 1171 CHU Lille.	Author	Interpreted the data. Revised the manuscript for intellectual content.
Charlotte Cordonnier	University of Lille. Inserm U 1171 CHU Lille.	Author	Interpreted the data. Revised the manuscript for intellectual content.
Jean-Pierre Pruvo	University of Lille. Inserm U 1171 CHU Lille.	Author	Designed and conceptualized the study. Revised the manuscript for intellectual content.
Didier Leys	University of Lille. Inserm U 1171 CHU Lille.	Author	Designed and conceptualized the study. Analyzed the data; draft the manuscript for intellectual content; final approval of the manuscript.

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Table 1. Comparison of baseline characteristics between patients included and non-included. Values are number of patients (percentages) unless specified. TIA: transient ischemic attack. mRS: modified Rankin scale. NIHSS: national institutes of health stroke scale. TOAST: Trials of Org 10172 in Acute Stroke Treatment. *Median (interquartile range). †Patients with unknown onset time.

	Patients included (n=944)	Patients non-included (n=191)	p value	Missing data
Demographic characteristics				
Sex (Men)	449 (47.6)	89 (46.6)	0.807	0
Age (years)*	75 (61-83)	77 (64-84)	0.089	0
Pre-existing medical status				
Arterial hypertension	609 (64.5)	130 (68.1)	0.348	0
Diabetes mellitus	173 (18.3)	40 (20.9)	0.398	0
Hypercholesterolemia	384 (40.7)	69 (36.1)	0.241	0
Smoking	160 (16.9)	28 (14.7)	0.438	0
Excessive alcohol consumption	69 (7.3)	16 (8.4)	0.609	0
Previous myocardial infarction	87 (9.2)	22 (11.5)	0.325	0
Atrial fibrillation	143 (15.1)	51 (26.7)	**<0.0001**	0
TIA < 7 days	39 (4.1)	1 (0.5)	**0.009**	0
Ischemic stroke or TIA > 7 days	141 (14.9)	30 (15.7)	0.786	0
Pre-stroke mRS 0-2	788 (83.5)	154 (80.6)	0.340	0
Any oral anticoagulant before	50 (5.3)	13 (6.9)	0.402	10
Any antiplatelet agent before	375 (40.1)	93 (49.2)	**0.020**	10
Admission characteristics				
Systolic blood pressure (mmHg)*	151 (136-166)	150 (137-165)	0.737	3
Serum glucose level (mg/dl)*	1.18 (1.03-1.46)	1.23 (1.07-1.43)	0.256	0
Platelet count (1,000/mm^3)*	236 (201-278)	224 (187-263)	**0.017**	4
NIHSS*	8 (4-16)	12 (7-18)	**<0.0001**	0
Emergency management				
Onset-to-needle time (min)*	140 (110-188)	150 (117-194)	0.167	148†
Mechanical thrombectomy	181 (19.2)	14 (7.3)	**<0.0001**	0
TOAST classification				
Atherosclerosis	89 (9.4)	19 (9.9)	0.823	0
Cardio-embolism	355 (37.6)	87 (45.5)	**0.040**	0
Small-vessel occlusion	22 (2.3)	0 (0.0)	**0.038**	0
Other determined causes	26 (2.8)	5 (2.6)	0.916	0
Unknown causes	448 (47.5)	77 (40.3)	0.071	0
Stroke mimics	4 (0.4)	3 (1.6)	0.180	0

Table 2. Imaging characteristics and outcomes in the study population. Values are number of patients (percentages) unless specified. MCA: middle cerebral artery. PCA: posterior cerebral artery. ACA: anterior cerebral artery. AChA: anterior choroidal artery. A single patient may have an infarct involving several territories. WMH: white matter hyperintensities. FLAIR: fluid attenuated inversion recovery. FVH: FLAIR vascular hyperintensity. ICH: intracerebral hemorrhage. BMB: brain microbleed. cSS: cortical superficial siderosis. ICA: internal carotid artery. BA: basilar artery. ICA occlusion includes both cervical and intracranial T occlusions, and tandem occlusions are classified as having both ICA and M1 or M2 occlusion. DWI: diffusion-weighted imaging. ADC: apparent diffusion coefficient. s-HT: symptomatic hemorrhagic transformation. ECASS2: European co-operative acute stroke study-II. *Median (interquartile range). ¥The mean ADC was missing in 2 patients and could not be determined in 104 patients in whom the diffusion abnormality was too small to be detectable on ADC map. Excellent outcome means a modified Rankin scale (mRS) 0-1 or similar to the pre-stroke mRS and good outcome means a modified Rankin scale (mRS) 0-2 or similar to the pre-stroke mRS, at 3 months.

