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Predicting The Risk of Symptomatic Intracerebral Hemorrhagic Transformation in Acute Ischemic Stroke Using Dwi-Aspect and Literature Review

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ABSTRACT

The Alberta Stroke Program Early Computed Tomography Score (ASPECTS), initially developed for computed tomography (CT) imaging, is a quantitative radiological score that provides a simple and reproducible method for assessing early signs of cerebral ischemia. These signs include effacement of the lenticular nucleus, insular ribbon, and cortical sulci, as well as discrete hypodensity in the cerebral parenchyma within the middle cerebral artery (MCA). This score is derived from two standard axial scans or magnetic resonance site plans: the first includes the thalamus and lenticular nuclei, and the second includes the lateral ventricles.

Between these two plans, the MCA was divided into ten areas of interest, each assigned one point. Three points were allocated for subcortical structures, and seven points were allocated to cortical structures. One point was subtracted for each region that showed early ischemic changes. Thus, an ASPECTS of 10 indicated a normal scan, whereas a 0 indicated diffuse ischemia throughout the extended or malignant MCA area.

Previous studies have demonstrated that diffusion-weighted imaging–ASPECTS is superior to CT-ASPECTS for detecting early signs of ischemia and in terms of inter-reader reproducibility. This score has been used in several studies to evaluate the functional prognosis and risk of symptomatic hemorrhagic transformation (HT) after a recanalization procedure, either by intravenous thrombolysis or thrombectomy. Radio-clinical criteria such as age, cardiovascular risk factors, blood pressure and blood glucose levels on admission, history of ischemic stroke and atrial fibrillation, use of antithrombotic agents, presence or absence of collateral circulation,

microbleeds, slow flow, and leukoaraiosis also influence functional prognosis and the risk of HT.

The therapeutic approach, along with the time between symptom onset and recanalization, affects the functional prognosis and risk of HT. The recurrent question that neurovascular clinicians, regardless of experience, encounter when managing a patient in a fibrinolysis alert is: which reliable tools and radio-clinical criteria can aid in therapeutic decision-making to prevent HT? Is it problematic to rely solely on the ASPECTS for therapeutic decision-making?

1. INTRODUCTION

We conducted a literature review-based retrospective study focusing on hemorrhagic transformation (HT) after recanalization procedures, adjusted for the diffusion-weighted imaging (DWI)-Alberta Stroke Program Early Computed Tomography Score (ASPECTS) and other variables.

We adopted the European Co-operative Acute Stroke Study II (ECASS-II) definition of symptomatic hemorrhagic transformation (SHT), which is a neurological deterioration of at least 4 points on the National Institute of Health Stroke Score (NIHSS) following therapeutic intervention.

This study is part of our endeavor to improve daily clinical practice. We included patients with a middle cerebral artery (MCA) ischemic stroke (IS). The first primary endpoint was SHT within 7 days, regardless of the vascular recanalization therapeutic approach; the second primary outcome was death within seven days; and the secondary endpoint was the functional assessment using the modified Rankin score (mRS) at 90 days.

2. MATERIAL AND METHODS

2.1. Type of study

We conducted a single-center, descriptive, retrospective, observational study of patients that presented with IS to the Neurology Department of Saint-Brieuc Hospital Center, and the Lannion-Trestel and Guingamp Hospitals, between January 1, 2017, and December 31, 2020.

2.2. Study population

The inclusion criteria were as follows: all ages; both sexes; MCA-IS with an onset time ≤4.5 h or with an unknown start time, regardless of etiology; confirmatory brain magnetic resonance imaging (MRI); revascularization through intravenous thrombolysis (IVT), thrombectomy (TM), or a combination of IVT and TM (IVT+TM). Patients with IS with hemorrhagic changes from the outset; those with IS in junctional territories, IS in anterior cerebral artery territories, multiple ISs, posterior fossa ISs, lacunar ISs, or transient ischemic attacks; those with no available brain MRI; those with an initial mRS ≥3, reflecting prior dependence

on IS; or those with endocarditis or arterial dissections were excluded from the study.

2.3. Management protocol

Patients who met the criteria for IVT underwent thrombolysis on site when admitted to the emergency room of Saint-Brieuc Hospital. Meanwhile, patients from the Côtes d'Armor Territorial Hospital Group (GHT d'Armor) at the Lannion-Trestel and Guingamp Hospitals underwent thrombolysis supported by a video telefibrinolysis system connecting the emergency doctors at these peripheral hospitals with the on-call neurologist at Saint-Brieuc. The patients were transferred to the Saint-Brieuc Hospital Group USINV for follow-up within 24 h. Patients who met the criteria for TM were transferred to Rennes or Brest University Hospital within 24 h before continuing their treatment at the Saint-Brieuc USINV.

All the patients underwent MRI (1.5 or 3 T) according to the following stroke protocol sequences: DWI, fluid-attenuated inversion recovery (FLAIR), T2*, and time-of-flight systematic angio-MRI (protocol of service). None of the patients underwent perfusion imaging by default. As a therapeutic approach, all patients were administered IVT (0.9 mg/kg alteplase) within 4.5 h of the IS onset and/or TM. Regardless of the therapeutic approach (IVT and/or TM), the patients underwent follow-up computed tomography (CT) imaging without contrast 24 h post-treatment. A post-stroke consultation was conducted at 90 days by a neurology team that included a vascular neurologist or nurse specializing in IS, and the functional prognosis was evaluated according to the mRS.

2.4. Data collection

We collected data on the following parameters: demographic criteria (age and sex); cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and tobacco use); vascular history (stroke and arrhythmia); ongoing treatment at admission (antiplatelet and anticoagulant); systolic and diastolic blood pressure (SBP and DBP, respectively) on admission; capillary blood glucose (HGT) on admission; neurological scores (mRS on admission; NIHSS on admission: mild, 0–10; moderate, 11–15; severe, ≥16; NIHSS 48–72 h after the procedure: mild, 0–10; moderate, 11–15; severe, ≥16); therapeutic approach (fibrinolysis [IVT] alone: appearance of symptoms, <3, 3–4, or 4–4.5 h; TM alone: appearance of symptoms, <4, 4–6, or >6 h; thrombolysis in cerebral infarction [TICI] score: 0/1, 2a, 2b, 2c, or 3; IVT+TM: time frame and TICI score); radiological criteria (DWI-ASPECTS, 0–4, 5–6, or 7–10; number of microbleeds, <10 or ≥10; degree of vascular leukopathy, 0–1 or ≥2; presence of slow flows in the FLAIR sequence; IS mechanism as per the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] classification [Appendix 2]); and evolutionary criteria (mRS at 3 months).

2.5. Radiological parameters

2.5.1. DWI-ASPECTS

The DWI-ASPECTS was dervied from two standard axial CT planes: the first passed through the thalamus and the lenticular nuclei; the second passed through the lateral ventricles and was adjacent to the upper border of the basal ganglia.

Between these planes, the territory of the MCA was divided into ten regions, each assigned one point, with three points allocated to subcortical structures and seven allocated to cortical structures. A point was subtracted for each region where an early ischemic change was observed, such that an ASPECTS of 10 indicated normal imaging, while an ASPECTS of 0 indicated ischemia throughout the MCA territory (Figure 1).

The ASPECTS was calculated retrospectively. Subsequently, an author performed a blind reevaluation of the DWI-ASPECTS. In two cases of disagreement, a third reevaluation by another neurologist was requested.

2.5.2. Other radiological parameters

The degree of vascular leukopathy was evaluated according to the Fazekas classification scale (Appendix 5) and was presented dichotomously, with Fazekas leukopathy scores ≥2 representing moderate to severe leukopathy.

- Hemorrhagic transformation (HT) was evaluated according to the ECASS-II classification (Figure 2): HI1, minimal petechiae on the periphery of the infarcted area; HI2, confluent petechiae within the infarcted area, without a mass effect; PH1, hematoma with a mass effect <30% of the volume of the infarcted area; and PH2, hematoma with a mass effect >30% of the volume of the infarcted area.

2.6. Functional prognosis

Functional prognosis was assessed according to the mRS, dichotomized into ≤2 indicating autonomy and ≥3 indicating dependence.

