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Predictive Factors for Intracranial Hemorrhage After Mechanical Thrombectomy in Acute Ischemic Stroke

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Dedication

This work is dedicated to my son, whose unwavering inspiration and boundless energy have driven my growth. You are my constant motivation, filling my life with wonder and purpose.

I am immensely grateful to my thesis mentor, Priv.-Doz. Dr. med. Marius Ringelstein, for his invaluable advice, guidance, and unwavering belief in my abilities. His support has been instrumental in shaping me into a better researcher.

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Finally, I express my heartfelt thanks to my family -especially my parents- whose unwavering support has been the foundation of my continuous growth. Without them, none of this would have been possible.

Summary (German)

Trotz des nachgewiesenen Vorteils der mechanischen Thrombektomie (MT) bei akutem ischämischem Schlaganfall erreicht ein erheblicher Anteil der Patienten keine funktionelle Unabhängigkeit, und die Sterblichkeitsrate bleibt hoch. Eine der schwerwiegendsten Komplikationen ist die symptomatische intrakranielle Blutung. Mehrere klinische und radiologische Faktoren konnten als Risikomarker identifiziert werden, wie die Zeit vom Auftreten der Symptome bis zur Rekanalisation, die Höhe des basalen Glukosespiegels, die Infarktgröße und die Anzahl der Rekanalisationsversuche. Trotz dieser Bemühungen ist das Auftreten von intrakraniellen Blutungen nach wie vor beachtlich. Das bei der MT verwendete Kontrastmittel ist bekanntermaßen neurotoxisch und kann zu fokalen neurologischen Symptomen, epileptischen Anfällen und kontrastmittelinduzierten Enzephalopathien führen. Obwohl der pathophysiologische Zusammenhang zwischen der Verwendung von Kontrastmitteln und intrakraniellen Blutungen bereits in der Ära der intraarteriellen Thrombolyse beschrieben wurde, ist er in der modernen Ära der Thrombektomie noch nicht umfassend untersucht worden.

Insgesamt wurden 236 Patienten analysiert, von denen 22 (9,3 %) eine symptomatische intrakranielle Blutung entwickelten. Logistische Regressionsmodelle ergaben, dass ein größeres Ausmaß des Infarkts (gemessen anhand des ASPECT-Scores) negativ mit einer symptomatischen intrakraniellen Blutung assoziiert war (OR 0,75, 95% CI 0,63-0,90, p=0,002), während eine größere Menge des verwendeten Kontrastmittels positiv assoziiert war (OR 1,13, 95% CI 1,02-1,25, p=0,02). Darüber hinaus war ASPECTS ≤6 mit einem erhöhten Risiko einer symptomatischen intrakraniellen Blutung im Vergleich zu ASPECTS >6 assoziiert (OR 3,67, 95% CI 1,06-12,79, p=0,04). Patienten, die eine hohe Kontrastmittelmenge (≥140 ml) erhielten, hatten ein signifikant höheres Risiko einer symptomatischen intrakraniellen Blutung im Vergleich zu denen mit einer niedrigen Kontrastmittelmenge (<140 ml) (OR 5,41, 95% CI 1,77-16,55, p=0,003).

Diese Ergebnisse deuten auf einen möglichen dosisabhängigen Zusammenhang zwischen Kontrastmittelgabe und sICH hin. Angesichts der Limitationen durch das retrospektive Design und die begrenzte Fallzahl sollten die Resultate in größeren, multizentrischen Studien validiert werden.

Summary (English)

Despite the positive effect of mechanical thrombectomy on functionality, quality of life, and reduced mortality in patients with acute ischemic stroke, approximately one-third of patients do not achieve a functional independence, and mortality rates remain high. Intracranial hemorrhage, particularly symptomatic intracranial hemorrhage, is the most feared complication. Efforts have been made to identify patients at higher risk of suffering an intracranial hemorrhage. Several clinical and radiological factors such as a symptom-onset-to-recanalization time, baseline glycemia, extensive infarction, and the number of recanalization attempts had been found to be associated with an increased risk. However, despite improvement of these factors, the occurrence of intracranial hemorrhages remains notably high. The contrast medium used during mechanical thrombectomy is known to be neurotoxic and can lead to focal neurological symptoms, epileptic seizures, and contrast-induced encephalopathies. Although the association between contrast use and intracranial hemorrhage had been described in the era of intraarterial thrombolysis, it has not been extensively investigated yet in the era of mechanical thrombectomy.

This retrospective, single-center study aims to reconfirm known risk factors associated with intracranial hemorrhage, but also to investigate other factors as well, with a particular focus on the amount of contrast medium used during the thrombectomy procedure.

A total of 236 patients who underwent mechanical thrombectomy were included, 22 (9.3%) of whom suffered a symptomatic intracranial hemorrhage. Logistic regression models revealed that a greater extent of infarction (measured by ASPECTS) was negatively associated with symptomatic intracranial hemorrhage (OR 0.75, 95% CI 0.63-0.90, *p*=0.002), while a greater amount of contrast medium used (measured as a continuous variable in ml) was positively associated (OR 1.13, 95% CI 1.02-1.25, p=0.02). Furthermore, ASPECTS ≤6 was associated with an increased risk of symptomatic intracranial hemorrhage compared to ASPECTS >6 (OR 3.67, 95% CI 1.06-12.79, p=0.04). Patients receiving a high contrast medium amount (≥140 ml) had a significantly higher bleeding risk compared to those with a low contrast medium amount (<140 ml) (OR 5.41, 95% CI 1.77-16.55, p=0.003). While the value of this study may be limited due to a relatively small sample size, it provides evidence of the association between contrast use and symptomatic intracranial hemorrhage in patients undergoing mechanical thrombectomy. This study should serve as a basis for future research, exploring this association in more detail using different populations and scenarios and with more rigorous control of the variables.

List of abbreviations

ACA	Anterior cerebral artery	**IRETAS**	Italian Registry of Endovascular Stroke Treatment in Acute Stroke
AIS	Acute Ischemic Stroke	**LVO**	Large-vessel occlusion
asICH	Asymptomatic intracranial hemorrhage	**MCA**	Media cerebral artery
ASPECTS	Alberta Stroke Program Early CT Score	**mRS**	Modified Rankin Score
BA	Basilar artery	**MT**	Mechanical thrombectomy
BBB	Blood-brain barrier	**NIHSS**	National Institutes of Health Stroke Scale
CIE	Contrast-induced Encephalopathy	**NINDS**	National Institute of Neurological Disorders and Stroke
CM	Contrast medium	**PCA**	Posterior cerebral artery
CrCl	Creatinine clearance	**PROACT**	Prolyse in Acute Cerebral Thromboembolism
CT	Computed tomography	**sICH**	Symptomatic intracranial hemorrhage
DM	Diabetes Mellitus	**SITS-MOST**	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
ECASS	European Cooperative Acute Stroke Study	**TAG**	TICI-ASPECTS-Glucose
EVF	Early Venous Filling	**TAGE**	TICI – ASPECTS – Glucose– Early Venous Filling
ICA	Internal carotid artery	**TICI**	Thrombolysis In Cerebral Infarction

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1 Introduction

In 2019 the incidence of ischemic stroke (IS) was 7.63 million (equivalent to 94.51 IS per 100,000 people), and the prevalence of stroke victims was 77.19 million globally (G. B. D. Stroke Collaborators, 2021). In relation to the prevalence of ischemic stroke in Europe, reliable data is currently unavailable; however, the combined worldwide prevalence of both hemorrhagic and ischemic strokes was reported to be 9.3 million cases in 2017 (Wafa et al., 2020). In the United States of America, approximately 795,000 persons are diagnosed with a new or recurrent stroke per year, and 87% of them are of the ischemic type.(Tsao et al., 2022) Acute Ischemic Stroke (AIS) is defined as an acute focal neurological symptom resulting from cerebral ischemia or necrosis due to abrupt occlusion of a cerebral vessel (Lee and Lee, 2020). According to the International Statistical Classification of Diseases and Related Health Problems (ICD-11), acute infarction can be diagnosed if either neurological symptoms persist for ≥24 hours or if neuroimaging demonstrates evidence of acute infarction (World Health Assembly, 2020).

AISs due to occlusion of large vessels (internal carotid artery (ICA), medial cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA) or basilar artery (BA)) are of essential importance since they involve greater loss of brain tissue and, consequently, more significant neurological deficits and worse functional outcomes. In a French population-based study, of all 971 registered AIS in five years, 284 (29.2%) had a proximal large vessel occlusion (LVO) (Duloquin et al., 2020). With the advent of mechanical thrombectomy (MT) the rapid detection of LVO infarcts is crucial. The positive impact of MT is unquestionable; in a meta-analysis of five randomized pivotal trials for mechanical thrombectomy, the number needed to treat to achieve one patient with reduced disability of at least one point in the modified Rankin Score (mRS) was 2.6.(Goyal et al., 2016) Nevertheless, 39% of the patients who underwent MT still had a poor functional outcome (mRS >2) and a mortality of 15%.(Goyal et al., 2016). This unsuccessful portion of patients may be due to the natural course of the disease or due to clinical, radiological, and interventional factors.

1.1 Intracranial Hemorrhage

Intracranial hemorrhage could be classified clinically (symptomatic vs. asymptomatic), radiologically (hemorrhagic infarct (HI) vs. parenchymal hemorrhage (PH)), or according to time of apparition (early vs. late) (Trouillas and von Kummer, 2006). The radiological evaluation of intracranial hemorrhages after recanalization therapies dates to the early 1990s and distinguished HI and PH) (Pessin et al., 1990, Maïer et al., 2020).

One of the most feared complications of MT is the symptomatic intracranial hemorrhage (sICH). There are several ways to determine if the intracranial hemorrhage is symptomatic,

and the rate of sICH varies according to the definition. The definitions of symptomatic intracranial hemorrhage were based on clinical trials of revascularization therapies in acute cerebral infarction. Levy et al. firstly introduced the concept of sICH in this context (Levy et al., 1994). In the NINDS (National Institute of Neurological Disorders and Stroke) trial (1995), sICH was defined as any evidence of hemorrhage on computed tomography (CT) associated with neurological deterioration within the first 36 hours after treatment initiation (National Institute of Neurological Disorders Stroke rt-PA Stroke Study Group, 1995). The PROACT II study defined neurological deterioration more precisely as an increase of ≥4 points in the NIHSS score, or worsening of one point in the level of consciousness within the first 24 hours of treatment (Furlan et al., 1999). Because the neurological deterioration in the NIHSS score may be due to other factors such as epilepsy, mass effect, and ischemic lesion growth, more recent studies specified symptomatic intracranial hemorrhage as the presumed responsible cause for neurological deterioration (Maïer et al., 2020, Hacke et al., 2008). The SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) definition of sICH is a local or remote parenchymal hemorrhage type 2 (PH-2) combined with a neurological deterioration of 4 or more points in the NIHSS score or leading to death (Wahlgren et al., 2007).

Recent data showed a rate of symptomatic intracranial hemorrhage after MT of 6% (van der Steen et al., 2022), but this rate varies considerably and ranges from 4-16% (Goyal et al., 2016, Mokin et al., 2019, Hao et al., 2017, Ospel et al., 2021, Venditti et al., 2021). Symptomatic intracranial hemorrhage in the present study was defined according to the European Cooperative Acute Stroke Study (ECASS) III as “apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of ≥4 points of the NIHSS score or that lead to death and that was identified as the predominant cause of the neurological deterioration” (Hacke et al., 2008).