	Study population (n=944)	Missing data
Baseline imaging		
Superficial MCA territory	620 (65.7)	0
Deep MCA territory	311 (33.0)	0
Superficial PCA territory	52 (5.5)	0
Deep PCA territory	69 (7.3)	0
ACA territory	39 (4.1)	0
AchA territory	18 (1.9)	0
Cerebellum	47 (5.0)	0
Brain stem	45 (4.8)	0
Fazekas scale (WMH)		1
0	248 (26.3)	
1	421 (44.6)	
2	169 (17.9)	
3	105 (11.1)	
Number of old infarcts		1
None	585 (62.0)	
Unique	175 (18.6)	
Multiple	183 (19.4)	
Strictly lacunar old infarct	100 (10.6)	1
Strictly territorial old infarct	196 (20.8)	1
Lacunar and territorial old infarct	62 (6.6)	1
FVH	638 (67.7)	1
Old ICH	21 (2.2)	2
Number of BMBs		2
0	814 (86.4)	
1	62 (6.6)	
2-4	43 (4.6)	
≥5	23 (2.4)	
Strictly deep or infratentorial BMBs	36 (3.8)	2
Strictly lobar BMBs	52 (5.5)	2
Lobar and deep or infratentorial BMBs	40 (4.2)	2
cSS scale = 0	911 (96.7)	2
M1 occlusion	246 (26.1)	2
M2 occlusion	160 (17.0)	2
MCA occlusion beyond M2	64 (6.8)	2
ICA occlusion	115 (12.2)	2
PCA occlusion	47 (5.0)	2
ACA occlusion	12 (1.3)	2
BA occlusion	24 (2.5)	2
Volume of DWI abnormality (cm^3)*	2.01 (0.40-9.44)	2
Mean ADC (10^{-6} mm^2/s)*	0.51 (0.49-0.53)	106¥
2nd imaging		
Any intra-cerebral bleeding	280 (29.7)	0
Hemorrhagic infarction type 1	69 (7.3)	0
Hemorrhagic infarction type 2	74 (7.8)	0
Parenchymal hemorrhage type 1	53 (5.6)	0
Parenchymal hemorrhage type 2	65 (6.9)	0
s-HT ECASS2	49 (5.2)	0
Clinical outcome at 3 months		
Excellent	457 (48.4)	0
Good	581 (61.5)	0
Death	120 (12.7)	0

Table 3. Comparison of patients with and without symptomatic intracerebral hemorrhagic transformation according to the European co-operative acute stroke study-II (ECASS2) criteria. Values are number of patients (percentages) unless specified. s-HT: symptomatic hemorrhagic transformation. AdjOR: adjusted odds ratio. 95%CI: 95% confidence interval. TIA: transient ischemic attack. mRS: modified Rankin scale. NIHSS: national institutes of health stroke scale. MCA: middle cerebral artery. A single patient may have an infarct involving several territories. WMH: white matter hyperintensities. FLAIR: fluid attenuated inversion recovery. FVH: FLAIR vascular hyperintensity. ICH: intracerebral hemorrhage. BMB: brain microbleed. cSS: cortical superficial siderosis. ICA: internal carotid artery. PCA: posterior cerebral artery. ACA: anterior cerebral artery. BA: basilar artery. ICA occlusion includes both cervical and intracranial T occlusions, and tandem occlusions are classified as having both ICA and M1 or M2 occlusion. DWI: diffusion-weighted imaging. ADC: apparent diffusion coefficient. TOAST: Trials of Org 10172 in Acute Stroke Treatment. *Median (interquartile range). †For 1-year increase. ‡For 1-point increase. ¥Dichotomized between 0 and 1 or more for the logistic regression analysis. ¶For 1-cubic centimeter increase. ♯The mean ADC was missing in 2 patients and could not be determined in 104 patients in whom diffusion abnormality was not detectable on ADC map. Excellent outcome means a modified Rankin scale (mRS) 0-1 or similar to the pre-stroke mRS and good outcome means a modified Rankin scale (mRS) 0-2 or similar to the pre-stroke mRS, at 3 months.

	s-HT (n=49)	No s-HT (n=895)	p value	AdjOR	95%CI	Missing data
Demographic characteristics						
Sex (Men)	27 (55.1)	422 (47.2)	0.278			0
Age (years)*	79 (71-86)	74 (60-83)	**0.014**	1.028†	1.004-1.052	0
Pre-existing medical status						
Arterial hypertension	39 (79.6)	570 (63.7)	**0.023**			0
Diabetes mellitus	10 (20.4)	163 (18.2)	0.699			0
Hypercholesterolemia	20 (40.8)	364 (40.7)	0.984			0
Smoking	7 (14.3)	153 (17.1)	0.610			0
Excessive alcohol consumption	8 (16.3)	61 (6.8)	**0.013**	3.129	1.320-7.415	0
Previous myocardial infarction	4 (8.2)	83 (9.3)	0.994			0
Atrial fibrillation	8 (16.3)	135 (15.1)	0.813			0
TIA < 7 days	5 (10.2)	34 (3.8)	**0.028**	2.877	1.042-7.947	0
Ischemic stroke or TIA > 7 days	7 (14.3)	134 (15.0)	0.896			0
Pre-stroke mRS 0-2	39 (79.6)	749 (83.7)	0.452			0
Any oral anticoagulant before	3 (6.5)	47 (5.3)	0.977			8
Any antiplatelet agent before	22 (47.8)	353 (39.7)	0.271			8
Admission characteristics						
Systolic blood pressure (mmHg)*	152 (140-170)	151 (135-166)	0.614			2
Serum glucose level (mg/dl)*	1.31 (1.05-1.61)	1.18 (1.03-1.45)	**0.021**			0
Platelet count (1,000/mm^3)*	226 (177-277)	236 (201-278)	0.477			4
NIHSS*	15 (9-18)	8 (4-16)	**<0.0001**	1.057‡	1.020-1.095	0
Emergency management						
Onset-to-needle time (min)*	142 (112-204)	140 (110-187)	0.941			148
Mechanical thrombectomy	10 (20.4)	171 (19.1)	0.822			0
Baseline imaging characteristics						
Superficial MCA territory	39 (79.6)	581 (64.9)	**0.035**			0
Deep MCA territory	19 (38.8)	292 (32.6)	0.372			0
Other hemispheric territories	11 (22.4)	141 (15.8)	0.214			0
Posterior fossa territories	4 (8.2)	73 (8.2)	1.000			0
Fazekas scale (WMH) 0-1	35 (71.4)	634 (70.9)	0.939			1
At least 1 old infarct	25 (51.0)	333 (37.2)	0.053	2.010¥	1.105-3.654	1
Strictly lacunar old infarct	6 (12.2)	94 (10.5)	0.702			1
Strictly territorial old infarct	15 (30.6)	181 (20.2)	0.082			1
Lacunar and territorial old infarct	4 (8.2)	58 (6.5)	0.869			1
FVH	44 (89.8)	594 (66.4)	**0.001**	3.887	1.499-10.082	1
Old ICH	3 (6.1)	18 (2.0)	0.162	3.677	0.997-13.569	2
At least 5 BMBs	3 (6.1)	20 (2.2)	0.215			2
Strictly deep or infratentorial BMBs	2 (4.1)	34 (3.8)	0.711			*2*
Strictly lobar BMBs	2 (4.1)	50 (5.6)	1.000			*2*
Lobar and deep or infratentorial BMBs	3 (6.1)	37 (4.1)	0.760			*2*
cSS scale = 0	46 (93.9)	865 (96.9)	0.465			2
M1 occlusion	17 (34.7)	229 (25.6)	0.160			2
M2 occlusion	8 (16.3)	152 (17.0)	0.900			2
MCA occlusion beyond M2	5 (10.2)	59 (6.6)	0.330			2
ICA occlusion	15 (30.6)	100 (11.2)	**<0.0001**			2
PCA occlusion	3 (6.1)	44 (4.9)	0.882			2
ACA occlusion	2 (4.1)	10 (1.1)	0.125			2
BA occlusion	2 (4.1)	22 (2.5)	0.358			2
Volume of DWI abnormality (cm^3)*	10.81 (2.88-27.61)	1.81 (0.37-8.82)	**<0.0001**	1.018¶	1.007-1.029	2
Mean ADC (10^{-6} mm^2/s)*	0.50 (0.48-0.52)	0.51 (0.49-0.53)	**0.001**			106♯
TOAST classification						
Atherosclerosis	5 (10.2)	84 (9.4)	0.849			0
Cardio-embolism	19 (38.8)	336 (37.5)	0.862			0
Small-vessel occlusion	0 (0.0)	22 (2.5)	0.623			0
Other determined causes	1 (2.0)	25 (2.8)	1.000			0