2.7. Statistical analyses

Normally distributed continuous variables are described as mean±standard deviation, while non-normally distributed variables are presented as medians and interquartile ranges. Qualitative variables are described as numbers and percentages. Clinical, demographic, and radiological characteristics were compared according to the variables of interest (HT and hemorrhagic death). Continuous variables were compared using the Student's t-test or Mann–Whitney U test, depending on the conditions. Qualitative variables were compared using the Chi-

squared or Fisher's exact test, depending on the conditions. Risk factors associated with the variables of interest (P<0.05) were included in the multivariate logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from the model as the effect size. Statistical tests were performed at a significance level of P<0.05. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

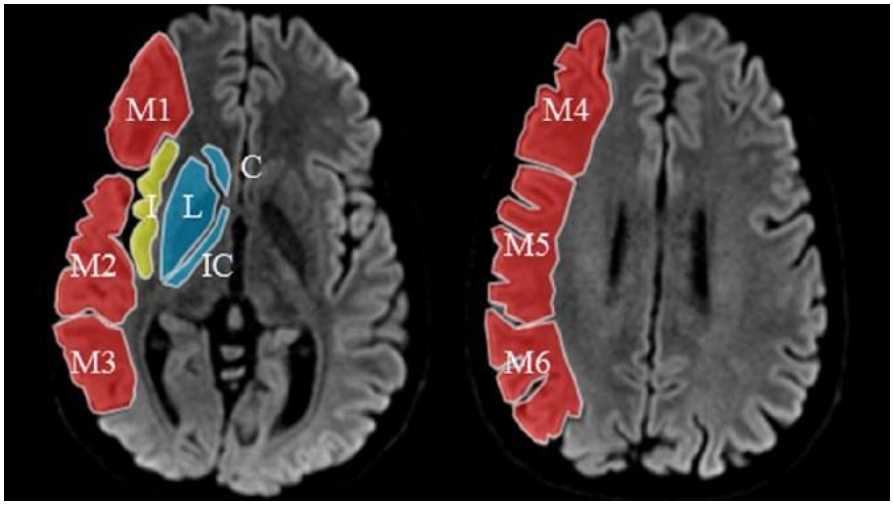

Figure 1: Three points are allocated to the subcortical structures (C, L, and IC), whereas 7 points are allocated to the cortical structures (M1–M6). C=caudate nucleus; I=island ribbon; IC=internal capsule; L=lenticular core; M1=anterior cortex of the ACM; M2=cortex of the MCA territory lateral to the insular ribbon; M3=posterior cortex of the ACM; M4, M5, and M6=anterior, lateral, and posterior cortices of the MCA immediately above M1, M2 and M3, above the basal ganglia, respectively.

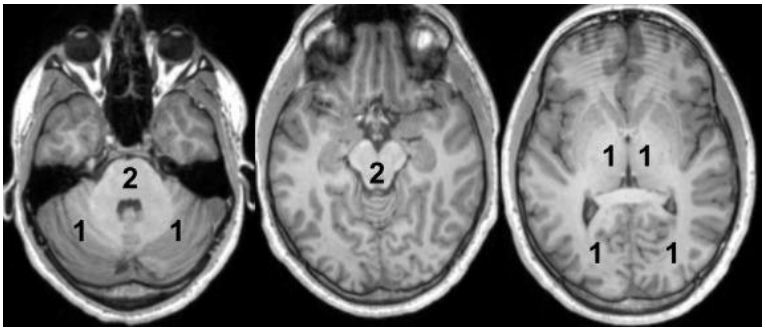

Figure 2: Two points are allocated to the midbrain and pons, 1 point for each side of the thalamus, 1 point for each occipital lobe, and 1 point for each cerebellar lobe.

3. RESULTS

A total of 172 patients with IS, who visited the hospitals (listed in Section 2.1) between January 1, 2017 and December 31, 2020, met the inclusion criteria for this study. Seven patients were excluded from the statistical analyses: six due to death unrelated to HT (one case each of active lung cancer with brain metastases, infectious sepsis, and massive cardiac myocardial infarction and four cases of pneumonia) and one was lost to follow-up

(the patient was hospitalized within 24 h outside of the region) (Figure 3).

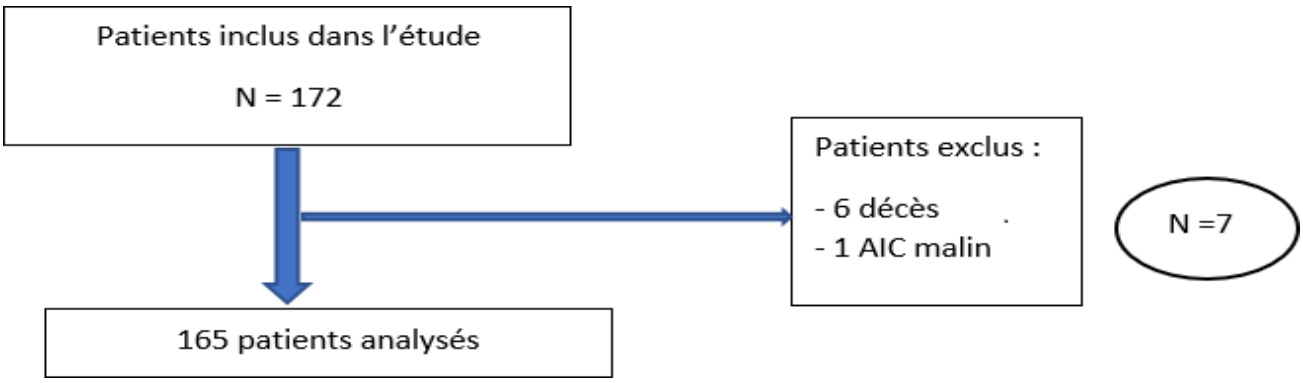

Figure 3: Flow diagram.

3.1. Baseline characteristics

A total of 165 patients with MCA IS were included in the study (average age, 70.5 years; 57% males and 43% females) (Table 1). Most patients experienced relatively little deficit after IS; the initial NIHSS scores ranged between 0 and 10 in 51.5%, between 11 and 15 in 18.8%, and were ≥16 in 29.7% of the patients. The maximum NIHSS score in our study was 23 (n=1). The NIHSS score at 24–72 h was between 0 and 10 in 67.3% of cases, between 11 and 15 in 7.9%, and was ≥16 in 24.8%. The DWI-ASPECTSs were between 7 and 10 in 74.5%, <5 in 10.3%, and between 5 and 6 in 15.2% of the patients. Among the cardiovascular risk factors, 53% of the patients had high blood pressure, 15.1% had diabetes, 35.1% presented with dyslipidemia, 25.4% were smokers, 15.2% had a history of stroke, and 13.3% had cardiac arrhythmia.

Regarding the therapeutic approach, 9.7% of patients underwent TM alone within >6 h in 68.8% of cases (effective revascularization [TICI ≥2c], 50%), IVT alone in 69.01%, including 57.8% within <3 h; and TM+IVT in 21.2% of patients (TICI: 2a, 5.71%; 2b, 20%; 2c, 8.57%; 3, 6%). Additionally, 28.5% of patients were on antiplatelet therapy, and 11.5% were on anticoagulant treatment.

The average blood glucose level and blood pressure on admission were 6.92 mmol/L and 158/86 mm Hg, respectively. Imaging revealed that most patients (98.5%) had <10 microbleeds (vs. 1.5% who had ≥10 microbleeds).

Leukopathy was absent or mild in 63.6% of cases, and leptomeningeal collaterals (slow flows) were found in 66.1% of cases. According to the TOAST classification, cardioembolic causes (atrial fibrillation) were identified in 44.5% of cases.