Table 1 summarizes the different definitions of symptomatic intracranial hemorrhage.

Study	Year	Definition of symptomatic intracranial hemorrhage (sICH)
NINDS	1995	Any hemorrhage visible on CT scan associated with neurological deterioration within the first 36 hours after thrombolysis(National Institute of Neurological Disorders Stroke rt-PA Stroke Study Group, 1995)
PROACT II	1999	Neurological deterioration of ≥4 on the NIHSS with any evidence of hemorrhage (Furlan et al., 1999)
SITS-MOST	2007	local or remote PH-2 on the 22–36 hours post-treatment CT scan, combined with a neurological deterioration of ≥4 points on the NIHSS or leading to death (Wahlgren et al., 2007)
ECASS II	1995	blood at any site on the CT scan and clinical deterioration of ≥4 points on the NIHSS (Hacke et al., 1998)
ECASS III	2008	blood at any site on the CT scan associated with clinical deterioration (increase of ≥4 points of the NIHSS) or that lead to death and that was identified as the predominant cause of the neurological deterioration (Hacke et al., 2008)
CT: computed tomography, ECASS: European Cooperative Acute Stroke Study, NIHSS: National Institutes of Health Stroke Scale, PH-2: parenchymal hemorrhage type 2, PROACT II: Prolyse in Acute Cerebral Thromboembolism II, sICH: symptomatic intracranial hemorrhage, SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study		

Table 1. Definitions of symptomatic intracranial hemorrhage after recanalization therapies in acute ischemic stroke

Factors Associated with sICH after mechanical thrombectomy

Several factors have been associated with sICH, such as older age (Cappellari et al., 2019), renal impairment (Laible et al., 2019), high National Institutes of Health Stroke Scale (NIHSS) on admission (Cappellari et al., 2019), grade of recanalization (van der Steen et al., 2022, Cappellari et al., 2019, Montalvo et al., 2019), angiographic poor collateral status (van der Steen et al., 2022, Zhang et al., 2020b), baseline hyperglycemia (van der Steen et al., 2022, Montalvo et al., 2019, Zhang et al., 2020b), high systolic blood pressure (van der Steen et al., 2022), prior antiplatelet use (van der Steen et al., 2022), myocardial infarction (van der Steen et al., 2022), ICA occlusion (van der Steen et al., 2022), low Alberta Stroke Program Early CT Score (ASPECTS) (meaning greater infarct size) (Montalvo et al., 2019, Zhang et al., 2020b), number of passes with catheter to achieve recanalization (Zhang et al., 2020b), time from

symptom onset to groin puncture (Zhang et al., 2020b), and duration of the endovascular procedure (van der Steen et al., 2022).

Risk assessment for sICH

In an attempt to predict the risk of sICH after mechanical thrombectomy some predictive scores have been evaluated in patients after MT. Although some of these scores have been validated externally, they have not achieved generalizability, and their use in clinical practice is nearly null.

The Italian Registry of Endovascular Stroke Treatment in Acute Stroke (IRETAS) collected data prospectively from patients with LVO in anterior circulation who received MT from 2011 to 2016. After multivariate logistic regression, the nomogram (IER-SICH) was generated. The predictor factors for sICH were higher NIHSS score, long onset-to-end-procedure time, high age, unsuccessful recanalization (TICI <2b), and poor collateral status (Cappellari et al., 2019).

Montalvo et al. retrospectively analyzed patients in the United States of America with AIS who underwent MT. Clinical, radiological, and interventional variables were compared between the sICH-group and the non-sICH group. In the univariate analysis, basal glucose, lower ASPECTS, and unsuccessful recanalization (TICI <2b) were statistically different. In the regression analysis, these variables remained significant and were associated with sICH. The results were validated in another cohort, and the TAG (TICI-ASPECTS-Glucose) score was derived (Montalvo et al., 2019).

Another retrospective study was conducted in a Chinese population to investigate the factors influencing the risk of sICH in AIS. The study derived the ASIAN Score, composed of ASPECTS, baseline glucose, poor collateral circulation, number of passes with Retriever, and Onset-to-Groin time as predictors of bleeding in AIS patients (Zhang et al., 2020b).

Another study on a French population retrospectively analyzed several clinical and radiological variants. Time from symptom onset to recanalization, low ASPECTS, baseline glycemia ≥7 mmol/L, and early venous filling (EVF) (defined as an early opacification at the arterial phase of a cortical or deep vein, which presumably leads to hyperemia and a reperfusion injury) were associated with increased risk of symptomatic intracranial hemorrhage. The studies were validated with two other French cohorts. The score was called TAGE for Time of Onset to Recanalization – ASPECTS – Glycemia – EVF (Janvier et al., 2022).

In addition to optimizing current thrombectomy approaches and developing innovative interventional strategies, it is crucial to identify modifiable preclinical and periprocedural factors that can reduce the risk of sICH and improve functional outcomes.

1.2 Ethical clearance

The Ethics Committee of the Heinrich Heine University Faculty of Medicine received an ethics application. According to the Ethics Committee's statement, there are no ethical or legal concerns about implementing the planned retrospective pseudonymized study. The favorable vote with the number 2020-1131 was issued on September 9th, 2020.

1.3 Aim of Thesis

This retrospective study aims to identify predictive factors for a sICH in patients with acute ischemic stroke undergoing MT. We intended to confirm the already known factors for symptomatic intracranial hemorrhage and hoped to identify novel factors with the help of this analysis.

Instead of a full-text thesis, a recent paper authored by Promovendus in a peer-reviewed journal will be presented.

2 Contrast Neurotoxicity and its Association with Symptomatic Intracranial Hemorrhage After Mechanical Thrombectomy. Lopez-Navarro ER, Delfs C, Jarre A, Sanio V, Greif G, Gutierrez J, et al. Clin Neuroradiol. 2022.

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ORIGINAL ARTICLE

Contrast Neurotoxicity and its Association with Symptomatic Intracranial Hemorrhage After Mechanical Thrombectomy

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Abstract

Purpose Despite improved techniques and sophisticated postinterventional care, symptomatic intracranial hemorrhage (sICH) remains the most feared complication of mechanical thrombectomy (MT). Based on peri-interventional parameters, we aimed to discover which patients have a higher risk of sICH.

Methods From March 2017 until March 2020 consecutive patients with acute ischemic stroke (AIS) and confirmed large-vessel occlusion who underwent MT were analyzed retrospectively. Demographic, clinical, and radiological variables and parameters specific to thrombectomy were reviewed. A univariate analysis was performed and statistically significant variables were included in a logistic regression model to identify independent factors predictive of sICH.

Results A total of 236 patients with confirmed large-vessel occlusion were included and 22 (9.3%) had sICH. Univariate predictors of sICH included diabetes mellitus, glucose >11.1 mmol/L, creatinine clearance (CrCl) ≤30 ml/min/1.73, ASPECTS indicating pretreatment infarct size, acute internal carotid artery (ICA) occlusion, stent implantation, tirofiban use, time from symptom onset to groin puncture >4.5 h and high contrast medium consumption. In the adjusted analysis, ASPECTS <6 (OR 3.673, $p=0.041$), and amount of contrast injected ≥140 ml (OR 5.412, $p=0.003$) were independent predictors of sICH, but not any more baseline glucose >11.1 mmol/L (OR 1.467, $p=0.584$), CrCl ≤30 ml/min/1.73 (OR 4.177, $p=0.069$), acute ICA occlusion (OR 2.079, $p=0.181$), stent implantation (OR 0.465, $p=0.512$), tirofiban use (OR 5.164, $p=0.167$), and time from onset-to-groin puncture (OR 1.453, $p=0.514$).

Conclusion The amount of contrast medium used is a modifiable factor associated with sICH. This association is novel and may be related to the neurotoxicity of the contrast medium disrupting the blood-brain barrier.

Keywords Risk factors · Logistic models · Stroke · Contrast medium · Endovascular therapy

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Abbreviations

AIS	Acute ischemic stroke
ASIAN	Alberta Stroke Program Early CT Score, Baseline Glucose, Poor Collateral Circulation, Passes with Retriever and Onset-to-Groin Puncture Time
ASPECTS	Alberta Stroke Program Early CT Score
CIE	Contrast-induced encephalopathy
CM	Contrast medium
CrCl	Creatinine clearance
ICA	Internal carotid artery
LVO	Large vessel occlusion
MT	Mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
SAVE	Stent retriever assisted vacuum-locked extraction
sICH	Symptomatic intracranial hemorrhage
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAG	Thrombolysis in Cerebral Ischemia Score, Alberta Stroke Program Early CT Score, and Glucose Level.

Introduction

In real-world practice, the rate of symptomatic intracranial hemorrhage (sICH) after mechanical thrombectomy (MT) varies from 4% to 16% [1–4]. Several factors have been associated with sICH, such as older age [5, 6], high glucose levels [7, 8], low Alberta Stroke Program Early CT Score (ASPECTS) [5, 7, 8], high National Institutes of Health Stroke Scale (NIHSS) on admission [6], grade of recanalization [6, 7], angiographic poor collaterals [5, 8], treatment with intra-arterial thrombolytics (GPIIb/IIIa inhibitor) [9], and renal impairment [10]. Given the severe short-term and long-term consequences of sICH, including higher mortality [2], it is essential to identify modifiable factors associated with the risk of sICH to optimize current procedures.

The administration of iodine-containing contrast media (CM) in radiological interventions is related to adverse reactions, such as transient cortical blindness (most common), transient focal neurological deficits, seizures [11], and in some instances, cerebral edema [12] and death [13]. These manifestations are also known as contrast-induced encephalopathy (CIE), which has primarily been studied in patients undergoing coronary angiography [11], and it can radiologically mimic subarachnoid hemorrhage [11, 14, 15]. CIE is a rare condition during neuroradiological interventions with an incidence as low as 0.38% [16]. CIE was also observed after MT: out of 421 patients who underwent this procedure, CIE was seen in 7 patients (1.7%) [17]. Contrast extravasation (CE) indicates blood-brain barrier damage [18] and has been reported as an independent risk factor of hemorrhagic transformation and poor outcome after MT [19]. Prior to the MT era, a study in acute ischemic stroke (AIS) and intra-arterial thrombolysis with recombinant tissue plasminogen activator (rtPA) showed that contrast injection through the microcatheter was associated with intracranial hemorrhage. The higher the number of injections via the microcatheter, the higher the intracranial bleeding rate, suggesting a dose-dependent effect [20]. The elimination of contrast medium by renal excretion is delayed in patients with renal failure. Delayed excretion causes a greater exposure of the BBB to CM, contributing again to a vicious circle with greater BBB permeability and increased risk of sICH.

However, the role of CM dosage during MT and its impact on the risk of sICH has not been well established.

Material and Methods

Data collection and retrospective analysis was approved by the ethic committee of the Heinrich-Heine-University Düsseldorf (2020-1131). We used the STROBE case-control checklist [21]. We retrospectively analyzed all patient files with AIS and proximal large vessel occlusion (LVO) on the computed tomography (CT) or magnetic resonance (MR) angiogram who underwent MT in our institution (Kliniken Maria Hilf) between March 2017 and March 2020. Patients with symptom onset within 24 h from the last known normal time and follow-up imaging within 36 h after thrombectomy were included. Patients with symptom onset within 4.5 h before admission and without any contraindications to thrombolysis were primarily treated with intravenous alteplase according to national [22] and international guidelines [23].