Unknown causes	24 (49.0)	424 (47.4)	0.827	0
Stroke mimics	0 (0.0)	4 (0.4)	1.000	0
Clinical outcome at 3 months				
Excellent	2 (4.1)	455 (50.8)	**<0.0001**	0
Good	5 (10.2)	576 (64.4)	**<0.0001**	0
Death	23 (46.9)	97 (10.8)	**<0.0001**	0

Table 4. Comparison of patients without hemorrhagic transformation vs. patients with different subtypes of hemorrhagic transformation. Values are number of patients (percentages) unless specified. HT: Hemorrhagic transformation. HI: hemorrhagic infarction. PH: parenchymal hemorrhage. TIA: transient ischemic attack. mRS: modified Rankin scale. NIHSS: national institutes of health stroke scale. MCA: middle cerebral artery. PCA: posterior cerebral artery. ACA: anterior cerebral artery. AChA: anterior choroidal artery. A single patient may have an infarct involving several territories. WMH: white matter hyperintensities. FLAIR: fluid attenuated inversion recovery. FVH: FLAIR vascular hyperintensity. ICH: intracerebral hemorrhage. BMB: brain microbleed. cSS: cortical superficial siderosis. ICA: internal carotid artery. BA: basilar artery. ICA occlusion includes both cervical and intracranial T occlusions, and tandem occlusions are classified as having both ICA and M1 or M2 occlusion. ADC: apparent diffusion coefficient. TOAST: Trials of Org 10172 in Acute Stroke Treatment. s-HT: symptomatic hemorrhagic transformation. ECASS2: European co-operative acute stroke study-II. *Median (interquartile range). ¥The mean ADC was missing in 2 patients and could not be determined in 104 patients in whom the diffusion abnormality was not detectable on ADC map.