Table 1: Patient baseline characteristics (n=165)

Age (years)	70.5±12.4
Male	94/165 (57.0)
Risk factors	
Hypertension	88/165 (53.3)
Diabetes	25/165 (15.1)
Dyslipidemia	58/165 (35.1)
Tobacco use	42/165 (25.4)
History	
History of IS	25/165 (15.2)
Arrythmias	22/165 (13.3)
Treatment	
Antiplatelet	47/165 (28.5)
Anticoagulant	19/165 (11.5)
Initial NIHSS (%)	
0–10	51.5
11–15	18.8
>16	29.7
Score 24–72 h post-stroke (%)	
0–10	67.3
11–15	7.9
>16	24.8
Biological and blood pressure parameters	49/165 (29.7)
HGT (mmol/L)	6.92±1.54
SBP (mm Hg)	158±25
DBP (mm Hg)	86±18
Therapeutic approach	
Fibrinolysis (intravenous thrombolysis) alone	114 (69.01)
Time frame	

<3 h	66/114 (57.8)
3–4 h	39/114 (34.21)
>4–4.5 h	9/114 (6.2)
Thrombectomy alone	16/165 (7.8)
Time frame	
<3 h	0/16 (0)
4–6 h	5/16 (31.2)
>6 h	11/16 (68.8)
TICI	
0–1	1/16 (6.25)
2a	2/16 (12.5)
2b	5/16 (31.25)
2c	3/16 (18.75)
3	5/16 (31.25)
Fibrinolysis+thrombectomy	35/165 (21.2)
Time to fibrinolysis	
<3 h	24/35 (68.5)
3–4 h	9/35 (25.7)
>4–4.5 h	2/35 (5.71)
Time to thrombectomy	
<4 h	0/35 (0)
4–6 h	16/35 (45.7)
>6 h	19/35 (54.2)
TICI	
0–1	2/35 (5.71)
2a	2/35 (5.71)
2b	7/35 (20)
2c	3/35 (8.57)
3	21/35 (60)

Radiological criteria	
ASPECTS	
<5	17/165 (10.3)
5–6	25/165 (15.2)
7–10	123/165 (74.5)
Microbleeds	
<10	135/165 (98.5)
>10	2/165 (1.5)
Fazekas scale	
0–1	105/165 (63.6)
>2	60/165 (36.4)
Stroke sequelae	42/165 (25.4)
Slow flow	109/165 (66.1)
TOAST classification	
1	6/165 (3.6)
2	73/165 (44.5)
3	2/165 (1.2)
4	9/165 (5.5)
5	75/165 (45.7)

Data are presented as mean±standard deviation or frequency (%). Calculations were performed on available data. IS=ischemic stroke; NIHSS=National Institutes of Health Stroke Scale; HGT=capillary blood glucose test; SBP=systolic blood pressure; DBP=diastolic blood pressure; TICI=thrombolysis in cerebral infarction; ASPECTS=Alberta Stroke Program Early Computed Tomography Score; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

3.2. Primary endpoint: HT

In our population, 22.1% (n=20/36) of patients had asymptomatic hemorrhagic transformation (AHT), while 9.7% (n=16/36) had SHT, and 30.6% (n=11/16) died. According to the ECASS-II classification, AHT presented as hematomas in 69.4% of cases (PH1 in 19.4% of cases and PH2 in 50% of cases) (Table 2).

Table 2: Baseline criteria (n=165)

Hemorrhagic transformation	
No	129/165 (78.1)
Yes	36/165 (23.01)
Symptomatic	16/36 (9.7)
Asymptomatic	20/36 (44.4)
Death	11/16 (30.6)
ECASS	
HI1	7/36 (19.4)
HI2	4/36 (11.1)
PH1	7/36 (19.4)
PH2	18/36 (50)
Death due to IS	21/165 (12.72)

Data are presented as frequency (%). Calculations were performed on available data. ECASS=European Cooperative Acute Stroke Study; IS=ischemic stroke.

Table 3: STH per trichotomized DWI-ASPECTS (n=165)

	ASPECTS		
	<5 (n=3)	**5–6 (n=3)**	**≥7 (n=10)**
Age (years)	76.3±6.4	77.3±7.1	78.2±7.3
Male	1 (33.3)	3 (100.0)	4 (40.0)
Risk factors			
Hypertension	2 (66.7)	1 (33.3)	7 (70.0)
Diabetes	1 (33.3)	0 (0.0)	3 (30.0)
Dyslipidemia	1 (33.3)	1 (33.3)	3 (30.0)
Smoking	0 (0.0)	1 (33.3)	2 (20.0)
Medical history			
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)
Treatment			
Antiplatelet agents	0 (0.0)	0 (0.0)	4 (40.0)

Anticoagulant	0 (0.0)	0 (0.0)	0 (0.0)
Initial NIHSS			
0–10	0 (0.0)	0 (0.0)	6 (60.0)
11–15	0 (0.0)	0 (0.0)	3 (30.0)
≥16	3 (100.0)	3 (100.0)	1 (10.0)
ECASS			
HI1	0 (0.0)	0 (0.0)	0 (0.0)
HI2	0 (0.0)	0 (0.0)	0 (0.0)
PH1	1 (33.3)	1 (33.3)	1 (10.0)
PH2	3 (100.0)	2 (66.7)	8 (80.0)
Biological and blood pressure parameters			
HGT (mmol/L)	7.1±0.4	9.4±3.0	7.2±2.0
SBP (mm Hg)	160±42	146±23	168±34
DBP (mm Hg)	93±21	78±6	88±23
Technique			
Fibrinolysis alone	1 (33.3)	1 (33.3)	8 (80.0)
Thrombectomy alone	0 (0.0)	1 (33.3)	0 (0.0)
Fibrinolysis+thrombectomy	2 (66.7)	1 (33.3)	2 (20.0)
Radiological criteria			
Microbleeds	0 (0.0)	0 (0.0)	0 (0.0)
Stroke sequelae			
Slow flow			

Data are presented as mean±standard deviation or frequency (%). STH=symptomatic hemorrhagic transformation; DWI=diffusion-weighted imaging; ASPECTS=Alberta Stroke Program Early Computed Tomography Score; ECASS=European Cooperative Acute Stroke Study; NIHSS=National Institutes of Health Stroke Scale; HGT=capillary blood glucose test; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Among the 16 patients who experienced HT, 100% of the patients with an ASPECTS <5 had a PH2 HT, 66.7% with an ASPECTS between 5 and 6 had a PH2 HT, and 33.3% had a PH1 HT. Of those with an ASPECTS ≥7,

80% experienced a PH2 and 10% a PH1 (*P*=0.79). Severe NIHSS scores ≥16 was present in 100% of the patients with an ASPECTS <5, in 100% of those with an ASPECTS between 5 and 6, and in 10% of those with an ASPECTS ≥7. Additionally, 60% of patients presented with mild NIHSS scores of 0–10 (*P*=0.005). SHT is also observed in patients with high ASPECTSs (≥7). Therefore, it is important to identify other parameters that can explain the risk of developing HT in these patients. The history of hypertension was distributed homogeneously: 66.7% in the ASPECTS <5 group, 33.3% in the 5–6 group, and 60% in the ≥7 group (*P*=0.76). Dyslipidemia was also distributed homogeneously among the subgroups: 33.3% in the ASPECTS <5 group, 33.3% in the 5–6 group, and 30% in the ≥7 group (*P*=1). Diabetes was evenly distributed among the ASPECTS groups: 33.3% in the ASPECT <5 group, 30% in the 5–6 group, and 30% in the ≥7 group (*P*=0.78). The average initial glycemia was distributed a little more widely in the ASPECTS 5–6 group (9.4 mmol/L) than in the ASPECTS >6 (7.1 mmol/L) and 7–10 groups (7.2 mmol/L) (*P*=0.62). Blood pressure on admission was higher at 168 mm Hg in the ASPECTS 7–10 group (vs. 160 mm Hg in the ASPECTS <5 group and 146 mm Hg in the ASPECTS 5–6 group; *P*=0.59). The effect of antiplatelet aggregation was observed in only 40% of the patients in the ASPECTS 7–10 group. Major leukopathy (Fazekas ≥2) was found in 70% of the cases in the ASPECTS 7–10 group and 33.3% in the ASPECTS <5 and 5–6 groups. Slow flow was present in 50% of the patients with an ASPECTS of 7–10 vs. 100% in the other two ASPECTS groups.

Eighty percent of the patients underwent IVT in the ASPECTS ≥7 group, while the combined therapeutic approach (IVT+TM) predominated in the ASPECTS <5 group 66.7% vs. 33.33% in the ASPECTS 5–6 group and 20% in the ≥7 group (*P* =0.15). Overall, 33.3% of the patients in the ASPECTS 5–6 group underwent TM alone. The low numbers in each trichotomization of the ASPECTS prevented a detailed analysis of the timing of therapeutic approaches and thrombolysis on the cerebral infarction scale. PH2 bleeding was observed in 100% of patients with ASPECTSs <5 and in 80% of those with a high ASPECTS >7; it is uncommon to find bleeding in patients with a high ASPECTS.

No criterion, whether clinical-demographic, biological, therapeutic, or radiological, was found to be statistically significant in explaining the risk of SHT in patients with an ASPECTS ≥7.