For diagnostic CT-Angiography (CT-A), all patients received a 60 ml bolus of the non-ionized contrast medium Iomeprol. For CT-Perfusion (CT-P) imaging, a dose of 40 ml of the same contrast medium was given.

During the study period 263 acute ischemic stroke patients with LVO were diagnosed, out of which 236 patients were included in this study. Reasons for exclusion were lack of follow-up CT imaging or MRI within 36 h after thrombectomy, spontaneous recanalization, recanalization due to thrombolysis before thrombectomy, or early death before control imaging (Fig. 1).

Mechanical Thrombectomy

The MT was performed by an experienced neuroradiologist (AR) or by a neuroradiologist in training under the experienced neuroradiologists' supervision. The MT was performed with the direct aspiration first pass technique

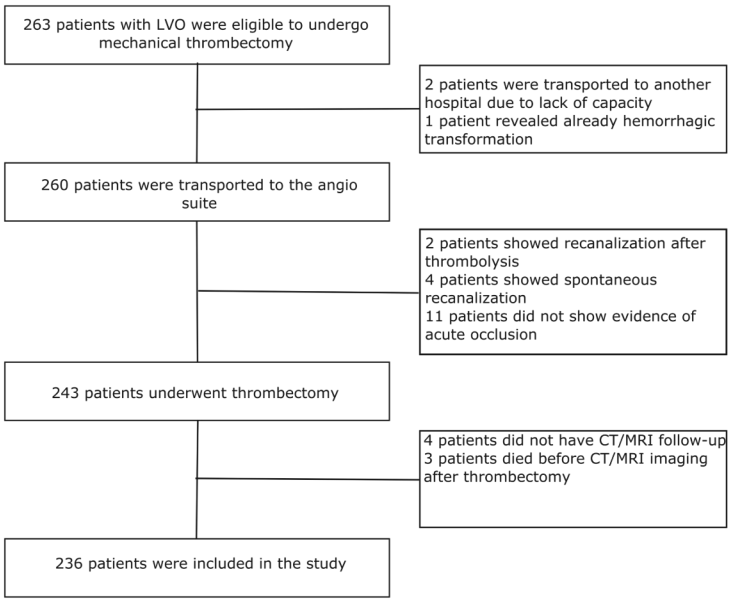

Fig. 1 Flow chart of patients who were eligible for mechanical thrombectomy between March 2017 and March 2020. *CT* computed tomography, *LVO* large-vessel occlusion, *MRI* magnetic resonance imaging

(ADAPT), rarely with a stent retriever alone, or mainly with the stent retriever-assisted, vacuum-locked extraction (SAVE) technique. If the ipsilateral internal carotid artery (ICA) was occluded, the decision of carotid stent implantation and the use of an intra-arterial antiplatelet agent (tirofiban) was left to the judgment of the treating neuroradiologist. For the MT the contrast medium Iomeprol with 350 mg iodine/ml (Imeron 350®, Bracco Imaging Deutschland GmbH, Konstanz, Germany) was used. Iomeprol is a non-ionic iodinated and low-osmolar (618 mosmol/kg) contrast agent. The contrast medium was administered via the guide catheter. During thrombectomy with a stent retriever, a super-selective angiogram was additionally performed with the help of a microcatheter.

Data Collection and Variables

We analyzed age and sex as demographic variables, and history of diabetes mellitus, arterial hypertension, atrial fibrillation, and stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) as clinical variables. The laboratory variables considered were blood glucose, hemoglobin, white blood cell count, platelet count, creatinine, creatinine clearance, and international normalized ratio (INR). We also considered the medication prior to admission, particularly the use of antiplatelet agents (yes or no; and if yes, monotherapy or dual therapy) and oral anticoagulants. The radiological variables were the size of the pretreatment infarction core measured with ASPECTS [24] for anterior circulation stroke and pc-ASPECTS [25] for posterior circulation infarcts, the site of occlusion (internal carotid artery, anterior cerebral artery, M1 or M2 segment of the middle cerebral artery, posterior cerebral artery or basilar artery) and time from symptom onset to groin puncture. After the procedure, the reperfusion rate was evaluated with the modified thrombolysis in cerebral infarction (mTICI) score [26]. In addition, the door to groin time and the amount (ml) of contrast agent administered during MT and for diagnostic CTA and CT perfusion were evaluated.

Symptomatic Intracranial Hemorrhage

A sICH was defined according to the European Cooperative Acute Stroke Study (ECASS) III as "apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of ≥4 points of the NIHSS score or that lead to death and that was identified as the predominant cause of the neurological deterioration" [27]. The clinical diagnosis of sICH was made by the treating physician and confirmed by a stroke neurologist.

Statistical Analysis

The statistical analysis was performed with SPSS software Version 27 (IBM Corp, Armonk, NY, USA). Shapiro-Wilk test was used to check for normal distribution. Differences between the groups were analyzed with the Mann-Whitney U-test for continuous variables without normal distribution, and t-test was used for continuous variables with normal distribution. For categorical variables, x^2 test or Fisher's exact test was used. *P* values <0.05 were considered statistically significant. For statistically significant variables, binary logistic regression models were applied.

Results

A total of 236 patients were included in the final study analysis. The mean age at AIS was 73 ± 13 years (range 23–99 years), and 134 (56.8%) were women. 22 patients (9.3%) had post-MT sICH. 189 patients (80.1%) underwent CT-A as a diagnostic tool; 87 (36.9%) received a CT-P additionally. In 47 patients (19.9%), an MRI was performed before MT. The median dose of contrast used during MT was 42 ml in the non-sICH group and 73.5 ml in the sICH group, $p = < 0.001$. The total median contrast applied for diagnostic (CT-A with or without CT-P) plus contrast amount used in the MT was 118 ml in the non-sICH group and 160 ml in the sICH group, $p = 0.001$.

The mean number of passes, which refers to the number of attempts to recanalize the occluded vessel, with available data of 134 (57%) patients, was 2.04 (standard deviation, SD ± 1.35). Subgroup analyses revealed that the non-sICH group had a mean of 1.95 passes (SD ± 1.29), and the sICH group of 2.80 passes (SD ± 1.61, $p = 0.018$). The difference between the two groups was statistically significant and is worth considering for further considerations; however, since the available data only corresponded to 57% of the total cohort, we decided not to include them in the final statistical analyses.

In univariate analysis, variables associated with sICH included history of diabetes mellitus (36.4% vs. 17.8%, $p = 0.036$), blood glucose >11.1 mmol/L on admission (22.7% vs. 7.5%, $p = 0.033$), CrCl ≤30 (18.2% vs. 5.6%, $p = 0.025$), ASPECTS (median 7 vs. 9, $p = 0.008$), ASPECTS dichotomized ≤6 (45.5% vs. 17.3%, $p = 0.002$), acute ICA occlusion (50% vs. 25.2%, $p = 0.013$), carotid stent implantation (31.8% vs. 14%, $p = 0.029$), tirofiban use (27.3% vs. 8.4%, $p = 0.005$), time from onset-to-groin >4.5 h (36.4% vs. 16.2%, $p = 0.021$) and total volume of contrast medium administered for diagnostic imaging and during MT (median 160 ml vs. 118 ml, $p = 0.001$), as well as total volume of contrast medium administered only during the MT procedure (median 73.5 ml vs. 42 ml, $p = < 0.001$) (Table 1).

Because of the wide overlap between baseline glucose >11.1 mmol/L and diabetes mellitus, we arbitrarily decided to include only baseline glucose >11.1 mmol/L for the subsequent regression analysis. We could not document the number of maneuvers to achieve reperfusion in all patients, but the median time of the duration of MT in the non sICH group was 34 min vs. 48.5 min in the sICH group, $p = 0.003$.

Variables with a *P* value of <0.05 in the univariate analysis were included in the multivariable logistic regression model (Table 2). Model 1 included ASPECTS and CM amount as continuous variables: baseline glucose >11.1 mmol/L (OR 1.401, 95% CI 0.354–5.540, $p = 0.630$), CrCl ≤30 ml/min/1.73 (OR 4.445, 95% CI 0.969–20.391, $p = 0.055$), ASPECTS (OR 0.749, 95% CI 0.625–0.899, $p = 0.002$), acute ICA occlusion (OR 1.529, 95% CI 0.511–4.578, $p = 0.448$), stent implantation (OR 0.475, 95% CI 0.045–4.964, $p = 0.534$), tirofiban use (OR 6.750, 95% CI 0.615–74.134, $p = 0.118$), time from onset-to-groin >4.5 h (OR 1.121, 95% CI 0.317–3.964, $p = 0.859$), and amount of CM used (OR 1.129, 95% CI 1.019–1.250, $p = 0.020$).

In model 2, ASPECTS score and contrast media amount were dichotomized (ASPECTS <6 or ≥6 and contrast media with a predefined cut-off of ≥140 ml) with the following results:

baseline glucose >11.1 mmol/L (OR 1.467, 95% CI 0.373–5.775, $p = 0.584$), CrCl ≤30 ml/min/1.73 (OR 4.177, 95% CI 0.894–19.528, $p = 0.069$), acute ICA occlusion (OR 2.079, 95% CI 0.711–6. 079, $p = 0.181$), stent implantation (OR 0.465, 95% CI 0.047–5.576, $p = 0.512$), and tirofiban use (OR 5.164, 95% CI 0.505–52.863, $p = 0.167$) were no longer significant, whereas ASPECTS <6 (OR 3.673, 95% CI 1.055–12.792, $p = 0.041$), CM amount ≥140 ml (5.412, 95% CI 1.770–16.551, $p = 0.003$) were still significantly associated with sICH.

In a model where only the contrast medium used during MT (per 10 ml) is taken into account, its association with the risk of sICH remained significant (OR 1.445 95% CI 1.028–1.275, $p = 0.014$).

In summary, according to the logistic regression, ASPECTS ≤6 and procedural contrast media dose ≥140 ml were independent predictors of sICH in our cohort.