	No HT (n=683)	HI1 (n=69)	HI2 (n=74)	PH1 (n=53)	PH2 (n=65)	p value	Missing data
Demographic characteristics							
Sex (Men)	328 (48.0)	35 (50.7)	30 (40.5)	26 (49.1)	30 (46.2)	0.755	0
Age (years)*	74 (59-83)	74 (63-84)	71 (59-84)	79 (69-84)	78 (69-83)	0.088	0
Pre-existing medical status							
Arterial hypertension	429 (62.8)	47 (68.1)	46 (62.2)	40 (75.5)	47 (72.3)	0.204	0
Diabetes mellitus	120 (17.6)	13 (18.8)	6 (8.1)	11 (20.8)	23 (35.4)	**0.001**	0
Hypercholesterolemia	270 (39.5)	32 (46.4)	25 (33.8)	24 (45.3)	33 (50.8)	0.202	0
Smoking	117 (17.1)	13 (18.8)	17 (23.0)	5 (9.4)	8 (12.3)	0.265	0
Excessive alcohol consumption	45 (6.6)	6 (8.7)	10 (13.5)	2 (3.8)	6 (9.2)	0.181	0
Previous myocardial infarction	61 (8.9)	9 (13.0)	5 (6.8)	7 (13.2)	5 (7.7)	0.558	0
Atrial fibrillation	103 (15.1)	9 (13.0)	10 (13.5)	10 (18.9)	11 (16.9)	0.890	0
TIA < 7 days	25 (3.7)	5 (7.2)	5 (6.8)	1 (1.9)	3 (4.6)	0.396	0
Ischemic stroke or TIA > 7 days	108 (15.8)	11 (15.9)	6 (8.1)	6 (11.3)	10 (15.4)	0.443	0
Pre-stroke mRS 0-2	571 (83.6)	57 (82.6)	66 (89.2)	43 (81.1)	51 (78.5)	0.526	0
Any oral anticoagulant before	38 (5.6)	1 (1.5)	3 (4.1)	4 (7.5)	4 (6.3)	0.560	8
Any antiplatelet agent before	265 (39.1)	28 (41.2)	28 (37.8)	25 (47.2)	29 (46.0)	0.643	8
Admission characteristics							
Systolic blood pressure (mmHg)*	151 (134-166)	154 (141-166)	150 (125-160)	151 (137-168)	150 (140-174)	0.069	2
Serum glucose level (mg/dl)*	1.16 (1.01-1.40)	1.20 (1.05-1.58)	1.20 (1.07-1.48)	1.33 (1.13-1.59)	1.40 (1.12-1.87)	**<0.0001**	0
Platelet count (1,000/mm^3)*	238 (203-280)	229 (196-281)	246 (206-278)	228 (182-259)	220 (190-258)	0.076	4
NIHSS*	7 (4-13)	10 (5-17)	16 (8-21)	15 (9-19)	16 (11-19)	**<0.0001**	0
Emergency management							
Onset-to-needle time (min)*	141 (110-190)	133 (111-162)	152 (115-207)	127 (105-185)	133 (111-173)	0.285	148
Mechanical thrombectomy	107 (15.7)	17 (24.6)	23 (31.1)	18 (34.0)	16 (24.6)	**<0.0001**	0
Baseline imaging characteristics							
Superficial MCA territory	425 (62.2)	48 (69.6)	53 (71.6)	41 (77.4)	53 (81.5)	**0.003**	0
Deep MCA territory	206 (30.2)	26 (37.7)	31 (41.9)	20 (37.7)	28 (43.1)	0.053	0
Superficial PCA territory	35 (5.1)	6 (8.7)	3 (4.1)	4 (7.5)	4 (6.2)	0.678	0
Deep PCA territory	48 (7.0)	6 (8.7)	6 (8.1)	6 (11.3)	3 (4.6)	0.681	0
ACA territory	22 (3.2)	4 (5.8)	7 (9.5)	2 (3.8)	4 (6.2)	0.095	0
AChA territory	15 (2.2)	0 (0.0)	1 (1.4)	1 (1.9)	1 (1.5)	0.769	0
Cerebellum	34 (5.0)	6 (8.7)	3 (4.1)	2 (3.8)	2 (3.1)	0.590	0
Brain stem	29 (4.2)	8 (11.6)	7 (9.5)	1 (1.9)	0 (0.0)	**0.004**	0
Fazekas scale (WMH) 0-1	476 (69.8)	51 (73.9)	56 (75.7)	37 (69.8)	49 (75.4)	0.701	1
Old infarct						0.436	1
None	428 (62.8)	42 (60.9)	47 (63.5)	28 (52.8)	40 (61.5)		
Unique	115 (16.9)	15 (21.7)	18 (24.3)	14 (26.4)	13 (20.0)		
Multiple	139 (20.4)	12 (17.4)	9 (12.2)	11 (20.8)	12 (18.5)		
Strictly lacunar old infarct	76 (11.1)	7 (10.1)	9 (12.2)	5 (9.4)	3 (4.6)	0.566	1
Strictly territorial old infarct	135 (19.8)	15 (21.7)	14 (18.9)	15 (28.3)	17 (26.2)	0.469	1
Lacunar and territorial old infarct	43 (6.3)	5 (7.2)	4 (5.4)	5 (9.4)	5 (7.7)	0.889	1
FVH	423 (62.0)	53 (76.8)	58 (78.4)	49 (92.5)	55 (84.6)	**<0.0001**	1
Old ICH	11 (1.6)	3 (4.3)	0 (0.0)	3 (5.7)	4 (6.3)	**0.018**	2
Number of BMBs						0.837	2
0	588 (86.2)	57 (82.6)	65 (87.8)	50 (94.3)	54 (84.4)		
1	47 (6.9)	7 (10.1)	3 (4.1)	1 (1.9)	4 (6.3)		
2-4	31 (4.5)	3 (4.3)	3 (4.1)	2 (3.8)	4 (6.3)		
≥5	16 (2.3)	2 (2.9)	3 (4.1)	0 (0.0)	2 (3.1)		
Strictly deep or infratentorial BMBs	29 (4.3)	3 (4.3)	2 (2.7)	0 (0.0)	2 (3.1)	0.585	2
Strictly lobar BMBs	35 (5.1)	6 (8.7)	2 (2.7)	3 (5.7)	6 (9.4)	0.345	2
Lobar and deep or infratentorial BMBs	30 (4.4)	3 (4.3)	5 (6.8)	0 (0.0)	2 (3.1)	0.443	2
cSS scale = 0	663 (97.2)	66 (95.7)	70 (94.6)	50 (94.3)	62 (96.9)	0.597	2
M1 occlusion	145 (21.3)	17 (24.6)	31 (41.9)	26 (49.1)	27 (42.2)	**<0.0001**	2
M2 occlusion	113 (16.6)	13 (18.8)	17 (23.0)	10 (18.9)	7 (10.9)	0.416	2
MCA occlusion beyond M2	46 (6.7)	4 (5.8)	3 (4.1)	1 (1.9)	10 (15.6)	**0.028**	2
ICA occlusion	61 (8.9)	13 (18.8)	15 (20.3)	12 (22.6)	14 (21.9)	**<0.0001**	2