3.2.1. HT in non-bleeders (n=16/149)

We analyzed the predictive factors for HT risk independent of the ASPECTS by comparing patients who did not bleed, including patients with AHT (n=149). The data of patients with asymptomatic bleeding (referred to as the bleeders group) were compared with those of non-bleeding patients (referred to as the non-bleeders group) and patients with AHT to identify factors that could predict the absence of a risk of bleeding to the detriment of the

inhomogeneity of the two groups (Table 4). Age was significantly lower in patients who did not present with SHT (69.8 vs. 77.7 years; *P*<0.0004). A low NIHSS score, between 0 and 10, was predominant among non-bleeders compared to patients with SHT (53% vs. 37.5%, *P*= 0.36), highlighting that a low initial NIHSS score favors non-bleeding.

A high ASPECTS (≥7) was found in 75.8% of non-bleeders (vs. 62.4% in symptomatic bleeders; *P*=0.29). Conversely, a low ASPECTS was observed in 9.4% of the non-bleeders (vs. 18.8% of bleeders; *P*=0.29).

The average blood glucose was slightly lower in non-bleeders, with an average of 6.8 mmol /L (vs. 7.6 mmol/L; *P*=0.19).

Fibrinolysis alone was performed in 69.8% of non-bleeding patients vs. 62.5% in patients with bleeding, with a timeframe of <3 h in 60.2% of non-bleeding patients vs. 70% of patients with bleeding.

TM alone was performed more often in non-bleeders, among whom 66.7% had a timing >6 h and 33.3% had a timing between 4 and 6 h vs. 100% in bleeders, of which there was only one.

In the combined approach, the fibrinolysis time was <3 h in 64.3% of the non-bleeding patients vs. 80% of those with bleeding. A 4–6 h time-to-TM was observed in 46.7% of non-bleeding patients vs. 40% of patients with bleeding, and 53.3% of non-bleeding patients had a delay of >6 h vs. 60% of patients with bleeding.

Recanalization was complete (TICI 2c-3) in 67.9% of non-bleeding patients vs. 40% of patients with bleeding. Absent or mild leukopathy (Fazekas score, 0–1) was found more often in non-bleeding patients than those with bleeding (65.8% vs. 43.8%, respectively; *P*= 0.08). Slow flow occurred equally between the two groups (*P*=0.81).

Table 4: Univariate analysis of factors associated with the risk of symptomatic hemorrhage

	SHT (n=16)	**AHT+NHT (n=149)**	***P* value**
Age (years)	77.7±6.7	69.9±12.6	0.0004
Male	8/16 (50.0)	86 (57.7)	0.55
Risk factors			
Hypertension	10/16 (62.5)	78/149 (52.3)	0.44
Diabetes	4/16 (25)	21/149 (14.1)	0.27
Dyslipidemia	5/16 (31.2)	53/149 (35.6)	0.73
Smoking	3/16 (18.7)	39/149 (26.2)	0.76
Medical history			

Arrhythmia	0/16 (0.0)	22/149 (14.8)	0.13
Treatment			
Antiplatelet agents	4/16 (25.0)	43/149 (28.9)	1
Anticoagulant	0/16 (0.0)	19/149 (12.7)	0.22
Initial NIHSS			0.36
0–10	6/16 (37.5)	79/149 (53)	
11–15	3/16 (18.7)	28/149 (18.8)	
≥16	7/16 (43.8)	42/149 (28.2)	
ECASS			0.003
HI1	0/16 (0.0)	7/20 (35)	
HI2	0/16 (0.0)	3/20 (15.0)	
PH1	2/16 (16.2)	5/20 (25)	
PH2	13/16 (81.2)	5/20 (25)	
ASPECTS			0.29
<5	3/16 (18.8)	14/149 (9.4)	
5–6	3/16 (18.8)	14/149 (9.4)	
7–10	10/16 (62.4)	113/149 (75.8)	
Biological and blood pressure parameters			
HGT (mmol/L)	7.6±2	6.8±2.1	0.19
SBP (mm Hg)	162±28	158±28	0.56
DBP (mm Hg)	87±20	86±18	0.85
Technique			0.81
Fibrinolysis alone	10/16 (62.5)	104/149 (69.8)	
Time to treatment			0.81
<3 h	7/10 (70)	59/102 (60.2)	
3–4 h	3/10 (30.0)	36/102 (36.7)	
4–4.5 h	0/10 (0.0)	3/102 (3.1)	
Thrombectomy alone	1/16 (6.3)	15/149 (10.7)	

Time to treatment			1.00
<4 h	0 (0.0)	0/15 (0.0)	
4–6 h	1/1 (100)	5/15 (33.3)	
>6 h	0 (0.0)	10/15 (66.7)	
TICI			
0–1	1/1 (100)	1/14 (7.1)	
2a	0/1 (0.0)	0/14 (0.0)	
2b	0/1 (0.0)	5/14 (35.7)	
2c	0/1 (0.0)	3/14 (21.4)	
3	0/1 (0.0)	5/14 (35.7)	
Combined fibrinolysis+thrombectomy		30/149 (20.1)	
Delay in fibrinolysis			0.11
<3 h	4/5 (80)	18/28 (64.3)	–
3–4 h	0/5 (0.0)	9/28 (32.1)	–
4–4.5 h	1/5 (20)	1/28 (3.6)	
Delay in thrombectomy			1.00
<4 h	0/5 (0.0)	0/30 (0.0)	
4–6 h	2/5 (40)	14/30 (46.7)	
>6 h	3/5 (60)	16/30 (53.3)	
TICI			0.19
0–1	1/5 (20)	1/28 (3.6)	
2a	0/5 (0.0)	2/28 (7.1)	
2b	2/5 (40)	3/28 (10.7)	
2c	0/5 (0.0)	3/28 (10.7)	
3	2/5 (40)	19/28 (67.9)	
Radiological criteria			
Microbleeds			0.18
<10	15/16 (93.7)	148/149 (99.3)	–

>10	1/16 (6.3)	1/149 (0.7)	–
Fazekas			–
0–1	7/16 (43.8)	98/149 (65.8)	
>2	9/16 (56.2)	51/149 (34.2)	–
Stroke sequelae	5/16 (31.2)	37/149 (24.8)	–0.38
Slow flow	11/16 (68.7)	98/149 (65.8)	0.81

Data are presented as mean±standard deviation or frequency (%). Calculations are based on available data. SHT=symptomatic hemorrhagic transformation; AHT+NHT=asymptomatic hemorrhagic transformation+no hemorrhagic transformation; NIHSS=National Institutes of Health Stroke Scale; ECASS=European Cooperative Acute Stroke Study; ASPECTS=Alberta Stroke Program Early Computed Tomography Score; HGT=hemoglucotest; SBP=systolic blood pressure; DBP=diastolic blood pressure; TICI=thrombolysis in cerebral infarction.

Given the diversity of the two groups, due to the very low number of patients with symptomatic bleeding, only age differed significantly between groups (P<0.0004). Owing to the trend toward Fazekas score significance and a statistical correlation with the NIHSS score, we chose to increase the number of patients with bleeding by pooling the asymptomatic (n= 20) and symptomatic (n= 16) patients and comparing them with non-bleeding patients (n=129), for a better analysis (Table 5).

3.2.2. HT/non-bleeders (n=36/129)

The average age was lower in the non-bleeders, at 69.8 years (vs. 73.3 years; P=0.13). The incidence of arterial hypertension was lower in non-bleeders than in bleeders (50.4% vs. 63.9%; P=0.15). An initial NIHSS score between 0 and 10 was found in 59.7% of non-bleeders (59.7% vs. 22%; P=).

The ASPECTS in 81.4% of cases was between 7 and 10 in non-bleeders (vs. 50%; P=0.0003). The HGT and SBP values were not significantly different between the groups (HGT: 6.89 vs. 7.08 mmol/L, P= 0.84; SBP: 159 vs. 158 mm Hg, P= 0.97). Regarding the therapeutic approach, IVT alone was performed more frequently in non-bleeders (73.6% vs. 52.8%), mainly within 3–4.5 h in 43.7% of the cases (vs. 27.8%). The therapeutic approach and timing were not predictive of the risk of HT. Fewer thrombectomies alone were performed in non-bleeders (9.3% vs. 11.1%). However, timing of <6 h was more frequent in those who did not bleed (33.3% vs. 25%), and timing of >6 h was less frequent in those who did not bleed (66.7% vs. 75% in bleeders).

Recanalization was better in non-bleeders than in bleeders (58.4% vs. 25% with TICI2c-3). Fewer patients benefited from the combined approach (17% vs. 36.1%). Fibrinolysis times <3 h were less important in non-bleeding patients. Bleeding (60% vs. 76.0%). The timeframes were between 3 and 4.5 h in 40% of the cases of bleeding (vs. 23.1% among those who did not bleed); most were at the right time. The timeframe was longer among non-bleeders 40% (vs. ??).