Discussion

Following acute ischemic stroke, hemorrhagic transformation of the brain parenchyma is multifactorial and, in some cases, represents part of the natural history of reperfusion and the ischemic process per se [18]. Disruption of the BBB after reperfusion treatment is associated with hemorrhagic transformation [28] but may even lead to pronounced intracerebral bleeding. Which modifiable factors play a role

Table 1 Univariate analysis of demographic, clinical and radiological variables

	No sICH *n* = 214	sICH *n* = 22	*P* value
Sex (% women)	118 (55.1%)	16 (72.7%)	0.113
Age (years, mean, SD)	73.1 (±13.6)	71.8 (±14.3)	0.831
Diabetes mellitus (%)	38 (17.8%)	8 (36.4%)	**0.036**
Arterial hypertension (%)	163 (76.2%)	18 (81.8%)	0.791
Atrial fibrillation (%)	72 (36.3%)	10 (45.5%)	0.268
Baseline glucose mmol/L (mean, SD)	7.5 (±2.8)	8.8 (±4.3)	0.373
Glucose ≥ 11.1 mmol/L (%)	16 (7.5%)	5 (22.7%)	**0.033**
WBC count K/ml (mean, SD)	9.16 (±3.28)	9.24 (±3.25)	0.607
Hemoglobin g/dl (mean, SD)	13.3 (±1.8)	12.4 (±2.7)	0.086
Creatinine µmol/L (median, IQR)	89.30 (71.62–115.17)	84.44 (69.63–123.12)	0.871
CrCl ml/min/1.73 (mean, SD)	63.56 (±22.22)	60.05 (±31.99)	0.621
CrCl ≤ 30 ml/min/1.73 (%)	12 (5.6%)	4 (18.2%)	**0.049**
INR (median, IQR)	1.0 (0.99–1.08)	1.05 (0.99–1.27)	0.404
Platelets × 10^9/L (mean, SD)	265.7 (±96.1)	252.5 (±76.6)	0.835
Antiplatelet therapy (%)	67 (31.3%)	6 (27.3%)	0.697
Dual antiplatelet therapy (%)	6 (2.8%)	2 (9.1%)	0.165
Anticoagulation (%)	47 (22%)	7 (31.8%)	0.295
NIHSS (median, IQR)	13.5 (8–19)	14 (7.5–17.8)	0.931
CT-Angiogram	171 (79.9%)	18 (81.8%)	> 0.999
CT-Perfusion	75 (35%)	12 (54.5%)	0.071
ASPECTS (median, IQR)	9 (7–10)	7 (5–9)	**0.008**
ASPECTS ≤ 6 (%)	37 (17.3%)	10 (45.5%)	**0.002**
ICA occlusion (%)	54 (25.2%)	11 (50%)	**0.013**
M1 occlusion (%)	102 (47.7%)	6 (27.3%)	0.068
M2 occlusion (%)	64 (29.9%)	11 (50%)	0.054
BA occlusion (%)	18 (8.4%)	0 (0%)	0.388
ACA occlusion (%)	5 (2.3%)	0 (0%)	> 0.999
PCA occlusion (%)	8 (3.7%)	1 (4.5%)	0.592
Tandem occlusion (%)	32 (15%)	6 (27.3%)	0.134
tPA thrombolysis (%)	116 (54.2%)	8 (36.4%)	0.111
Time from onset-to-groin puncture > 4.5 h	35 (16.2%)	8 (36.4%)	**0.021**
Door-to-groin time (min) (median, IQR) [a]	85 (72–104)	84 (63.5–116)	0.841
Length of Procedure (min) (median, IQR) [b]	34 (19–63)	48.5 (33.75–111.75)	**0.003**
TICI Score (mean, SD)	4 (±1.5)	4 (±1.3)	0.129
TICI ≥ 2b (%)	186 (86.9%)	19 (86.4%)	> 0.999
Stent implantation (%)	30 (14%)	7 (31.8%)	**0.029**
Tirofiban (%)	18 (8.4%)	6 (27.3%)	**0.005**
CM dosage (ml) (median, IQR)	42 (28–70)	73.5 (52.5–112)	**< 0.001**
CM total (diagnostic + MT) (ml) (median, IQR)	118 (81–142)	160 (134–195)	**0.001**
CM dosage ≥ 140 ml (%)	57 (34.6%)	16 (72.7%)	**< 0.001**

ACA anterior cerebral artery, *ASPECTS* Alberta Stroke Program Early CT Score, *BA* basilar artery, *CM* contrast medium, *CrCl* creatinine clearance, *ICA* internal carotid artery, *INR* international normalized ratio, *IQR* interquartile range, *M1* M1 segment of the medial cerebral artery, *M2* M2 segment of the medial cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *PCA* posterior cerebral artery, *sICH* symptomatic intracranial hemorrhage, *TICI* thrombolysis in cerebral infarction, *tPA* tissue plasminogen activator, *WBC* white blood cell count

[a]Data from 201 patients (184 no sICH, 17 sICH)

[b]Data from 235 patients (213 no sICH, 22 sICH)

Table 2 Regression model with continuous and categorical independent variables and symptomatic intracranial hemorrhage

		Multiple regression model			
		Regression coefficient	SE	OR (95% CI)	*P* Value
Model 1	Glucose ≥ 11.1 mmol/L	0.337	0.701	1.401 (0.354–5.540)	0.630
	CrCl ≤ 30 ml/min/1.73	1.492	0.777	4.445 (0.969–20.391)	0.055
	ASPECTS	–0.289	0.093	0.749 (0.625–0.899)	**0.002**
	ICA occlusion	0.425	0.559	1.529 (0.511–4.578)	0.448
	Stent implantation	–0.745	1.197	0.475 (0.045–4.964)	0.534
	Tirofiban	1.909	1.223	6.750 (0.615–74.134)	0.118
	Time from onset-to-groin > 4.5 h	0.114	0.664	1.121 (0.137–3.964)	0.859
	CM amount (per 10 ml)	0.121	0.052	1.129 (1.019–1.250)	**0.020**
Model 2	Glucose ≥ 11.1 mmol/L	0.383	0.699	1.467 (0.373–5.775)	0.584
	CrCl ≤ 30 ml/min/1.73	1.430	0.787	4.177 (0.894–19.528)	0.069
	ASPECTS ≤ 6	1.301	0.637	3.673 (1.055–12.792)	**0.041**
	ICA occlusion	0.732	0.547	2.079 (0.711–6.079)	0.181
	Stent implantation	–0.765	1.166	0.465 (0.047–4.576)	0.512
	Tirofiban	1.642	1.187	5.164 (0.505–52.863)	0.167
	Time from onset-to-groin > 4.5 h	0.374	0.573	1.453 (0.472–4.470)	0.514
	CM dosage ≥ 140 ml	1.689	0.570	5.412 (1.770–16.551)	**0.003**

ASPECTS Alberta Stroke Program Early CT Score, *CM* contrast medium, *CrCl* creatinine clearance, *ICA* internal carotid artery

in sICH is not entirely clear but identifying these factors could reduce the risk of sICH and its associated morbidity and mortality. In particular, the abrupt increase in perfusion pressure following MT may lead to a reperfusion injury enhancing tissue damage [18, 29]. Another intriguing risk factor appears to be the amount of CM given during the MT procedure. This study reports an independent association between CM amounts ≥ 140 ml and sICH. In addition, we replicated the impact of several known predictors of sICH.

Contrast media are considered neurotoxic since they increase the BBB permeability due to their toxic effect on the basal lamina [18]. Contrast media neurotoxicity is thought to be due to their hyperosmolarity compared to blood. Non-ionized CM have less osmolarity than ionized ones. Due to their safer profile, non-ionized CM are preferred for most radiological interventions. Intra-arterial hyperosmolar solutions cause the exit of water from the endothelial cells, thus opening the tight junctions and allowing BBB damage [30]; however, a study in rabbits demonstrated greater BBB permeability with non-ionized CM than with mannitol, the osmolarity of which is twice that of the CM, suggesting that BBB damage occurs mainly due to their chemotoxic properties rather than due to hyperosmolarity [31]. Moreover, some evidence suggests that contrast-induced adverse reactions are related to injection dosage and speed. Patients with injection doses ≥ 100 ml and an injection speed of ≥ 5 ml/s were at higher risk of experiencing contrast-induced adverse reactions [32]. Although Kathri et al. demonstrated an association between higher numbers of contrast injections via microcatheter and intracranial hemorrhage, they could not demonstrate an association with the total dose of CM applied [20]. Therefore, our study adds a novel aspect regarding the CM used during MT and its association with sICH.

In animal studies, hyperglycemia has been associated with more extensive cerebral infarction, severe BBB disruption, and greater hemorrhagic transformation than normoglycemia [33]; however, unlike other studies in which baseline glucose was an independent predictor for sICH (such as the ASIAN score [8] or TAG score [7]), we were not able to prove baseline glucose as an independent predictive factor of sICH; however, in the univariate analysis, a subgroup with admission glucose ≥ 11.1 mmol/l showed a statistically significant increase in bleeding complications but statistical significance could not be replicated in the logistic regression.

Lower ASPECTS (≤ 6) is another well-known predictive factor for sICH and our findings are in concordance with previous studies [5, 7, 8].

Amazingly, incomplete reperfusion (TICI score < 2b) was not associated with sICH in the present study. A possible explanation for the lack of association in our study may relate to the low rates of incomplete reperfusion in both groups (13.6% vs. 13.1% in patients with and without sICH, respectively) as compared to the TAG score derivation study, where the incomplete reperfusion rates were much higher (15.3% in the no sICH group vs. 47.4% in the sICH group) [7].

We can deduce that patients with large cerebral infarcts leading to a severe disruption of the BBB, combined with high doses of CM for diagnostic and procedural purposes,

are at particular risk of sICH because both these factors potentiate their damaging effect.

Based on our results, we hypothesize that patients with large cerebral infarction (ASPECTS ≤ 6) and high amounts of CM used during MT are at higher risk of sICH.

The group of sICH, as shown in Table 1, had higher glucose levels at presentation, had more frequent renal failure (measured by CrCl ≤ 30 ml/min/1.73), had lower ASPECT scores, and had more ICA occlusions. Those patients with ICA occlusion received an ICA stent and were treated with tirofiban post-procedurally, and the time from onset to groin puncture was > 4.5 h. One explanation why the sICH group received more CM is that these patients underwent significantly more stent implantations than the non-sICH group, and this intervention directly implies more lengthy procedures.

Limitations of our study include its relatively small sample size and retrospective, single-center design. We could not accurately document the time from onset to groin in an ordinal manner, only as categorical variable as (> or < 4.5 h), and the number of passes during MT to achieve reperfusion. The generalizability of our results without these details could be limited, and even though our sICH ranges are consistent with other publications [2, 4, 8], our results should be interpreted carefully. Since there is only evidence that microcatheter injections of CM are associated with intracranial hemorrhage, and no studies compared the CM amount with the incidence of sICH so far, it is impossible to reliably generate a cut-off value beyond the risk of sICH increases. The cut-off value we used (≥ 140 ml) was arbitrarily predefined. It is well-known that not all of the CM used is administered entirely to the patient; for example, some milliliters will be discarded when mixed with blood, and the difficulty of precisely measuring the amount of CM administered is also a limitation to consider. We do not include the number of passes or maneuvers in the statistical analysis because this information was only available in 57% of the cohort population.

Another point to consider is that in patients with more complicated interventions, the procedure takes longer. This is precisely the case in our study, where the procedures in the sICH group were significantly longer ($p = 0.003$), implying more maneuvers (passes) to achieve reperfusion and a more significant amount of CM complicating the interaction of adverse factors. Logically, the more passes for reperfusion are needed, the greater the amount of CM administered.

The collateral status is another important point that could not be evaluated in this retrospective study but should be considered in future prospective clinical trials since there is evidence that good collaterals are associated with decreased rates of sICH [34].

A crucial question for future clinical trials is whether the number of maneuvers needed for recanalization primarily facilitates intracranial bleeding due to mechanical side effects of the catheter leading to endothelial injury or whether the amount of CM favors intracranial bleeding as the main culprit.

Our study shows a clear association between the amount of CM used during MT with sICH, especially in patients with large infarcts.

Our main findings may also be of scientific relevance in that they could stimulate researchers to investigate the toxic role of CM during MT prospectively.