PCA occlusion	36 (5.3)	5 (7.2)	1 (1.4)	4 (7.5)	1 (1.6)	0.191	2
ACA occlusion	7 (1.0)	0 (0.0)	3 (4.1)	1 (1.9)	1 (1.6)	0.201	2
BA occlusion	11 (1.6)	5 (7.2)	5 (6.8)	2 (3.8)	1 (1.6)	**0.006**	2
Volume of DWI abnormality (cm^3)*	1.18 (0.21-5.62)	2.31 (0.97-12.71)	11.59 (1.87-18.94)	10.81 (2.77-28.28)	9.55 (3.76-19.15)	**<0.0001**	2
Mean ADC (10^{-6} mm^2/s)*	0.52 (0.50-0.54)	0.51 (0.49-0.53)	0.50 (0.49-0.52)	0.50 (0.48-0.53)	0.49 (0.47-0.51)	**<0.0001**	106[¥]
TOAST classification							
Atherosclerosis	59 (8.6)	12 (17.4)	6 (8.1)	5 (9.4)	7 (10.8)	0.206	0
Cardio-embolism	240 (35.1)	26 (37.7)	32 (43.2)	28 (52.8)	29 (44.6)	0.052	0
Small-vessel occlusion	20 (2.9)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	0.350	0
Other determined causes	20 (2.9)	2 (2.9)	4 (5.4)	0 (0.0)	0 (0.0)	0.252	0
Unknown causes	340 (49.8)	28 (40.6)	31 (41.9)	20 (37.7)	29 (44.6)	0.205	0
Stroke mimics	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.820	0

Figure 1. Flow chart of patients' selection. rt-PA: recombinant tissue-plasminogen activator. CT: computed tomography. MRI: magnetic resonance imaging. HI: hemorrhagic infarction. PH: parenchymal hemorrhage.

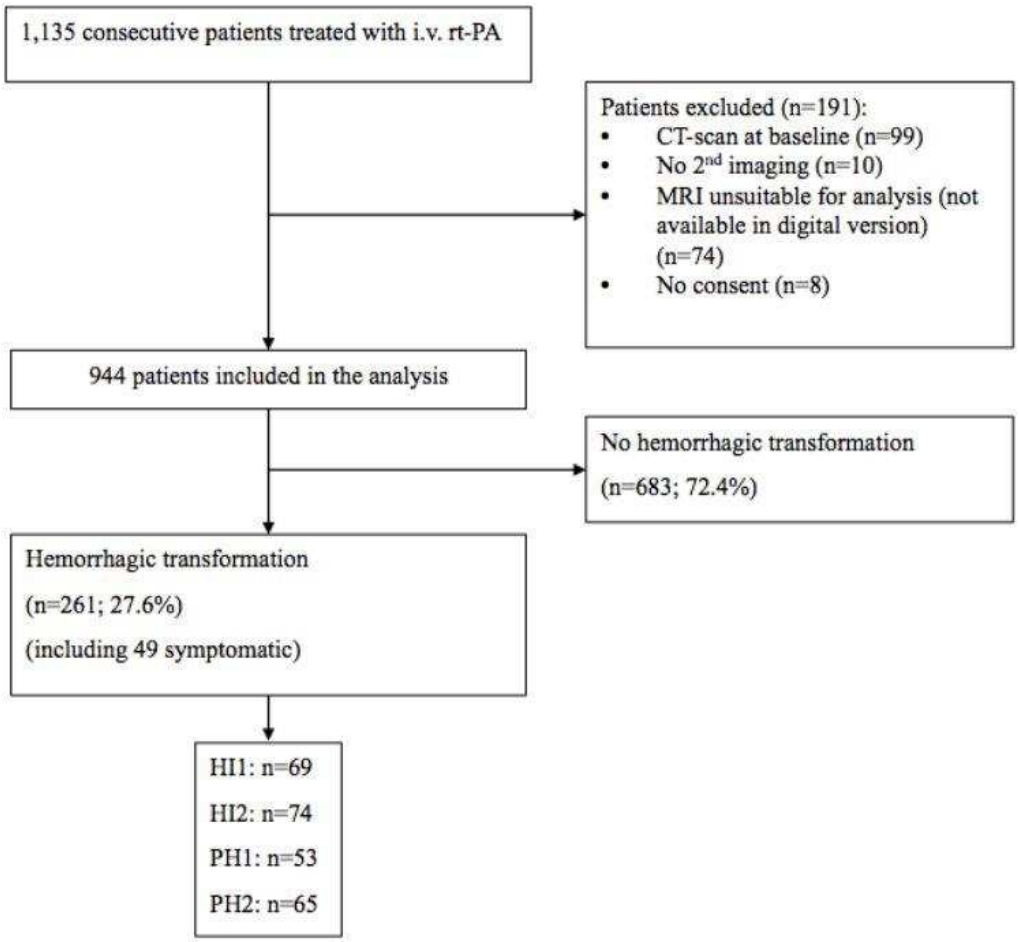


Figure 2. Outcome according to each type of hemorrhagic transformation (Heidelberg classification) represented by the proportions of excellent and good outcome, death and symptomatic hemorrhagic transformation (ECASS2 definition). HT: hemorrhagic transformation. HI: hemorrhagic infarction. PH: parenchymal hemorrhage. s-HT: symptomatic hemorrhagic transformation. ECASS2: European co-operative acute stroke study-II. Excellent outcome means a modified Rankin scale (mRS) 0-1 or similar to the pre-stroke mRS and good outcome means a modified Rankin scale (mRS) 0-2 or similar to the pre-stroke mRS, at 3 months.