For TM in the combined approach, timeframes of <6 h were more often found in non-bleeders (54.5% vs. 30.8%) and timeframes >6 h were less frequently represented in non-bleeders (45.5% vs. 69.2%). The quality of recanalization was better in those who did not bleed (85.7% had a TICI of 2c-3 vs. 50% in bleeders). It is a good predictor of the risk of developing TH. No or minor leukopathy was found more often in non-bleeders (65.1% vs. 58.3%; *P*=0.45), and slow flow occurred less often in non-bleeders (62.8% vs. 77%; *P*=0.45).

Table 5: Univariate analysis of factors associated with hemorrhagic transformation

	Hemorrhagic transformation		
	Yes (n=36)	**No (n=129)**	***P* value**
Age (years)	73.3±12.4	69.6±12.3	0.13
Male	21/36 (58.3)	73/129 (56.6)	0.85
Risk factors			
Hypertension	23/36 (63.9)	65/129 (50.4)	0.15
Diabetes	5/36 (13.9)	20/129 (15.5)	0.81
Dyslipidemia	12/36 (33.3)	46/129 (36.7)	0.80
Smoking	8/12 (22.2)	34/129 (26.4)	0.61
Medical history			
Arrhythmia	3/12 (8.3)	19/129 (14.7)	0.41
Treatment			
Antiplatelet agents	8/12 (22.2)	39/129 (30.2)	0.19
Anticoagulant	4/12 (11.1)	15/129 (11.6)	1
Initial NIHSS			<0.0001
0–10	8/12 (22.2)	77/129 (59.7)	
11–15	6/12 (16.7)	15/129 (11.6)	
≥16	22/12 (61.1)	27/129 (20.9)	
ECASS			
HI1	7/36 (19.4)		
HI2	4/36 (11.1)		
PH1	7/36 (19.4)		
PH2	18/36 (50.0)		
ASPECTS			0.0003
<5	9/36 (25.0)	8/129 (6.2)	
5–6	9/36 (25.0)	16/129 (12.4)	
7–10	18/36 (50.0)	105/129 (81.4)	
mRS at 24 h			<0.0001
≤2	8/36 (22.2)	87/129 (67.4)	

3–5	17/36 (47.2)	29/129 (22.5)	
>5	11/36 (30.6)	10/129 (7.9)	
Biological parameters			
HGT (mmol/L)	7.0±1.7	6.8±1.7	0.84
SBP (mm Hg)	158±27	159±25	0.97
DBP (mm Hg)	86±17	86±18	0.49
Fibrinolysis alone	19/36 (52.8)	95/129 (73.6)	0.32
Time to treatment			
<3 h	13/18 (72)	53/94 (56.4)	
3–4 h	5/18 (27.8)	34/94 (36.2)	
4–4.5 h	0/18 (0.0)	7/94 (7.5)	
Thrombectomy alone	4/36 (11.1)	12/129 (9.3)	0.75
Time to treatment			
<4 h	0/4 (0.0)	0/12 (0.0)	
4–6 h	1/4 (25)	4/12 (33.3)	
>6 h	3/4 (75)	8/12 (66.7)	
TICI			0.57
0–1	0/4 (0.0)	1/12 (8.3)	
2a	0/4 (0.0)	0/12 (0.0)	
2b	1/4 (25)	4/12 (33.3)	
2c	1/4 (25)	2/12 (16.7)	
3	0/4 (0.0)	5/12 (41.7)	
Combined fibrinolysis+thrombectomy	13/36 (36.1)	22/129 (17)	
Time to treatment fibrinolysis			0.46
<3	10/13 (76.9)	12/20 (60)	
3–4 h	2/13 (15.4)	7/20 (35)	
4–4.5 h	1/13 (7.7)	1/20 (5)	
Time to treatment thrombectomy			0.17
<4 h	0/13 (0.0)	0/22 (0.0)	

4–6 h	4/13 (30.8)	12/22 (54.5)	
>6 h	9/13 (69.2)	10/22 (45.5)	
TICI			0.15
0–1	2/12 (16.7)	0/21 (0.0)	
2a	4/13 (30.8)	1/21 (4.8)	
2b	6/13 (69.2)	2/21 (9.5)	
2c	1/12 (8.3)	2/21 (9.5)	
3	5/12 (41.7)	16/21 (76.2)	
Radiological criteria			0.39
Microbleeds			
<10	35/36 (97.2)	128/129 (99.2)	
>10	1/36 (2.8)	1/129 (0.8)	
Fazekas			0.45
0–1	21/36 (58.3)	84/129 (65.1)	
>2	15/36 (41.7)	45/129 (34.8)	
Stroke sequelae	11/36 (30.6)	31/129 (24)	0.43
Slow flow	28/36 (77.8)	81/129 (62.8)	0.09

Data are presented as mean±standard deviation or frequency (%). Calculations are based on available data. NIHSS=National Institutes of Health Stroke Scale; ECASS=European Cooperative Acute Stroke Study; ASPECTS=Alberta Stroke Program Early Computed Tomography Score; mRS=modified Rankin score; HGT=hemoglucotest; SBP=systolic blood pressure; DBP=diastolic blood pressure; TICI=thrombolysis in cerebral infarction.

Previous studies have classified mortality into two groups based on the therapeutic approach: TM and IVT. We recorded nine deaths in patients who underwent IVT and two in those who underwent TM alone. Fifty percent of patients who received IVT alone died, and 12.5% of patients (n = 16) who presented with HT (50% for IVT and 12.5% for TM alone) died. The IVT/TM therapeutic approach was used in 16 patients with symptomatic bleeding patients (n=16). Based on IVT/TM therapeutic approach in a group out of 149.

In a univariate analysis of factors associated with SHT, the average age of patients was 77 years, 50% were

females, 63% had hypertension, the initial NIHSS score was >16, mean blood sugar was 7.5 mmol /L, and SBP at admission was 148 mmHg. The majority were hypertensive with severe NIHSS scores on admission, and ASPECTSs were mainly >7, with deterioration within 72 h following massive HT (mainly PH2). Most received timely thrombolysis and had slow flow and severe leukopathy without MB.

Table 6: Univariate analysis of factors associated with hemorrhagic transformation death

	Hemorrhagic analysis associated with death		
	Yes (n=11)	**No (n=25)**	***P* value**
Age (years)	77.4±7.4	71.5±13.8	0.10
Male	6/11 (54.5)	15/25 (60)	1
Risk factors			
Hypertension	7/11 (63.6)	16/25 (64)	1
Diabetes	2/11 (18.2)	3/25 (12)	0.63
Dyslipidemia	3/11 (27.3)	9/25 (36)	0.71
Smoking	2/11 (18.2)	6/25 (24)	1
Medical history			
Arrhythmia	1/11 (9.1)	2/25 (8)	1
Treatment			
Antiplatelet agents	4/11 (36.4)	4/25 (16)	0.46
Anticoagulant	1/11 (9.1)	3/25 (12)	1
Initial NIHSS			0.36
0–10	4/11 (36.4)	4/25 (16)	
11–15	2/11 (18.2)	4/25 (16)	
≥16	5/11 (45.4)	17/25 (68)	
ECASS			0.04
HI1	2/11 (18.2)	5/25 (20)	
HI2	0/11 (0.0)	4/25 (16)	
PH1	0/11 (0.0)	7/25 (28)	
PH2	9/11 (81.8)	9/25 (36)	

ASPECTS			0.41
<5	3/11 (27.3)	6/25 (24)	
5–6	1/11 (9.1)	8/25 (32)	
7–10	7/11 (63.6)	11/25 (44)	
Biological and blood pressure parameters			
HGT (mmol/L)	7.5±2.2	6.9±1.5	0.18
SBP (mm Hg)	14±27	162±26	0.96
DBP (mm Hg)	86±16	71±4	0.05
Fibrinolysis alone	8/11 (72.7)	11/25 (44)	0.61
Time to treatment			
<3 h	5/8 (62.5)	8/11 (80)	
3–4 h	3/8 (37.5)	2/11 (20)	
4–4.5 h	0/8 (0.0)	2/25 (8)	
Thrombectomy alone	2/11 (18.2)	2/25 (8)	1.00
Time to treatment			
<4 h	0/2 (0.0)	0/2 (0.0)	
4–6 h	0/2 (0.0)	1/2 (50)	
>6 h	2/2 (100)	1/2 (50)	
TICI			
0–1	0/2 (0.0)	0/2 (0.0)	
2a	0/2 (0.0)	0/2 (0.0)	
2b	0/2 (0.0)	1/2 (50)	
2c	0/2 (0.0)	0/2 (0.0)	
3	0/2 (0.0)	0/2 (0.0)	
Combined fibrinolysis + thrombectomy	1/11 (9.1)	12/25 (48)	1.00
Time to treatment fibrinolysis			
<3	1/1 (100)	9/12 (75)	
3–4 h	0/1 (0.0)	2/12 (16.7)	
4–4.5 h	0/1 (0.0)	1/12 (8.3)	

Time to treatment thrombectomy			1.00
<4 h	0/1 (0.0)	0/12 (0.0)	

Data are presented as mean±standard deviation or frequency (%). Calculations are based on available data. NIHSS=National Institutes of Health Stroke Scale; ECASS=European Cooperative Acute Stroke Study; ASPECTS=Alberta Stroke Program Early Computed Tomography Score; HGT=hemoglucotest; SBP=systolic blood pressure; DBP=diastolic blood pressure; TICI=thrombolysis in cerebral infarction.