Summary

Although the scientific value of this study could be limited due to the small sample size, retrospective design, and lack of control of all potentially relevant factors, our study shows some evidence that the administration of CM should be carefully controlled both in the diagnostic and therapeutic part in patients with AIS.

This paper provides evidence that the amount of CM used during MT impacts the risk of sICH after that. Stroke teams should be aware that the dose of CM is an independent risk factor for sICH. More validation studies are necessary to clarify prospectively what amount of CM could be used safely in order to avoid intracranial hemorrhage after MT.

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References

1. Mokin M, Abou-Chebl A, Castonguay AC, Nogueira RG, English JD, Farid H, Gupta R, Martin C, Holloway WE, Haussen DC,

Mueller-Kronast N, Zaidat OO; NASA and TRACK investigators. Real-world stent retriever thrombectomy for acute ischemic stroke beyond 6 hours of onset: analysis of the NASA and TRACK registries. J Neurointerv Surg. 2019;11:334–7.
2. Hao Y, Yang D, Wang H, Zi W, Zhang M, Geng Y, Zhou Z, Wang W, Xu H, Tian X, Lv P, Liu Y, Xiong Y, Liu X, Xu G; ACTUAL Investigators (Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry). Predictors for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of Acute Ischemic Stroke. Stroke. 2017;48:1203–9.
3. Ospel JM, Qiu W, Menon BK, Mayank A, Demchuk A, McTaggart R, Nogueira RG, Poppe AY, Jayaraman M, Buck B, Haussen D, Roy D, Joshi M, Zerna C, Almekhlafi M, Tymianski M, Hill MD, Goyal M; ESCAPE-NA1 Investigators. Radiologic Patterns of Intracranial Hemorrhage and Clinical Outcome after Endovascular Treatment in Acute Ischemic Stroke: Results from the ESCAPE-NA1 Trial. Radiology. 2021;300:402–9.
4. Venditti L, Chassin O, Ancelet C, Legris N, Sarov M, Lapergue B, Mihalea C, Ozanne A, Gallas S, Cortese J, Chalumeau V, Ikka L, Caroff J, Labreuche J, Spelle L, Denier C. Pre-procedural predictive factors of symptomatic intracranial hemorrhage after thrombectomy in stroke. J Neurol. 2021;268:1867–75.
5. Boisseau W, Fahed R, Lapergue B, Desilles JP, Zuber K, Khoury N, Garcia J, Maïer B, Redjem H, Ciccio G, Smajda S, Escalard S, Taylor G, Mazighi M, Michel P, Gory B, Blanc R; ETIS Investigators. Predictors of Parenchymal Hematoma After Mechanical Thrombectomy: A Multicenter Study. Stroke. 2019;50:2364–70.
6. Cappellari M, Mangiafico S, Saia V, Pracucci G, Nappini S, Nencini P, Konda D, Sallustio F, Vallone S, Zini A, Bracco S, Tassi R, Bergui M, Cerrato P, Pitrone A, Grillo F, Saletti A, De Vito A, Gasparotti R, Magoni M, Puglielli E, Casalena A, Causin F, Baracchini C, Castellan L, Malfatto L, Menozzi R, Scoditti U, Comelli C, Duc E, Comai A, Franchini E, Cosottini M, Mancuso M, Peschillo S, De Michele M, Giorgianni A, Delodovici ML, Lafe E, Denaro MF, Burdi N, Internò S, Cavasin N, Critelli A, Chiumarulo L, Petruzzellis M, Doddi M, Carolei A, Auteri W, Petrone A, Padolecchia R, Tassinari T, Pavia M, Invernizzi P, Turcato G, Forlivesi S, Ciceri EFM, Bonetti B, Inzitari D, Toni D; Listing of IER Collaborators. IER-SICH Nomogram to Predict Symptomatic Intracerebral Hemorrhage After Thrombectomy for Stroke. Stroke. 2019;50:909–16. Erratum in: Stroke. 2019;50:e341.
7. Montalvo M, Mistry E, Chang AD, Yakhkind A, Dakay K, Azher I, Kaushal A, Mistry A, Chitale R, Cutting S, Burton T, Mac Grory B, Reznik M, Mahta A, Thompson BB, Ishida K, Frontera J, Riina HA, Gordon D, Parella D, Scher E, Farkas J, McTaggart R, Khatri P, Furie KL, Jayaraman M, Yaghi S. Predicting symptomatic intracranial haemorrhage after mechanical thrombectomy: the TAG score. J Neurol Neurosurg Psychiatry. 2019;90:1370–4.
8. Zhang X, Xie Y, Wang H, Yang D, Jiang T, Yuan K, Gong P, Xu P, Li Y, Chen J, Wu M, Sheng L, Liu D, Liu X, Xu G. Symptomatic Intracranial Hemorrhage After Mechanical Thrombectomy in Chinese Ischemic Stroke Patients: The ASIAN Score. Stroke. 2020;51:2690–6.
9. Neuberger U, Seker F, Schönenberger S, Nagel S, Ringleb PA, Bendszus M, Pfaff JAR, Möhlenbruch MA. Prediction of intracranial hemorrhages after mechanical thrombectomy of basilar artery occlusion. J Neurointerv Surg. 2019;11:1181–6.
10. Laible M, Jenetzky E, Möhlenbruch MA, Neuberger U, Bendszus M, Ringleb PA, Rizos T. Renal Impairment Is Associated with Intracerebral Hemorrhage after Mechanical Thrombectomy in Vertebrobasilar Stroke. Cerebrovasc Dis. 2019;47:48–56.
11. Spina R, Simon N, Markus R, Muller DW, Kathir K. Contrast-induced encephalopathy following cardiac catheterization. Catheter Cardiovasc Interv. 2017;90:257–68.
12. Junck L, Marshall WH. Fatal brain edema after contrast-agent overdose. AJNR Am J Neuroradiol. 1986;7:522–5.
13. Zhao W, Zhang J, Song Y, Sun L, Zheng M, Yin H, Zhang J, Wang W, Han J. Irreversible fatal contrast-induced encephalopathy: a case report. BMC Neurol. 2019;19:46.
14. Harada Y, Kairamkonda SR, Ilyas U, Pothineni NVK, Samant RS, Shah VA, Kapoor N, Onteddu S, Nalleballe K. Pearls & Oy-sters: Contrast-induced encephalopathy following coronary angiography: A rare stroke mimic. Neurology. 2020;94:e2491–4.
15. Velden J, Milz P, Winkler F, Seelos K, Hamann GF. Nonionic contrast neurotoxicity after coronary angiography mimicking subarachnoid hemorrhage. Eur Neurol. 2003;49:249–51.
16. Zhang G, Wang H, Zhao L, Li T, Sun M, Zhang Y, Hu H, Teng G, Chen J, Jian Y, Liu J. Contrast-Induced Encephalopathy Resulting From Use of Ioversol and Iopromide. Clin Neuropharmacol. 2020;43:15–9.
17. Chu YT, Lee KP, Chen CH, Sung PS, Lin YH, Lee CW, Tsai LK, Tang SC, Jeng JS. Contrast-Induced Encephalopathy After Endovascular Thrombectomy for Acute Ischemic Stroke. Stroke. 2020;51:3756–9.
18. Khatri R, McKinney AM, Swenson B, Janardhan V. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. Neurology. 2012;79(13 Suppl 1):S52–7.
19. Chen Z, Zhang Y, Su Y, Sun Y, He Y, Chen H. Contrast Extravasation is Predictive of Poor Clinical Outcomes in Patients Undergoing Endovascular Therapy for Acute Ischemic Stroke in the Anterior Circulation. J Stroke Cerebrovasc Dis. 2020;29:104494.
20. Khatri P, Broderick JP, Khoury JC, Carrozzella JA, Tomsick TA; IMS I and II Investigators. Microcatheter contrast injections during intra-arterial thrombolysis may increase intracranial hemorrhage risk. Stroke. 2008;39:3283–7.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9.
22. Ringleb PA, Hametner C, Köhrmann M, Frank B, Jansen O. Akuttherapie des ischämischen Schlaganfalls, S2e-Leitlinie. https://www.awmf.org/uploads/tx_szleitlinien/030-046l_S2e_Akuttherapie-des-ischaemischen-Schlaganfalls_2021-05.pdf. Accessed 10 Mar 2022
23. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344–418. Erratum in: Stroke. 2019;50:e440–1.
24. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355:1670–4. Erratum in: Lancet 2000;355:2170.
25. Puetz V, Sylaja PN, Coutts SB, Hill MD, Dzialowski I, Mueller P, Becker U, Urban G, O'Reilly C, Barber PA, Sharma P, Goyal M, Gahn G, von Kummer R, Demchuk AM. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. Stroke. 2008;39:2485–90.
26. Almekhlafi MA, Mishra S, Desai JA, Nambiar V, Volny O, Goel A, Eesa M, Demchuk AM, Menon BK, Goyal M. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TICI scoring system. Interv Neuroradiol. 2014;20:21–7.
27. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombol-

ysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–29.
28. Arba F, Rinaldi C, Caimano D, Vit F, Busto G, Fainardi E. Blood-Brain Barrier Disruption and Hemorrhagic Transformation in Acute Ischemic Stroke: Systematic Review and Meta-Analysis. Front Neurol. 2021;11:594613.
29. Janardhan V, Qureshi AI. Mechanisms of ischemic brain injury. Curr Cardiol Rep. 2004;6:117–23.
30. Brightman MW, Hori M, Rapoport SI, Reese TS, Westergaard E. Osmotic opening of tight junctions in cerebral endothelium. J Comp Neurol. 1973;152:317–25.
31. Wilson AJ, Evill CA, Sage MR. Effects of nonionic contrast media on the blood-brain barrier. Osmolality versus chemotoxicity. Invest Radiol. 1991;26:1091–4.
32. Li X, Liu H, Zhao L, Liu J, Cai L, Liu L, Zhang W. Clinical observation of adverse drug reactions to non-ionic iodinated contrast media in population with underlying diseases and risk factors. Br J Radiol. 2017;90:20160729.
33. Desilles JP, Syvannarath V, Ollivier V, Journé C, Delbosc S, Ducroux C, Boisseau W, Louedec L, Di Meglio L, Loyau S, Jandrot-Perrus M, Potier L, Michel JB, Mazighi M, Ho-Tin-Noé B. Exacerbation of Thromboinflammation by Hyperglycemia Precipitates Cerebral Infarct Growth and Hemorrhagic Transformation. Stroke. 2017;48:1932–40.
34. Qian J, Fan L, Zhang W, Wang J, Qiu J, Wang Y. A meta-analysis of collateral status and outcomes of mechanical thrombectomy. Acta Neurol Scand. 2020;142:191–9.

3 Discussion

Of 236 patients with acute ischemic infarct and undergoing MT, 22 (9.3%) suffered from sICH. In the univariate analysis, we found that blood glucose level ≥11.1 mmol/L, creatinine clearance (CrCl) of ≤30 ml/min/1.73, ASPECTS (as a continuous variable and dichotomized), ipsilateral ICA occlusion, cerebral stent implantation during the procedure, tirofiban use, time of symptom onset to groin puncture >4.5 hours and higher contrast medium amount were statistically significant between sICH-group and non-sICH-group. In subsequent logistic regression models, we found that only the parameters ASPECTS and amount of contrast medium (OR 1.13, 1.02-1.25, p=0.02) were independent predictive factors for sICH (Lopez-Navarro et al., 2022).