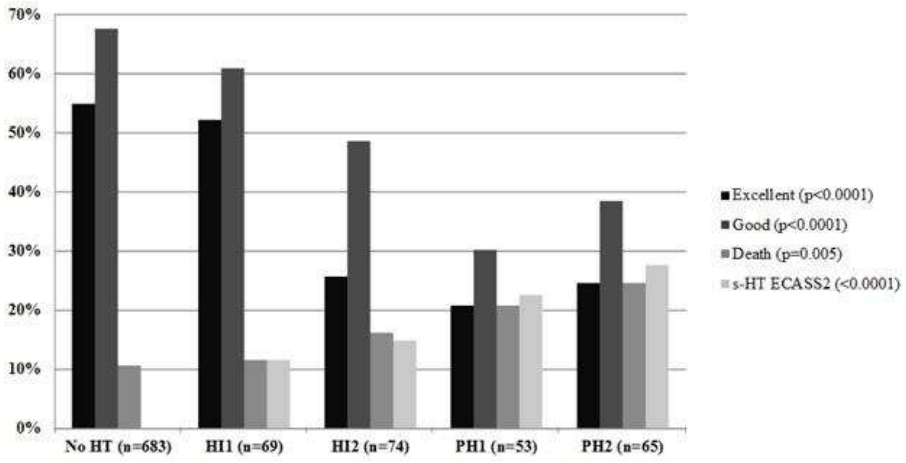
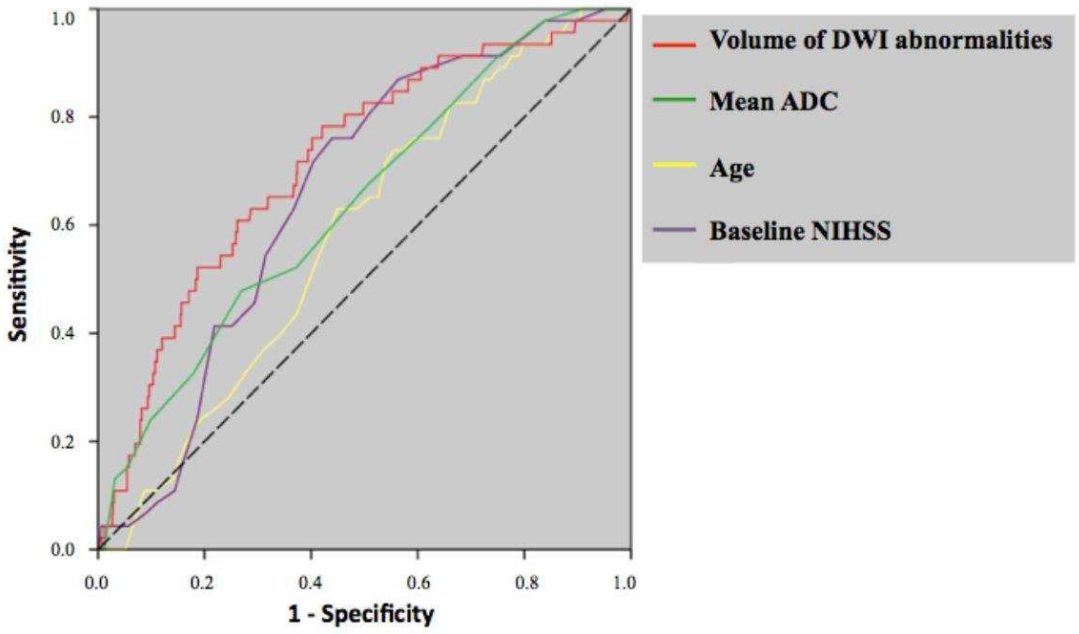


Figure 3. Receiver operating characteristic curves with the 4 quantitative variables independently associated with s-HT (age, baseline NIHSS, volume of DWI abnormality, mean ADC). s-HT: symptomatic hemorrhagic transformation. NIHSS: national institutes of health stroke scale. DWI: diffusion-weighted imaging. ADC: apparent coefficient diffusion.



DISCUSSION GENERALE

Dans notre étude, près de 30% des patients ont présenté une TH parmi lesquels 6% ont présenté des symptômes en lien avec cette TH. Nous avons identifié plusieurs facteurs prédictifs, cliniques et radiologiques, de la survenue d'une transformation hémorragique symptomatique (s-TH) selon les critères de *l'European co-operative acute stroke study-II* (ECASS 2). La survenue d'une TH était associée à un plus mauvais pronostic, notamment pour les hémorragies parenchymateuses (PH) de types 1 et 2.

Concernant les facteurs prédictifs cliniques, un âge plus élevé et un score national institutes of health stroke scale (NIHSS) plus élevé ont déjà été associés à un risque plus élevé de TH dans des études précédents.[1] Le score NIHSS reflète la sévérité clinique de l'infarctus cérébral et est fortement corrélé à son volume ce qui explique qu'il soit associé à un risque plus élevé de TH et l'influence de l'âge est probablement expliquée par une proportion plus importante de patients présentant une microangiopathie. La fibrillation atriale, qui apparaît comme un facteur de risque de TH dans de nombreuses études,[1,2] n'est pas indépendamment associée à la survenue d'une TH dans notre étude ce qui peut être expliqué par l'exclusion de nombreux patient présentant une fibrillation auriculaire du fait d'une anticoagulation efficace contre-indiquant la thrombolyse intraveineuse.

L'un des résultats majeurs de notre étude est l'association entre le volume des anomalies en séquence de diffusion et le risque de s-TH. Les données de la littérature sont contradictoires concernant cette association[1,3] et notre étude apporte donc des éléments nouveaux issus d'une large cohorte de patients thrombolysés avec une évaluation quantitative et reproductible du volume des lésions ischémiques

en diffusion. Cette relation est expliquée par une plus grande susceptibilité à l'hémorragie du tissu ischémié, de surcroit après une thrombolyse intraveineuse. Le fait qu'une hémorragie cérébrale ancienne soit associée au risque de s-TH dans un modèle et tende à l'être dans le second modèle reflète l'existence d'une microangiopathie sous-jacente à risque hémorragique, dont les effets sont potentiellement cumulatifs à celui de la souffrance tissulaire induite par l'ischémie. Enfin, l'existence de ralentissements circulatoires sur la séquence *fluid attenuated inversion recovery* (FLAIR) est probablement corrélée à l'existence d'une occlusion proximale et à l'étendue et la sévérité de l'hypoperfusion, ces paramètres ayant déjà été associés à une majoration du risque de remaniement hémorragique dans des études précédentes.[4,5]

Dans notre étude, le volume de la lésion ischémique évalué en séquence de diffusion apparaît comme le meilleur prédicteur du risque de s-TH et un volume de 4 cm^3 apparait comme le meilleur seuil de prédiction d'une s-TH. Ce seuil pourrait paraitre faible mais il est déterminé dans un groupe de patients bénéficiant tous d'une thrombolyse intraveineuse et qui bénéficient donc d'une imagerie par résonance magnétique (IRM) cérébrale dans les 4h30 suivant le début de la symptomatologie. Ainsi, au vu de la précocité de la réalisation de l'IRM cérébrale, le volume de la lésion ischémique est probablement très faible comparativement à l'étendue de l'hypoperfusion et donc de la souffrance tissulaire.