3.3. Analysis of mRS according to ASPECTS

For the secondary endpoint related to mRS and death, we analyzed the elements from previous analyses. The therapeutic approach was deliberately excluded from the Rankin analysis because of the small numbers and data dispersion between the different techniques and the trichotomization of time frames. We observed 68.7% deaths among all patients and 30.5% among those who presented with HT in a broad sense. Among those who died, 45.4% had a high NIHSS score (≥16, vs. 18.2% with an NIHSS score between 11 and 15, and 36.4% with that between 0 and 10). The ASPECTS was >7 in 63.6% of cases, and the NIHSS discharge score was ≥16 in 63% of cases.

Among patients with an unfavorable prognosis, 76.5% had an initial NIHSS score ≥16 (vs. 11.8% with an NIHSS score between 11 and 15, and 11.8% with that between 0 and 10), an ASPECTS evenly distributed across to the trichotomization, and an exit NIHSS score ≥16 in 53% of the cases.

Table 7: Analysis of mRS according to ASPECTS

ASPECTS	**mRS**		
	≤2	**3–5**	**Death**
<5 (17)	6 (35)	7 (41)	5 (2)
5–6 (27)	9 (33)	10 (37)	6 (29)
7–10 (121)	84 (69)	27 (22)	8 (8)

In the analysis of the mRS according to the ASPECTS, most of the patients had ASPECTS <2, and in those with mRS <5, 41% had mRS between 3 and 5. mRS=modified Rankin Scale; ASPECTS=Alberta Stroke Program Early Computed Tomography.

3.4. LITERATURE REVIEW

3.4.1. CT-ASPECTS and HT

Barber et al., 2000

This prospective study [2] of 203 patients demonstrated the validity and reliability of the CT ASPECTS for predicting functional prognosis and SHT post-IVT. A CT-ASPECTS ≤7 predicted the risk of SHT post-IVT with an OR of 14 (95% CI, 23–290; *P*<0.012) and the functional prognosis with an OR of 82 (95% CI, 23–290; *P*<0.001).The sensitivity of the CT-ASPECTS for predicting the risk of HT was estimated to be 0.90, with a specificity of

0.62. The sensitivity for estimating functional prognosis was 0.78, with a specificity of 0.96. The CT-ASPECTS predicted the risk of SHT regardless of whether the time between symptom onset and IVT was 0–3 h or 3–6 h. It also demonstrated an inverse correlation with IS severity, as measured using the NIHSS (r=–0.56, *P*<0.001). An NIHSS score >15 also predicted functional prognosis (OR, 6.8; 95% CI, 3.4–1.4) but did not predict the risk of SHT. However, for the same ASPECTS, age (<78 vs. ≥78 years) appeared to predict functional prognosis (*P*=0.002), whereas the admission blood sugar (>10 vs. ≤10 mmol/L) predicted symptomatic cerebral hemorrhage (OR, 4.9; 95% CI, 1–21; *P*=0.032).

Hill et al., 2003

This study [3] retrospectively evaluated the CT-ASPECTS of patients in the PROACT-II clinical trial, which aimed to evaluate the effectiveness of prourokinase (vs. placebo) in the 6 h following cerebral infarction (average time to treatment was 5.3 h). Patients with a CT-ASPECTS >7 had a better functional prognosis on day 90 than those in the placebo group, whereas patients with a score ≤7 had the same functional prognosis as those in the placebo group.

Demchuk et al., 2005

We retrospectively analyzed the CT-ASPECTS of patients in the NINDS clinical trial to evaluate the efficacy of recombinant tissue plasminogen activator (rtPA) vs. placebo. This study [4] evaluated whether dichotomized CT-ASPECTS ≤7 or >7 could affect the functional prognosis 90 days post-rtPA treatment. It was shown that 48% of patients with a CT-ASPECTS >7 had an mRS ≤1 compared with 29% of those who had a score ≤7. Patients with a score between 3 and 7 had an improved functional prognosis (36% in the rtPA group vs. 23% in the placebo group; mRS ≤1). However, a reduction in mortality was noted only in the thrombolysis group with an ASPECTS <7 (12% vs. 18% in the placebo group).

3.4.2. CT-ASPECTS and TM

Therapeutic clinical trials: SWIFT PRIME, ESCAPE, REVASCAT, MR CLEAN, and EXTEND-IA,

2015

Four of the five randomized trials demonstrated the benefits of TM. Patients with CT-ASPECTS of <6 or 7 were excluded. These studies demonstrated the benefits of TM in patients with high CT-ASPECTS. The CT-ASPECT tool was used as one of the patient inclusion criteria across these clinical trials, with scores <6 being an exclusion criterion in some cases and scores <7 in others.

Cagnazzo et al., 2019 (meta-analysis)

Seventeen studies, with 1378 patients, were included to evaluate the functional prognosis at 3 months (mRS 0–2), HT risk, and mortality rate in patients who had benefitted from a revascularization procedure by TM versus medical treatment only, for ASPECTS from 0 to 6 (evaluated using CT or DWI-ASPECTS).

TM offered better results than medical treatment alone (OR, 4.76; *P*=0.01). Patients with an ASPECTS between 5 and 6 had comparable rates of favorable prognosis (37.7% and 33.3%, respectively). The mRS was favorable in 36.8% (OR, 5.3; 95% CI, 2.7–10). Mortality rates were 45% in the TM group and 51% in the IVT only group (*P*=0.8). Overall, 17.1% of the patients with an ASPECTS between 0 and 4 had an mRS between 0 and 2. A meta-analysis [6] showed that patients with ASPECTS between 0 and 6 benefited from TM. Successful TICI 2b-3 recanalization increased the likelihood of independence at 3 months without increasing the risk of HT (OR, 5.2; *P*=0.001). The mechanical TM group had a lower probability of developing SHT than the control group (OR, 0.48; *P*=0.06). Patients aged <70 years had higher frequency of mRS of 0–2 than those aged >70 years (40.3% vs. 16.2%). Patients with ASPECTS of 5–6 showed comparable results. TM can still allow approximately one in four patients with an ASPECTS of 4 to be independent, whereas only 14% of patients with an ASPECTS of 0–3 had a good functional prognosis.

HERMES meta-analysis, 2016

This study [7] included five clinical trials that evaluated the efficacy of TM (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA). The study conducted with 1287 patients, of whom 634 underwent TM with or without IVT and 653 received IVT alone. The primary endpoint of this meta-analysis was functional prognosis at 3 months using mRS, and the secondary endpoints were SHT and mortality. An mRS ≤2 was favorable in 46% for TM (OR, 2.35; *P*<0.01) vs. 26.5% for IVT. However, this technique cannot predict bleeding. TM was more robust, with an average delay of 300 min. The average delay for IVT was 3 h 16 min in patients who received IVT + TM. The hemorrhagic risk in this set was 4.4% in the TM group with or without IVT, and 4.3% in the control group, with an OR of 1.06 (95% CI, 0.62–1.83; *P*=0.81). The mortality rates were 15.3% vs. 18.9%, with an OR of 0.77 (95% CI, 0.51–1.26; *P*=0.16).