Elevated basal glucose levels have been associated with intracranial bleeding after MT (van der Steen et al., 2022, Montalvo et al., 2019, Janvier et al., 2022). In an animal model, hyperglycemia was associated with a significant blood-brain barrier (BBB) rupture and hemorrhagic transformation of the infarcted area (Desilles et al., 2017). In our study, this statistically significant difference was seen only when blood glucose values were dichotomized (≥11.1mmol/L or <11.1 mmol/L), and no association was seen any longer in the logistic regression analysis. However, there was a trend towards higher blood glucose levels in the sICH group.

Regarding renal dysfunction, literature results are contradictory. One study did not show an association between renal dysfunction and the risk of an intracerebral hemorrhage in patients with anterior circulation stroke (Laible et al., 2017). However, another study in patients with a stroke of the vertebrobasilar circulation showed that renal dysfunction was associated with any intracranial hemorrhages but not specifically with symptomatic ones, although these results have to be interpreted carefully due to the low rate of symptomatic intracranial hemorrhages (only three out of 106 patients, i.e. 2.8%) (Laible et al., 2019).

The Alberta Stroke Program Early CT Score (ASPECTS) measures early ischemic changes in CT and is a surrogate of infarct size. Several studies and trials have shown an association between lower ASPECTS (greater infarct size) and worse functional outcomes or intracranial hemorrhage (Boisseau et al., 2019, Montalvo et al., 2019, Zhang et al., 2020b). Recent clinical trials have demonstrated that patients with large infarct cores (ASPECTS 3–5) may benefit from MT, even though the rates of sICH were higher compared than in the medical treatment arm—though this increase was not statistically significant (Yoshimura et al., 2022, Huo et al., 2023). Another retrospective study did not show this association (van der Steen et al., 2022). Our results are concordant with most of the studies and demonstrate a significant association between ASPECTS, both as a continuous variable (ranging from 0 to 10) (OR 0.749, 0.625-0.899, p=0.002) and as a dichotomized variable (ASPECTS ≤6 vs ASPECTS >6) (OR 3.673, 1.055-12.792, p=0.041) and the occurrence of sICH (Lopez-Navarro et al., 2022).

Ipsilateral carotid stent implantation during MT is currently a common practice (Simonato et al., 2022). A carotid stent study of 23 patients with tandem lesions showed a sICH rate of 22%. Although a favorable outcome was achieved in 52%, the 90-day mortality was as high as 39%, so there is strong concern about both, the effectiveness and safety of carotid stent implantation in this context (Heck and Brown, 2015).

A recent randomized study in China included 950 patients who underwent MT in the anterior circulation. The study aimed to compare the administration of tirofiban versus placebo after thrombectomy. The results indicated significantly higher rates of any radiological intracranial hemorrhage among patients who received tirofiban. Although there was a trend towards more cases of sICH and higher rate of ninety-day mortality in the tirofiban group, these differences were not statistically significant (Rescue BT Trial Investigators et al., 2022). A meta-analysis of 12 studies of tirofiban use in patients who underwent MT showed no difference in symptomatic intracranial hemorrhage between patients who received tirofiban and patients who did not. Only three trials reported "fatal intracranial hemorrhage," and patients having been treated with tirofiban turned out to be at higher risk of a fatal intracranial hemorrhage. There was no difference in terms of mortality between tirofiban use and no use (Zhang et al., 2020a). We observed a difference between the two groups in the univariate analysis, but the logistic regression model could not demonstrate an association (Lopez-Navarro et al., 2022).

The documentation of the timespan between symptom onset and initiation of the recanalizing procedure (referred to as onset-to-groin time) was limited to a dichotomized variable in our study, categorizing it as either greater than 4.5 hours or less than or equal to 4.5 hours (Lopez-Navarro et al., 2022). Unfortunately, we were unable to analyze this variable as a continuous measure. Nevertheless, existing evidence suggests that delayed treatment, measured from the onset of symptoms to groin puncture, is associated with an increased risk of sICH (Zhang et al., 2020b, Cappellari et al., 2019).

We did not find any difference between the two groups in terms of intravenous thrombolysis (Lopez-Navarro et al., 2022). This is in accordance with the current guidelines, which recommend thrombolysis, MT, or both (if eligible) in the acute treatment of AIS (Powers et al., 2019, Ringleb et al., 2022).

To the best of our knowledge, since MT has become a standard therapy for AIS, no studies have analyzed the role of contrast medium for the risk of sICH. As we cited in our article, contrast neurotoxicity has already been well-described in diagnostic neurointerventions and during cardiac catheterizations (Lopez-Navarro et al., 2022). Contrast agents are neurotoxic for the basal lamina and favor BBB disruption (Khatri et al., 2012). Injury of basal lamina increases the risk of intracranial hemorrhage (Rosenberg, 2009). Contrast neurotoxicity is caused by the hyperosmolarity of contrast agents as compared to the blood(Lopez-Navarro et al., 2022), and may also result from the chemotoxic properties of the contrast agents (Wilson et al., 1991). In 2008, *Kathri* et al. demonstrated that a higher number of contrast injections

with microcatheter during intraarterial thrombolysis was associated with a higher intracranial bleeding risk (Khatri et al., 2008). In the present study and in the univariate analysis, the amount of contrast used during MT was significantly higher in the sICH group than in the non-sICH group (median 73.5 ml vs. 42 ml, respectively). The total contrast medium used during the diagnostic procedure (CT-angiography with or without CT Perfusion) and during the MT was 160 ml in the sICH group as opposed to 118 ml in the non-sICH group, resulting in a statistically significant difference of p=001. Our logistic regression models revealed a significant association between the amount of contrast medium and an increased risk of intracranial hemorrhage, both as a continuous variable (OR 1.129, 95% CI 1.019-1.250, p=0.020) and when dichotomized with a threshold of CM ≥ 140 ml (OR 5.412, 95% CI 1.770–16.551, p=0.003) (Lopez-Navarro et al., 2022).

We observed a total of 47 (19.9%) cases of intracranial hemorrhages when considering any intracranial bleeding. After excluding the 22 sICH, 25 cases of asymptomatic hemorrhages remained (25 asICH among 236 patients, 10.6%). The clinical and prognostic significance of these asymptomatic hemorrhages remains to be explored in further research. There is a theoretical possibility that asymptomatic bleeding may impact the disease's progression and long-term prognosis. A Chinese trial provided evidence suggesting that patients with asICH are more likely to experience less excellent outcomes, measured by mRS scores of 0-1, compared to those without intracranial hemorrhage. However, that trial did not find any differences in mortality rates or overall favorable outcomes (mRS scores from 0 to 2) (Hao et al., 2019).

In summary, we can conclude that the hemorrhagic transformation and intracranial hemorrhage may result from or may be enhanced by a blood-brain barrier disruption caused in part by neurotoxic effects of contrast media used for diagnostic purposes.

Hemorrhagic transformation after an ischemic stroke is multifactorial and can be considered as part of the natural history of the disease (Khatri et al., 2012), but it appears to be precipitated by reperfusion therapies, a phenomenon well known as reperfusion injury (Bernardo-Castro et al., 2020).

Reperfusion achieved through MT or thrombolysis) is necessary to preserve brain tissue for a better clinical prognosis. However, it is also true that reperfusion, whether attained by MT or thrombolysis, may contribute to enhanced cerebral tissue damage due to increased hyperemia and direct endothelial compromise from the catheters utilized in MT (Bernardo-Castro et al., 2020).

In this study, we found an association between a higher amount of contrast agent with an increased risk of sICH. To illustrate this relationship and emphasize the need for cautious contrast use, we present our findings in Figure 1. The contrast medium, with its known neurotoxic effect plays a major role in order to caution its overuse. Other factors, such as renal impairment, may also contribute by delaying the elimination of contrast medium, which thus

could contribute indirectly to the pathophysiology of intracranial hemorrhage. In addition, a hyperglycemic state could enhance the degradation of the blood-brain barrier.

Image 1 shows the proposed mechanisms that lead to intracranial hemorrhage after cerebral infarction and mechanical thrombectomy.

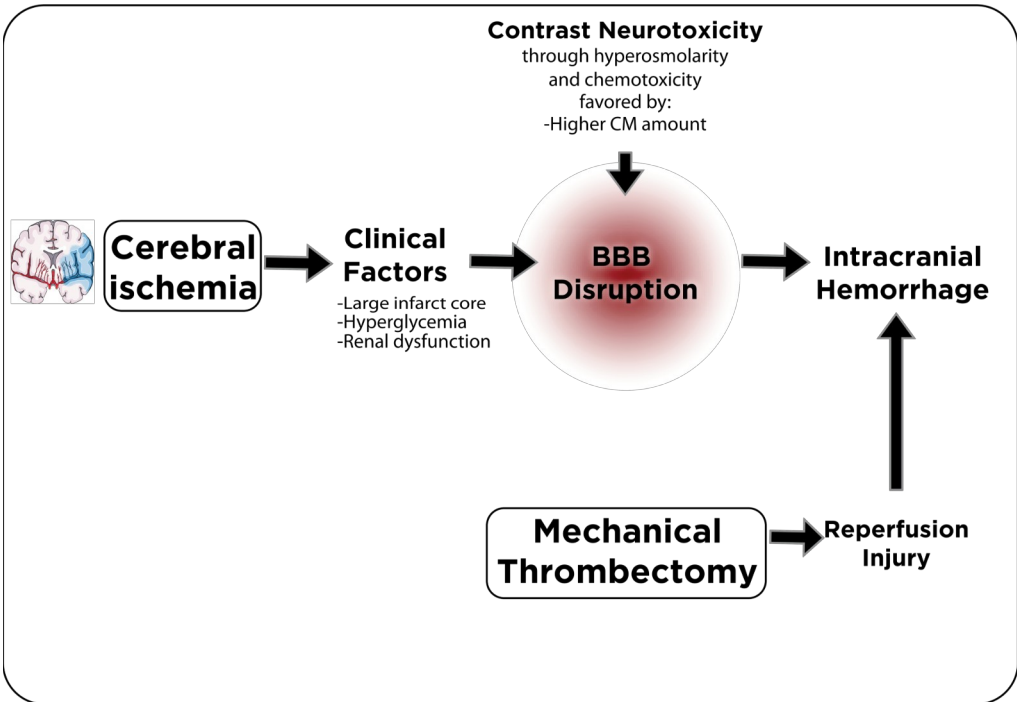

Image 1. Cerebral ischemia, potentiated by clinical factors such as large infarction, hyperglycemia, and renal dysfunction, leads to disruption of the blood-brain-barrier (BBB), which in turn causes intracranial hemorrhage. Contrast neurotoxicity through hyperosmolarity, chemotoxicity and higher contrast media (CM) amount also favors a disruption of the BBB. Mechanical thrombectomy, when effective, could also promote the appearance of intracranial hemorrhage through a reperfusion injury.

Our study has several limitations. Firstly, the sample size is small, and the design is monocentric and retrospective. We could not capture other essential variables such as collateral status, the number of passes during MT to achieve reperfusion, time of onset-to-groin puncture, and procedure time. The last two were not consistently recorded for all patients and were therefore excluded from the analysis to preserve statistical power. The non-availability of these parameters is undoubtedly a drawback since these variables had been described in the literature as factors increasing the risk of intracranial hemorrhage. These limitations could bias our results.