L'intégration de ces résultats dans l'organisation de la prise en charge des patients présentant une ischémie cérébrale pourrait permettre de limiter la survenue d'une s-TH notamment au vu des avancées thérapeutiques récentes ou en cours d'évaluation. En effet, chez les patients présentant un risque élevé de s-TH

l'utilisation de rt-PA à plus faible dose pourrait être discutée.[6] Par ailleurs, chez des patients présentant une indication de thrombolyse intraveineuse et de thrombectomie mécanique, la présence de facteurs prédictifs de s-TH pourrait amener à considérer la réalisation d'une thrombectomie seule.

CONCLUSION GENERALE

Notre étude apporte donc des données nouvelles concernant les transformations hémorragiques compliquant une thrombolyse intraveineuse dans une cohorte de patients présentant une ischémie cérébrale. En plus des facteurs prédictifs cliniques que sont l'âge et le score NIHSS à l'admission, notre étude apporte des éléments nouveaux sur un grand nombre de paramètres radiologiques grâce à l'utilisation systématique de l'IRM. L'intégration de ces résultats dans l'organisation de la prise en charge des patients présentant une ischémie cérébrale en phase aigüe semble importante afin de minimiser le risque de s-TH.

Références en rapport avec la discussion générale

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5. Fiehler J, Remmele C, Kucinski T, Rosenkranz M, Thomalla G, Weiller C, et al. Reperfusion after severe local perfusion deficit precedes hemorrhagic transformation: an MRI study in acute stroke patients. *Cerebrovasc Dis.* 2005;19:117–24.

6. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee T-H, et al. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. *N Engl J Med.* 2016;374:2313–2323.

ANNEXES

ANNEXE 1: Score de Rankin modifié (mRS)[1]

Score	Description
0	**Pas de symptôme**
1	**Symptômes minimes:** n'interférant pas avec les activités de la vie courante
2	**Handicap mineur**: restriction de certaines activités de la vie courante. Autonomie conservée.
3	**Handicap modéré**: nécessité d'une aide partielle. Marche possible sans aide.
4	**Handicap modérément sévère**: marche impossible sans assistance. Restriction notable de l'autonomie mais sans nécessité d'une aide permanente.
5	**Handicap sévère**: grabataire, incontinence et nécessité de soins de nursing constants.
6	**Décès**

1. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-607.

ANNEXE 2: The Heidelberg Bleeding Classification[2]

Class	Type	Description
1	Hemorrhagic transformation of infarcted brain tissue	
1a	HI1	Scattered small petechiae, no mass effect
1b	HI2	Confluent petechiae, no mass effect
1c	PH1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
2	Intracerebral hemorrhage within and beyond infarcted brain tissue	
	PH2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3	Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage	
3a	Parenchymal hematoma remote from infarcted brain tissue	
3b	Intraventricular hemorrhage	
3c	Subarachnoid hemorrhage	
3d	Subdural hemorrhage	

HI indicates hemorrhagic infarction; and PH, parenchymatous hematoma.

2. von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke 2015;46:2981-2986.

ANNEXE 3: Lettre de soumission du manuscrit à « *Neurology* »

Dear Editor

My colleagues and I are pleased to submit to *Neurology* a Research Article entitled : **"Predictors of symptomatic hemorrhagic transformation after IV thrombolysis for cerebral ischemia"** by François Caparros and colleagues.

We submit it in the category "article".

There is no redundant or duplicate publication and no pre-publication on a pre-print server. There were no previous reports that might be regarded as overlapping with the current work. However, we submitted by April 16th another article currently under review in Neurology entitled "Remote brain hemorrhage after IV thrombolysis: role of pre-existing silent lesions" by Agathe Drelon and colleagues (NEUROLOGY/2019/990895). These 2 articles addressed two different issues (hemorrhagic transformation of the infarcted area here, and remote hemorrhages in the previous one), but the 2 studies were conducted in the same cohort of patients and used similar materials. If one of the two articles is accepted for publication, may we suggest to reduce the method section of the second one (and cite the first), because there are some redundancies in the method section (setting and inclusion criteria are very close).

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As principal investigator and corresponding author, take full responsibility for the data, analyses and interpretation, and for the conduct of the research. The authors have full access to all the data. I have the right to publish any and all data, separate and apart from guidance of any sponsor.

The method section includes a statement that an IRB has approved the use of humans.

We do not cite any personal communication that would have needed permission from the authors.

All coauthors have reviewed and approved the contents of the manuscript, and the *Neurology* requirements for authorship are met. All authors have approved the conditions noted on the authorship agreement form.

The study was approved by French health authorities and by the relevant ethical committee in 2003 and revised by March 9th, 2010, under registration number 10.677. The study was classified as observational without any intervention done for the study that is not part of the usual management of the patients. We were requested to inform the patient, to give a written information form, and to inform them that they can refuse to have their data analyzed for scientific purposes. There was no need to obtain a written informed consent. A significant part of the patients were recruited in the OPHELIE study (registered under ClinicalTrials.gov Identifier n° NCT01614080) whose main results were published in Neurology in 2016 (*Leys et al, Neurology. 2016;87:2416-26*).