Roman et al., 2018

This meta-analysis [8] of seven randomized trials comparing TM and medical treatment showed that endovascular treatment offered a better functional prognosis at 90 days than medical treatment, even if the ASPECTS was <6. However, the risk of symptomatic intracranial hemorrhage was higher in these patients than in the placebo group.Comparison of DWI-ASPECT and CT-ASPECT

Currently, DWI-ASPECTS is frequently used in the acute care of patients and allows for the detection of early ischemic signs in the first few minutes of the diffusion sequence, whereas these signs appear later on CT scans [10]. Signs of early ischemia (effacement of the insular ribbon and discrete hypodensity) appear much later on CT than radiological signs of ischemia in the diffusion sequence.

McTaggart et al., 2014

This multicenter study [11] was conducted using the DEFUSE2 cohort to compare the performance of DWI-ASPECTS with that of double readings in predicting functional prognosis against CT-ASPECTS. The inter-individual correlation for reading scores was better for DWI-ASPECTS than for CT-ASPECTS (k at 0.74 for DWI vs. 0.46 for CT).

The trichotomized DWI-ASPECTS (0–4, 5–7, 8–10, with the majority between 8 and 10) had a much better ability to predict a favorable outcome (mRS ≤2) than CT-ASPECTS (53%, 27%, and 10%; *P*=0.004 vs. 39%, 37%, and 20%; *P*=0.534) which could be explained by an underestimation by CT-ASPECTS.

The correlation between the infarct volume and DWI-ASPECTS was more pronounced than that between the infarct volume and CT-ASPECTS. McTaggart et al. showed that the time between symptom onset and TM had no impact on functional prognosis. This is explained by the fact that the study included a small number of patients with ischemic volumes <70 mL, for whom ischemia was reversible in the early stages; however, this was not demonstrated in the DEFUSE2 study.

Nezu et al., 2010

This retrospective study [12] evaluated functional predictability at 3 months (mRS ≤2) as the primary outcome, and the risk of HT as the secondary outcome, in 477 patients who had been treated with rtPA (0.6 mg/kg alteplase). Among these patients, the median NIHSS score was 13, the median DWI-ASPECTS was 8, and SHT was identified in 3.1% of patients. Patients with mRS 0–2 had a higher median ASPECTS than other patients, with a shift of 1 point (9 vs. 8; *P*<0.001). The ASPECTS threshold for predicting an mRS of 0 to 2 was ≥7 (OR, 1.85; 95% CI, 1.07–3.24), an ASPECTS ≤4 was linked to death (OR, 3.61; 95% CI, 1.23–9.91), and an

ASPECTS ≤5 was linked to the risk of SHT (OR, 4.74; 95% CI, 1.54–13.64).

Nezu et al., 2011

This multicenter prospective observational study [13], conducted by the Japanese SAMURAI registry, compared the abilities of DWI-ASPECTS and CT-ASPECTS (double readings) to predict the risk of SHT within 36 h and functional prognosis within 3 months (mRS between 0 and 2) in 360 patients treated with alteplase (rtPA). This study showed the superiority of the inter-rater correlation of DWI-ASPECTS (k=0.818; *P*<0.001) compared with that of CT-ASPECTS (k=0.634; *P*<0.001). The higher the ASPECTS, the greater was the inter-rater agreement. The DWI-ASPECTS results were significantly and positively correlated with the CT-ASPECTS results; however, the correlation was weak (k=0.511; *P*<0.001). The area under the curve for predicting the risk of HT was 0.673 (95% CI, 0.603–0.807) for CT and 0.764 (95% CI, 0.635–0.858) for DWI (*P*=0.275). The area under the curve predicting independence at 3 months was 0.621 (0.564–0.674) for CT and 0.639 (0.580–0.694) for DWI (*P*=0.535).

Desilles et al., 2017

The authors prospectively conducted a combined study [14] by Rothschild and Foch from two registries of 959 patients treated with TM between 2012 and 2015. The goal of the study was to evaluate the impact of reperfusion in patients with a DWI-ASPECTS ≤6. Of the 218 patients with a DWI-ASPECTS ≤6, 145 underwent a recanalization (TM) procedure. Patients who benefited from the revascularization procedure had more favorable outcomes (38.7% vs. 17.1%; *P*=0.002) and reduced mortality at 3 months (22.5% vs. 39.1%; *P*=0.013) than those who were not reperfused. However, the rate of symptomatic intracranial hemorrhage was not significantly different between the two groups (13.0% vs. 14.1%; *P*=0.83). Nevertheless, in patients with a DWI-ASPECTS <5, the favorable outcome rate was poor (13% vs. 9.5%; *P*=0.68), with a high mortality rate (45.7 vs. 57.1%); *P*= 0.38). Therefore, the extent of the initial lesion should not be an exclusion criterion for TM, given the non-significant results for low ASPECTS.

3.4.3. ASPECTS-infarcted volume correlation

Margerie-Mellon et al., 2013

The authors conducted a prospective monocentric study [15] of 330 patients treated with IVT and TM who presented with IS in the MCA over 12 years. The DWI-ASPECTS was trichotomized (0–3, 4–6, and 7–10) and calculated independently by a neurologist and a neuroradiologist, with good inter-observer correlation. All patients with an ASPECTS between 0 and 3 had a large infarct volume, whereas all patients with a DWI-

ASPECTS >7 had an infarcted DWI volume <70 mL. The DWI-ASPECTS and the volume measured on a DWI sequence were strongly correlated (ρ=−0.82), but each calculated point corresponded to a large diffusion volume. All patients with a DWI-ASPECTS ≥7 had a volume <70 mL, whereas 32 of the 33 patients with a DWI-ASPECTS <4 had a volume >100 mL. However, intermediate DWI-ASPECTS (between 4 and 6) corresponded to highly variable ischemic volumes (median, 66 mL). The limitation of the ASPECTS lies in its intermediate scores, and the therapeutic approach and prediction of prognosis in this area are challenging . In such situations, volume measurements are more reliable.

Schröder et al., 2016

This study [16] showed that the same DWI-ASPECTS corresponded to very different infarcted volumes, possibly because the weighting of the scores in the cerebral territories was unequal between the superficial and deep territories. The DWI-ASPECTS can estimate the volume without calculations using MRI. While it can be reliable and serve as a substitute for extreme scores (<4 and >7), in cases of intermediate scores, it cannot replace diffusion volumetric measurements to identify eligible patients for revascularization therapy.

Schröder et al., 2014

This prospective observational study [17] showed that ASPECTS had limitations and was not correlated with the volume of deep lesions (r=- 0.19; *P*=0.038) compared with superficial lesions (r=- 0.72; *P*<0.001). Receiver operating characteristic curve analysis revealed that an ASPECTS ≤6 is the best threshold for identifying a DWI lesion volume ≥100 mL, but with a low negative predictive value (0.35). The volume varies greatly depending on the location of the infarct because more points may be lost over a small area deep within the brain compared to on the surface, owing to the spatial distribution of the structures involved.

Brieg Disseaux et al., 2022 (Brest University Hospital)

This retrospective study [18] used four readers to analyze emergency and follow-up scans one week apart to measure the relative cerebral blood volume (rCBV). It used perfusion imaging to measure perfusion volume using an rCVB perfusion scanner and a new model-based iterative reconstruction (MBIR). MBIR measures volume and compares it with that measured using reperfusion imaging.

3.5.5. Radiological criteria

Singer et al., 2009

In this multicenter retrospective study [22] of 217 patients, the aim was to evaluate the predictive value of the DWI-ASPECTS for the risk of HT, defined as a loss of 4 points on the NIHSS, in patients who presented with

an IS of the anterior circulation and were treated either with rtPA or a revascularization procedure within 6 h of the appearance of symptoms. The study variables were admission NIHSS score, manual volume measurement (ABC/2), blood pressure, and therapeutic approach, and the corresponding time frames. The DWI-ASPECTS correlated well with the lesion volume during diffusion (r=0.77; *P*<0.001, Spearman's test).

The inter-observer reliability of the DWI-ASPECTS assessed by two investigators was moderate (weighted kappa, 0.441; 95% CI, 0.373–0.509). The rate of SHT was significantly higher in patients with DWI-ASPECTS of 0–7 than in those with scores of 8–10 (*P*=0.004).

The risk of HT was 20.3%, 10%, and 2.6% for the 0–5, 6–7, and 8–10 groups, respectively. The DWI-ASPECTS remained an independent prognostic factor for SHT risk after adjusting for baseline clinical variables (age, NIHSS score, time from symptom onset, and thrombolysis).