It is difficult to demonstrate an association between the amount of contrast medium used and an increased risk of intracranial bleeding because of its impact on other essential cofactors. As soon as a greater amount of contrast medium was used, automatically more attempts of recanalization (i. e. number of passes) and consequently longer intervention times were implicated. More passes during an intervention imply more manipulation of the affected vessel, which means more injury to the vessel wall, specifically of the endothelial cells and

consecutively of the brain-blood barrier. Thus, determining whether the number of passes, the amount of contrast, or both factors are responsible for brain-blood barrier injury and consecutively cause a higher risk of intracranial bleeding is not reliably possible with the available data set.

Regarding contrast agents, it is impossible to determine the exact amount of CM that was used in the individual patient; for instance, it is well-known that some milliliters of contrast will be discharged when mixed with blood. However, the number of vials used during the procedure allowed for a reasonable estimate of the contrast medium used.

4 Conclusions

Our study provides preliminary evidence that the contrast medium used during MT may exacerbate BBB damage and increase the risk of sICH. Although these findings must be interpreted cautiously due to study limitations, they underline the need to optimize contrast usage during MT.

Furthermore, emerging data suggest that selected patients with lower ASPECTS might still benefit from mechanical thrombectomy. These observations highlight the complex interplay between contrast neurotoxicity, infarct size, and other patient-specific factors such as hyperglycemia or renal impairment. Ultimately, our results call for further multicenter, prospective studies to better define the optimal contrast volume and refine patient selection criteria, thereby improving the safety and efficacy of thrombectomy.

5 Reference List / Bibliography

BERNARDO-CASTRO, S., SOUSA, J. A., BRÁS, A., CECÍLIA, C., RODRIGUES, B., ALMENDRA, L., MACHADO, C., SANTO, G., SILVA, F., FERREIRA, L., SANTANA, I. & SARGENTO-FREITAS, J. 2020. Pathophysiology of Blood–Brain Barrier Permeability Throughout the Different Stages of Ischemic Stroke and Its Implication on Hemorrhagic Transformation and Recovery. *Frontiers in Neurology,* 11.

BOISSEAU, W., FAHED, R., LAPERGUE, B., DESILLES, J. P., ZUBER, K., KHOURY, N., GARCIA, J., MAIER, B., REDJEM, H., CICCIO, G., SMAJDA, S., ESCALARD, S., TAYLOR, G., MAZIGHI, M., MICHEL, P., GORY, B., BLANC, R. & INVESTIGATORS, E. 2019. Predictors of Parenchymal Hematoma After Mechanical Thrombectomy: A Multicenter Study. *Stroke,* 50**,** 2364-2370.

CAPPELLARI, M., MANGIAFICO, S., SAIA, V., PRACUCCI, G., NAPPINI, S., NENCINI, P., KONDA, D., SALLUSTIO, F., VALLONE, S., ZINI, A., BRACCO, S., TASSI, R., BERGUI, M., CERRATO, P., PITRONE, A., GRILLO, F., SALETTI, A., DE VITO, A., GASPAROTTI, R., MAGONI, M., PUGLIELLI, E., CASALENA, A., CAUSIN, F., BARACCHINI, C., CASTELLAN, L., MALFATTO, L., MENOZZI, R., SCODITTI, U., COMELLI, C., DUC, E., COMAI, A., FRANCHINI, E., COSOTTINI, M., MANCUSO, M., PESCHILLO, S., DE MICHELE, M., GIORGIANNI, A., DELODOVICI, M. L., LAFE, E., DENARO, M. F., BURDI, N., INTERNO, S., CAVASIN, N., CRITELLI, A., CHIUMARULO, L., PETRUZZELLIS, M., DODDI, M., CAROLEI, A., AUTERI, W., PETRONE, A., PADOLECCHIA, R., TASSINARI, T., PAVIA, M., INVERNIZZI, P., TURCATO, G., FORLIVESI, S., CICERI, E. F. M., BONETTI, B., INZITARI, D., TONI, D. & LISTING OF, I. E. R. C. 2019. IER-SICH Nomogram to Predict Symptomatic Intracerebral Hemorrhage After Thrombectomy for Stroke. *Stroke,* 50**,** 909-916.

DESILLES, J. P., SYVANNARATH, V., OLLIVIER, V., JOURNE, C., DELBOSC, S., DUCROUX, C., BOISSEAU, W., LOUEDEC, L., DI MEGLIO, L., LOYAU, S., JANDROT-PERRUS, M., POTIER, L., MICHEL, J. B., MAZIGHI, M. & HO-TIN-NOE, B. 2017. Exacerbation of Thromboinflammation by Hyperglycemia Precipitates Cerebral Infarct Growth and Hemorrhagic Transformation. *Stroke,* 48**,** 1932-1940.

DULOQUIN, G., GRABER, M., GARNIER, L., CRESPY, V., COMBY, P.-O., BAPTISTE, L., MOHR, S., DELPONT, B., GUÉNIAT, J., BLANC-LABARRE, C., HERVIEU-BÈGUE, M., OSSEBY, G.-V., GIROUD, M. & BÉJOT, Y. 2020. Incidence of Acute Ischemic Stroke With Visible Arterial Occlusion. *Stroke,* 51**,** 2122-2130.

FURLAN, A., HIGASHIDA, R., WECHSLER, L., GENT, M., ROWLEY, H., KASE, C., PESSIN, M., AHUJA, A., CALLAHAN, F., CLARK, W. M., SILVER, F. & RIVERA, F. 1999. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *Jama,* 282**,** 2003-11.

G. B. D. STROKE COLLABORATORS 2021. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol,* 20**,** 795-820.

GOYAL, M., MENON, B. K., VAN ZWAM, W. H., DIPPEL, D. W., MITCHELL, P. J., DEMCHUK, A. M., DAVALOS, A., MAJOIE, C. B., VAN DER LUGT, A., DE MIQUEL, M. A., DONNAN, G. A., ROOS, Y. B., BONAFE, A., JAHAN, R., DIENER, H. C., VAN DEN BERG, L. A., LEVY, E. I., BERKHEMER, O. A., PEREIRA, V. M., REMPEL, J., MILLAN, M., DAVIS, S. M., ROY, D., THORNTON, J., ROMAN, L. S., RIBO, M., BEUMER, D., STOUCH, B., BROWN, S., CAMPBELL, B. C., VAN OOSTENBRUGGE, R. J., SAVER, J. L., HILL, M. D., JOVIN, T. G. & COLLABORATORS, H. 2016. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet,* 387**,** 1723-31.

HACKE, W., KASTE, M., BLUHMKI, E., BROZMAN, M., DAVALOS, A., GUIDETTI, D., LARRUE, V., LEES, K. R., MEDEGHRI, Z., MACHNIG, T., SCHNEIDER, D., VON KUMMER, R., WAHLGREN, N., TONI, D. & INVESTIGATORS, E. 2008. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med,* 359**,** 1317-29.

HACKE, W., KASTE, M., FIESCHI, C., VON KUMMER, R., DAVALOS, A., MEIER, D., LARRUE, V., BLUHMKI, E., DAVIS, S., DONNAN, G., SCHNEIDER, D., DIEZ-

TEJEDOR, E. & TROUILLAS, P. 1998. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet,* 352**,** 1245-51.

HAO, Y., LIU, W., WANG, H., ZI, W., YANG, D., WANG, W., TIAN, X., GUO, F., JIN, P., XIONG, Y., LIU, X. & XU, G. 2019. Prognosis of asymptomatic intracranial hemorrhage after endovascular treatment. *J Neurointerv Surg,* 11**,** 123-126.

HAO, Y., YANG, D., WANG, H., ZI, W., ZHANG, M., GENG, Y., ZHOU, Z., WANG, W., XU, H., TIAN, X., LV, P., LIU, Y., XIONG, Y., LIU, X., XU, G. & INVESTIGATORS, A. 2017. Predictors for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of Acute Ischemic Stroke. *Stroke,* 48**,** 1203-1209.

HECK, D. V. & BROWN, M. D. 2015. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J Neurointerv Surg,* 7**,** 170-175.

HUO, X., MA, G., TONG, X., ZHANG, X., PAN, Y., NGUYEN, T. N., YUAN, G., HAN, H., CHEN, W., WEI, M., ZHANG, J., ZHOU, Z., YAO, X., WANG, G., SONG, W., CAI, X., NAN, G., LI, D., WANG, A. Y.-C., LING, W., CAI, C., WEN, C., WANG, E., ZHANG, L., JIANG, C., LIU, Y., LIAO, G., CHEN, X., LI, T., LIU, S., LI, J., GAO, F., MA, N., MO, D., SONG, L., SUN, X., LI, X., DENG, Y., LUO, G., LV, M., HE, H., LIU, A., ZHANG, J., MU, S., LIU, L., JING, J., NIE, X., DING, Z., DU, W., ZHAO, X., YANG, P., LIU, L., WANG, Y., LIEBESKIND, D. S., PEREIRA, V. M., REN, Z., WANG, Y. & MIAO, Z. 2023. Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. *N Engl J Med,* 388**,** 1272-1283.

JANVIER, P., KERLEROUX, B., TURC, G., PASI, M., FARHAT, W., BRICOUT, N., BENZAKOUN, J., LEGRAND, L., CLARENÇON, F., BRACARD, S., OPPENHEIM, C., BOULOUIS, G., HENON, H., NAGGARA, O. & BEN HASSEN, W. 2022. TAGE Score for Symptomatic Intracranial Hemorrhage Prediction After Successful Endovascular Treatment in Acute Ischemic Stroke. *Stroke***,** 101161strokeaha121038088.

KHATRI, P., BRODERICK, J. P., KHOURY, J. C., CARROZZELLA, J. A., TOMSICK, T. A., IMS, I. & INVESTIGATORS, I. I. 2008. Microcatheter contrast injections during intra-arterial thrombolysis may increase intracranial hemorrhage risk. *Stroke,* 39**,** 3283-7.

KHATRI, R., MCKINNEY, A. M., SWENSON, B. & JANARDHAN, V. 2012. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. *Neurology,* 79**,** S52-7.

LAIBLE, M., JENETZKY, E., MOHLENBRUCH, M. A., NEUBERGER, U., BENDSZUS, M., RINGLEB, P. A. & RIZOS, T. 2019. Renal Impairment Is Associated with Intracerebral Hemorrhage after Mechanical Thrombectomy in Vertebrobasilar Stroke. *Cerebrovasc Dis,* 47**,** 48-56.

LAIBLE, M., MÖHLENBRUCH, M. A., PFAFF, J., JENETZKY, E., RINGLEB, P. A., BENDSZUS, M. & RIZOS, T. 2017. Influence of Renal Function on Treatment Results after Stroke Thrombectomy. *Cerebrovasc Dis,* 44**,** 351-358.

LEE, C.-H. & LEE, S.-H. 2020. General Facts of Stroke. *In:* LEE, S.-H. (ed.) *Stroke Revisited: Pathophysiology of Stroke: From Bench to Bedside.* Singapore: Springer Singapore.

LEVY, D. E., BROTT, T. G., HALEY, E. C., JR., MARLER, J. R., SHEPPARD, G. L., BARSAN, W. & BRODERICK, J. P. 1994. Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. *Stroke,* 25**,** 291-7.