The authors have no financial or other relationships that might lead to a perceived conflict of interest. Minor disclosures are reported in the manuscript.

We did not suggest reviewers' names because you might be in favor of assigning the same reviewers than those who review the other manuscript.

I hope you will find this manuscript of interest for your readership.

Best wishes

Prof. Didier Leys

ANNEXE 4: Confirmation de soumission du manuscrit à « *Neurology* »

De : Journal@neurology.org <Journal@neurology.org>
Envoyé : lundi 6 mai 2019 18:11
À : LEYS Didier <Didier.LEYS@CHRU-LILLE.FR>
Objet : NEUROLOGY Manuscript Submission

NEUROLOGY MS ID#: NEUROLOGY/2019/996405 MS TITLE: Predictors of symptomatic hemorrhagic transformation after IV thrombolysis for cerebral ischemia

Dear Prof. LEYS:

The above mentioned manuscript has been submitted to NEUROLOGY by the Corresponding Author. If you did not approve the submission, please contact the Editorial Office immediately at journal@neurology.org.

Please use the assigned manuscript number in all further correspondence. We will contact you once the review process has been completed.

Be sure to visit NPub.org/submit and log in to your Author Area. Once logged in, you may check on the status of your manuscript.

If you have any questions or concerns about your paper, do not hesitate to contact us by e-mail: journal@neurology.org or by phone: (612) 928-6400.

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FOR FULL-LENGTH ARTICLE SUBMISSIONS ONLY, PLEASE NOTE:

Short Article in Print/Full Article Online Pilot for Research Articles in 2018: All Articles that are ultimately accepted and scheduled to be published in the January-December 2018 issues will appear in a short, one-page format in print. The full article, the version of record, will be published online. We are piloting this electronic-long, paper-short to further assess reader preference. The first issue containing short-form articles in print, the January 2, 2018 issue, will be published on December 26, 2017. Please review an example of the short-form article, published in the September 6, 2016 issue as a pilot:
http://www.neurology.org/content/suppl/2016/09/01/WNL.0000000000003078.DC4/kappos.pdf.

The short-form article places the research in context by summarizing the study question and answer, what is known and what the paper adds, design and setting, primary outcomes or main results, confounding factors, and generalizability to other populations. Authors will not be requested to write the short article (this will be done by a medical writer after acceptance), but will have the opportunity to edit and proof the short article.

Thank you for giving NEUROLOGY this opportunity to consider your work.

Sincerely,

NEUROLOGY Editorial Office

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AUTEUR : Nom : CAPARROS **Prénom :** François

Date de Soutenance : 25 Juin 2019

Titre de la Thèse : Facteurs prédictifs de transformation hémorragique symptomatique après thrombolyse intraveineuse pour ischémie cérébrale.

Thèse - Médecine - Lille 2019

Cadre de classement : Neurologie

DES + spécialité : Neurologie

Mots-clés : Accident vasculaire cérébral. Ischémie cérébrale. Thrombectomie. Thrombolyse. Transformation hémorragique. Hémorragie intracérébrale. Hémorragie intracrânienne.

Résumé :

Objectif : déterminer les facteurs prédictifs de transformation hémorragique (TH) symptomatique (s-TH) chez des patients consécutifs traités par *recombinant tissue-plasminogen activator* (rt-PA) par voie intraveineuse (IV) et sélectionnés en imagerie par résonance magnétique (IRM).

Méthode : nous avons définis les s-TH comme des TH remplissant les critères cliniques selon la définition de l'étude ECASS 2 et nous avons étudié les s-TH de classes 1 et 2 selon la classification d'Heidelberg. Nous avons évalué les facteurs prédictifs de s-TH avec les courbes *receiver operating characteristic* en considérant une valeur d'aire sous la courbe (AUC) de 0,70 ou plus comme l'indicateur d'une discrimination acceptable.

Résultats : parmi les 944 patients inclus, 261 (27,6%) ont présenté une TH de classe 1 ou 2, dont 49 s-TH. Les facteurs indépendamment associés à la survenue d'une s-TH étaient l'âge (odds ratio ajusté [adjOR] 1.028 for pour une augmentation d'un an; intervalle de confiance [IC] à 95% 1.004-1.052), la consommation excessive d'alcool (adjOR 3.129; IC à 95% 1.320-7.415), un accident ischémique transitoire récent (adjOR 2.877; IC à 95% 1.042-7.947) et le national institutes of health stroke scale à l'admission (adjOR 1.057 pour une augmentation d'un point; IC à 95% 1.020-1.095) dans le modèle clinique et l'existence de flux lents (adjOR 3.887; IC à 95% 1.499-10.082), la présence d'un infarctus ancien (adjOR 2.010; IC à 95% 1.105-3.654) et le volume des anomalies en séquence de diffusion (adjOR 1.018 pour une augmentation d'un cm^3; IC à 95% 1.007-1.029) dans le modèle radiologique. La seule variable permettant de prédire de manière acceptable le risque de s-TH était le volume des anomalies en séquence de diffusion (0,719 IC à 95% 0,644-0,793), une valeur de 4 cm^3 permettant de prédire une s-TH avec une sensibilité de 78,3% et une spécificité de 58.0%.

Conclusion : déterminer le volume des anomalies en séquence de diffusion à l'admission peut permettre d'identifier des patients à risque de s-TH après administration IV de rt-PA, un volume de 4cm^3 ou plus étant le meilleur facteur prédictif de s-TH.

Composition du Jury :

Président : Monsieur le Professeur Jean-Pierre PRUVO

Assesseurs : Madame le Professeur Charlotte CORDONNIER, Madame le Professeur Hélène ZEPHIR, Madame le Docteur Nelly DEQUATRE-PONCHELLE, Monsieur le Professeur Didier LEYS