The patients in this study were trichotomized in relation to the ASPECTS, with a category of 7–10 being considered more important. Only 69/217 patients had an ASPECTS of 0–5, which most often explains the correlation between small volumes and a high ASPECTS (7–10).

The risk of HT depends on the volume of the IS, and ASPECTS is used to assess the hemorrhagic risk in the acute phase because manual volumetric calculation is not practical in emergencies.

h and functional prognosis within 3 months (mRS between 0 and 2) in 360 patients treated with alteplase (rtPA). This study showed the superiority of the inter-rater correlation of DWI-ASPECTS (k=0.818; *P*<0.001) compared with that of CT-ASPECTS (k=0.634; *P*<0.001). The higher the ASPECTS, the greater was the inter-rater agreement. The DWI-ASPECTS results were significantly and positively correlated with the CT-ASPECTS results; however, the correlation was weak (k=0.511; *P*<0.001). The area under the curve for predicting the risk of HT was 0.673 (95% CI, 0.603–0.807) for CT and 0.764 (95% CI, 0.635–0.858) for DWI (*P*=0.275). The area under the curve predicting independence at 3 months was 0.621 (0.564–0.674) for CT and 0.639 (0.580–0.694) for DWI (*P*=0.535). Regardless of the therapeutic approach (thrombolysis and/or TM), patients benefited from follow-up CT imaging without contrast 24 h after treatment. A post-stroke consultation was conducted at 90 days by a neurology team that included a vascular neurologist or nurse specializing in IS, and the functional prognosis was evaluated according to the modified mRS.

5. DISCUSSION

It is important to note that we collected data from 16 patients who experienced SHT compared to the non-bleeding group, which was nearly 10 times larger, indicating significant heterogeneity. The search for predictive

factors of HT risk has been extensive. We provide the reader with only a descriptive overview of our dataset.

The definition of SHT used in our study was based on the ECASSII classification. The proportion of patients who experienced SHT within 7 days, excluding hemorrhagic deaths, was 2.4%, which is consistent with previous studies [7,12]. When hemorrhagic deaths were included in the dataset, the proportion increased to 9.7%.

An ASPECTS <7 has been described as having good sensitivity for predicting the risk of post-treatment HT in the MCA territory [1,30]. Since the advent of the ADC diffusion/mapping sequence, DWI-ASPECTS has been shown to be superior to CT-ASPECTS in the detection of early ischemic lesions from the first minute and in the best assessment of the extent of ischemia. It also provides better inter-reader correlation [13,17]. The DWI-ASPECTS was used in our study. To compensate for the margin of error in a single reading, we conducted double readings [9].

We did not exclude patients with DWI-ASPECTS, as has been done in many therapeutic trials. In our study, patients who presented with HT were homogeneously distributed according to the ASPECT trichotomization. All patients with an ASPECTS <5 had HT (PH2), while 66.7% of those with an ASPECTS of 5–6 had HT. Similarly, 80% of the patients with HT (PH2) had an ASPECTS >7. patients with HT have been found to have a low ASPECTS, which is in line with our data [5,6]. However, bleeding in patients with high ASPECTS did not correspond with that reported in the literature. Similarly, the group of non-bleeders in our series formed the majority, with 76.8% having an ASPECTS >7, which is in agreement with previous studies.

This inversion of the correlation between SHT and the ASPECTS in the bleeding patients' group could be explained by the low numbers or overestimation of the score, as our dataset was read twice by the same person; the average ASPECTS in this category was 8. A possible overestimation would not have influenced the subcategory if there had been a loss of 1 or 2 points [19].

This particularity can also be explained by the fact that the cerebral spatial distribution of the ASPECTS points is unequal between the deep (three points) and superficial (seven points) territories, thus underestimating the worsening of deep lesions [14,15].

The location of ischemia is crucial for prognosis because not all areas of the brain are functionally equivalent, which could explain the high ASPECTS with a poor prognosis. Hence, in literature, interventional and diagnostic neuroradiologists recommend associating the DWI-ASPECTS with volumetric quantification of ischemia in the diffusion sequence and/or on ADC mapping and measurement of the decrease of the ADC (significant and irreversible from the threshold $\leq 600\times10^{-6}$/mL) [15].

Without neglecting the intermediate ASPECTS (5–6), which poses a problem for the therapeutic approach in practice, in extreme cases, a lesion volume <70 mL corresponds to an ASPECTS >7 and a volume >100 mL corresponds to an ASPECTS <4 [17], whereas the intermediate ASPECTS correspond to very different volume variables and prognoses. Intermediate ASPECTS and overestimation of the ASPECTS could be associated with the DWI-ASPECTS volume measurement [18]. Statistical analyses of HT according to the ASPECTS, sociodemographic and radiological criteria, and the therapeutic approach to predict the risk of HT do not explain this risk due to the small sample size. Given the inhomogeneity in the number of the two groups, 16 vs. 149 (bleeders vs. non-bleeders and asymptomatic bleeders), we initially compared them. Second, all bleeders (n=36) were compared to non-bleeders. We noted a significant correlation between severe NIHSS score and the risk of HT as well as that of advanced age, which is frequently found in the literature [22,28].

We noted a trend toward the significance of moderate-to-severe leukopathy ≥2 (P=0.08), especially Fazekas 3 leukopathy, as found in the literature [23]. However, slow flow was present equally in both groups (77.8% in those who had HT vs. 62.8% in those who did not), whereas in the literature, the presence of collaterals indicated a better prognosis [24] because leptomeningeal replacements are associated with prolonged maintenance of the penumbra, leading to small ischemic volumes and better prognosis after treatment. The effectiveness of collaterality depends on the thrombus location, NIHSS score, time to treatment, correct therapeutic decision, age, and DWI/perfusion mismatch volume. Fibrinolysis alone was evenly distributed, and at 3–4.5 h, it was used in the majority of non-bleeders, with the timing of <3 h being more represented in non-bleeders [22]. This explains why technique and time are not predictive of bleeding [14,29]. Similarly, for TM alone, most studies were conducted within >6 h in non-bleeders [14].

Regarding the combined approach, nothing was found in our series, apart from the fact that a time-to-treatment of >6 h was observed more often in non-bleeders than in bleeders; however, they were successfully recanalized. Cohort studies and therapeutic trials on TM have found that the time-to-treatment does not influence the risk of HT and that TM has a good prognosis even with a low ASPECTS (<4) [14], and an increased probability of functional independence at 3 months without an increased risk of HT [6,11].

Our second primary criterion was death, and we observed 11 hemorrhagic deaths of the 16 SHT (9.6%); the majority were PH2. According to the therapeutic approach, there were 62.5% deaths for IVT vs. 6.25% (n=2/16) for TM. Severe leukopathy and slow flow were observed in all deaths.

According to a meta-analysis by Goyal et al. in 2018 [7], which focused on analyzing two groups: TM+/-IVT and IVT, mortality rates were 15.3% vs. 18.9% (P=0.15), respectively. A meta-analysis by Cagnazzo et al. [6]

including five studies, comprising 1,378 patients (TM and IVT groups), and excluding low ASPECTSs <6, found that mortality rates in the TM group was 45% vs. 51% in the IVT-only group (*P*=0.8).

Few patients underwent TMs during the 3 years of the study (n=48/165), with only one TM performed among the 11 deceased patients. The discordance between the presence of slow flows and few TMs led us to investigate TM indications, which could have been affected by the geographical location of the NRI centers (>1 h distance) between Saint-Brieuc and Rennes or Brest University Hospitals, as patients were sometimes not admitted due to the distance and transport logistics, with functional prognosis being impacted accordingly.

In the functional secondary endpoint evaluated using the mRS over a period of 90 days, the mRS was favorable for a high ASPECTS for the entire series. These results are consistent with those reported in the literature [6]. This inventory corresponded to high HT and death rates in the ASPECTS in our datasets, with the limitation of low descriptive numbers. The ASPECT tool needs to be evaluated in large cohorts, in two groups measuring the DWI-ASPECTS alone and measuring the ischemic volume using DWI-ASPECTS, to provide specificity and sensitivity to the ASPECT tool for more effective and precise therapeutic decisions and, consequently, a good functional prognosis.

6. CONCLUSION

The DWI-ASPECTS is a robust tool that is closely linked to age and NIHSS score to predict the risk of HT and functional prognosis in patients with low ASPECTS. This is not necessarily the case for intermediate and high DWI-ASPECTS. Hence, there is interest in combining it with multiple radiological examinations to reinforce its sensitivity and specificity, thus making acute-phase therapeutic decisions more convenient for neurologists.

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