LOPEZ-NAVARRO, E. R., DELFS, C., JARRE, A., SANIO, V., GREIF, G., GUTIERREZ, J., RINGELSTEIN, E. B., MEUTH, S. G., HAENSCH, C. A., RINGELSTEIN, A. & RINGELSTEIN, M. 2022. Contrast Neurotoxicity and its Association with Symptomatic Intracranial Hemorrhage After Mechanical Thrombectomy. *Clin Neuroradiol,* 32**,** 961-969.

MAÏER, B., DESILLES, J. P. & MAZIGHI, M. 2020. Intracranial Hemorrhage After Reperfusion Therapies in Acute Ischemic Stroke Patients. *Front Neurol,* 11**,** 599908.

MOKIN, M., ABOU-CHEBL, A., CASTONGUAY, A. C., NOGUEIRA, R. G., ENGLISH, J. D., FARID, H., GUPTA, R., MARTIN, C., HOLLOWAY, W. E., HAUSSEN, D. C., MUELLER-KRONAST, N., ZAIDAT, O. O., NASA & INVESTIGATORS, T. 2019. Real-world stent retriever thrombectomy for acute ischemic stroke beyond 6 hours of onset: analysis of the NASA and TRACK registries. *J Neurointerv Surg,* 11**,** 334-337.

MONTALVO, M., MISTRY, E., CHANG, A. D., YAKHKIND, A., DAKAY, K., AZHER, I., KAUSHAL, A., MISTRY, A., CHITALE, R., CUTTING, S., BURTON, T., MAC GRORY, B., REZNIK, M., MAHTA, A., THOMPSON, B. B., ISHIDA, K., FRONTERA, J., RIINA, H. A., GORDON, D., PARELLA, D., SCHER, E., FARKAS, J., MCTAGGART, R., KHATRI, P., FURIE, K. L., JAYARAMAN, M. & YAGHI, S. 2019. Predicting symptomatic intracranial haemorrhage after mechanical thrombectomy: the TAG score. *J Neurol Neurosurg Psychiatry,* 90**,** 1370-1374.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS STROKE RT-PA STROKE STUDY GROUP 1995. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med,* 333**,** 1581-7.

OSPEL, J. M., QIU, W., MENON, B. K., MAYANK, A., DEMCHUK, A., MCTAGGART, R., NOGUEIRA, R. G., POPPE, A. Y., JAYARAMAN, M., BUCK, B., HAUSSEN, D., ROY, D., JOSHI, M., ZERNA, C., ALMEKHLAFI, M., TYMIANSKI, M., HILL, M. D., GOYAL, M. & INVESTIGATORS, E.-N. 2021. Radiologic Patterns of Intracranial Hemorrhage and Clinical Outcome after Endovascular Treatment in Acute Ischemic Stroke: Results from the ESCAPE-NA1 Trial. *Radiology,* 300**,** 402-409.

PESSIN, M. S., DEL ZOPPO, G. J. & ESTOL, C. J. 1990. Thrombolytic agents in the treatment of stroke. *Clin Neuropharmacol,* 13**,** 271-89.

POWERS, W. J., RABINSTEIN, A. A., ACKERSON, T., ADEOYE, O. M., BAMBAKIDIS, N. C., BECKER, K., BILLER, J., BROWN, M., DEMAERSCHALK, B. M., HOH, B., JAUCH, E. C., KIDWELL, C. S., LESLIE-MAZWI, T. M., OVBIAGELE, B., SCOTT, P. A., SHETH, K. N., SOUTHERLAND, A. M., SUMMERS, D. V. & TIRSCHWELL, D. L. 2019. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke,* 50**,** e344-e418.

RESCUE BT TRIAL INVESTIGATORS, QIU, Z., LI, F., SANG, H., LUO, W., LIU, S., LIU, W., GUO, Z., LI, H., SUN, D., HUANG, W., ZHANG, M., ZHANG, M., DAI, W., ZHOU, P., DENG, W., ZHOU, Z., HUANG, X., LEI, B., LI, J., YUAN, Z., SONG, B., MIAO, J., LIU, S., JIN, Z., ZENG, G., ZENG, H., YUAN, J., WEN, C., YU, Y., YUAN, G., WU, J., LONG, C., LUO, J., TIAN, Z., ZHENG, C., HU, Z., WANG, S., WANG, T., QI, L., LI, R., WAN, Y., KE, Y., WU, Y., ZHU, X., KONG, W., HUANG, J., PENG, D., CHANG, M., GE, H., SHI, Z., YAN, Z., DU, J., JIN, Y., JU, D., HUANG, C., HONG, Y., LIU, T., ZHAO, W., WANG, J., ZHENG, B., WANG, L., LIU, S., LUO, X., LUO, S., XU, X., HU, J., PU, J., CHEN, S., SUN, Y., JIANG, S., WEI, L., FU, X., BAI, Y., YANG, S., HU, W., ZHANG, G., PAN, C., ZHANG, S., WANG, Y., CAO, W., YANG, S., ZHANG, J., GUO, F., WEN, H., ZHANG, J., SONG, J., YUE, C., LI, L., WU, D., TIAN, Y., YANG, J., LU, M., SAVER, J. L., NOGUEIRA, R. G., ZI, W. & YANG, Q. 2022. Effect of Intravenous Tirofiban vs Placebo Before Endovascular Thrombectomy on Functional Outcomes in Large Vessel Occlusion Stroke: The RESCUE BT Randomized Clinical Trial. *JAMA,* 328**,** 543-553.

RINGLEB, P. A., KÖHRMANN, M. & JANSEN, O. 2022. *Akuttherapie des ischämischen Schlaganfalls, S2e-Leitlinie* [Online]. Deutsche Gesellschaft für Neurologie. Available: www.dgn.org/leitlinien [Accessed].

ROSENBERG, G. A. 2009. Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. *Lancet Neurol,* 8**,** 205-16.

SIMONATO, D., BORCHERT, R. J., LABEYRIE, M.-A., FUSCHI, M., THIBAULT, L., HENKES, H., FIORELLA, D., TAN, B. Y., YEO, L. L., MAKALANDA, H. L., WONG, K. & BHOGAL, P. 2022. Glycoprotein IIb/IIIa inhibitors for the neurointerventionalist. *Interventional Neuroradiology,* 0**,** 84-91.

TROUILLAS, P. & VON KUMMER, R. 2006. Classification and pathogenesis of cerebral hemorrhages after thrombolysis in ischemic stroke. *Stroke,* 37**,** 556-61.

TSAO, C. W., ADAY, A. W., ALMARZOOQ, Z. I., ALONSO, A., BEATON, A. Z., BITTENCOURT, M. S., BOEHME, A. K., BUXTON, A. E., CARSON, A. P., COMMODORE-MENSAH, Y., ELKIND, M. S. V., EVENSON, K. R., EZE-NLIAM, C., FERGUSON, J. F., GENEROSO, G., HO, J. E., KALANI, R., KHAN, S. S., KISSELA, B. M., KNUTSON, K. L., LEVINE, D. A., LEWIS, T. T., LIU, J., LOOP, M. S., MA, J., MUSSOLINO, M. E., NAVANEETHAN, S. D., PERAK, A. M., POUDEL, R., REZK-HANNA, M., ROTH, G. A., SCHROEDER, E. B., SHAH, S. H., THACKER, E. L., VANWAGNER, L. B., VIRANI, S. S., VOECKS, J. H., WANG, N.-Y., YAFFE, K. & MARTIN, S. S. 2022. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. *Circulation,* 145**,** e153-e639.

VAN DER STEEN, W., VAN DER ENDE, N. A. M., VAN KRANENDONK, K. R., CHALOS, V., VAN OOSTENBRUGGE, R. J., VAN ZWAM, W. H., ROOS, Y., VAN DOORMAAL, P. J., VAN ES, A., LINGSMA, H. F., MAJOIE, C., VAN DER LUGT, A., DIPPEL, D. W. J., ROOZENBEEK, B., TRIAL, M. C. & INVESTIGATORS, M. C. R. 2022. Determinants of Symptomatic Intracranial Hemorrhage After Endovascular Stroke Treatment: A Retrospective Cohort Study. *Stroke,* 53**,** 101161TROKEAHA121036195.

VENDITTI, L., CHASSIN, O., ANCELET, C., LEGRIS, N., SAROV, M., LAPERGUE, B., MIHALEA, C., OZANNE, A., GALLAS, S., CORTESE, J., CHALUMEAU, V., IKKA, L., CAROFF, J., LABREUCHE, J., SPELLE, L. & DENIER, C. 2021. Pre-procedural predictive factors of symptomatic intracranial hemorrhage after thrombectomy in stroke. *J Neurol,* 268**,** 1867-1875.

WAFA, H. A., WOLFE, C. D. A., EMMETT, E., ROTH, G. A., JOHNSON, C. O. & WANG, Y. 2020. Burden of Stroke in Europe. *Stroke,* 51**,** 2418-2427.

WAHLGREN, N., AHMED, N., DÁVALOS, A., FORD, G. A., GROND, M., HACKE, W., HENNERICI, M. G., KASTE, M., KUELKENS, S., LARRUE, V., LEES, K. R., ROINE, R. O., SOINNE, L., TONI, D. & VANHOOREN, G. 2007. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet,* 369**,** 275-282.

WILSON, A. J., EVILL, C. A. & SAGE, M. R. 1991. Effects of nonionic contrast media on the blood-brain barrier. Osmolality versus chemotoxicity. *Invest Radiol,* 26**,** 1091-4.

WORLD HEALTH ASSEMBLY. 2020. *International statistical classification of diseases and related health problems (ICD). ICD-11 Mortality and Morbidity Statistics* [Online]. Available: https://icd.who.int/browse11/l-m/en [Accessed January].

YOSHIMURA, S., SAKAI, N., YAMAGAMI, H., UCHIDA, K., BEPPU, M., TOYODA, K., MATSUMARU, Y., MATSUMOTO, Y., KIMURA, K., TAKEUCHI, M., YAZAWA, Y., KIMURA, N., SHIGETA, K., IMAMURA, H., SUZUKI, I., ENOMOTO, Y., TOKUNAGA, S., MORITA, K., SAKAKIBARA, F., KINJO, N., SAITO, T., ISHIKURA, R., INOUE, M. & MORIMOTO, T. 2022. Endovascular Therapy for Acute Stroke with a Large Ischemic Region. *N Engl J Med,* 386**,** 1303-1313.

ZHANG, P., GUO, Y., SHEN, J., LI, H., WANG, R., WANG, Y., YU, X. & YAO, Q. 2020a. Efficacy and safety of tirofiban therapy in patients receiving endovascular treatment after large vessel ischaemic stroke: A systematic review and meta-analysis. *J Clin Neurosci,* 80**,** 112-120.

ZHANG, X., XIE, Y., WANG, H., YANG, D., JIANG, T., YUAN, K., GONG, P., XU, P., LI, Y., CHEN, J., WU, M., SHENG, L., LIU, D., LIU, X. & XU, G. 2020b. Symptomatic Intracranial Hemorrhage After Mechanical Thrombectomy in Chinese Ischemic Stroke Patients: The ASIAN Score. *Stroke,* 51**,** 2690-2696.

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