ORIGINAL ARTICLE

Inflammatory Biomarkers and Intracranial Hemorrhage after Endovascular Thrombectomy

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ABSTRACT: ***Background:*** Intracranial hemorrhage after endovascular thrombectomy is associated with poorer prognosis compared with those who do not develop the complication. Our study aims to determine predictors of post-EVT hemorrhage – more specifically, inflammatory biomarkers present in baseline serology. ***Methods:*** We performed a retrospective review of consecutive patients treated with EVT for acute large vessel ischemic stroke. The primary outcome of the study is the presence of ICH on the post-EVT scan. We used four definitions: the SITS-MOST criteria, the NINDS criteria, asymptomatic hemorrhage, and overall hemorrhage. We identified nonredundant predictors of outcome using backward elimination based on Akaike Information Criteria. We then assessed prediction accuracy using area under the receiver operating curve. Then we implemented variable importance ranking from logistic regression models using the drop in Naegelkerke R^2 with the exclusion of each predictor. ***Results:*** Our study demonstrates a 6.3% SITS (16/252) and 10.0% NINDS (25/252) sICH rate, as well as a 19.4% asymptomatic (49/252) and 29.4% (74/252) overall hemorrhage rate. Serologic markers that demonstrated association with post-EVT hemorrhage were: low lymphocyte count (SITS), high neutrophil count (NINDS, overall hemorrhage), low platelet to lymphocyte ratio (NINDS), and low total WBC (NINDS, asymptomatic hemorrhage). ***Conclusion:*** Higher neutrophil counts, low WBC counts, low lymphocyte counts, and low platelet to lymphoycyte ratio were baseline serology biomarkers that were associated with post-EVT hemorrhage. Our findings, particularly the association of diabetes mellitus and high neutrophil, support experimental data on the role of thromboinflammation in hemorrhagic transformation of large vessel occlusions.

RÉSUMÉ : Biomarqueurs inflammatoires et hémorragie intracrânienne à la suite d'une thrombectomie endovasculaire. ***Contexte :*** Le fait d'être victime d'une hémorragie intracrânienne (HIC) à la suite d'une thrombectomie endovasculaire (TEV) est associé à un pronostic plus défavorable par rapport à des patients qui ne développent pas cette complication. Notre étude vise ainsi à déterminer les prédicteurs d'une hémorragie post-TEV, plus particulièrement les biomarqueurs inflammatoires présents dans la sérologie de base. ***Méthodes :*** Nous avons réalisé une étude rétrospective de patients vus consécutivement qui ont été traités au moyen d'une TEV dans le cas d'AVC ischémiques aigus affectant de larges vaisseaux sanguins. Le principal aspect mesuré dans cette étude a été la présence d'une HIC détectée à l'occasion d'un examen de tomodensitométrie post-TEV. Nous avons aussi fait appel à quatre définitions : SITS-MOST (*safe implementation of thrombolysis in stroke-monitoring study*), NINDS (*National Institute of Neurological Disorders and Stroke*), hémorragie asymptomatique et hémorragie globale. De plus, nous avons identifié des prédicteurs non-redondants en utilisant une rétro-élimination basée sur le critère d'information d'Akaike. Nous avons ensuite évalué la précision de ces prédicteurs en utilisant la fonction d'efficacité du récepteur. Finalement, nous avons mis en œuvre le classement par importance des variables à partir de modèles de régression logistique en utilisant la diminution du R^2 de Naegelkerke avec l'exclusion de chaque prédicteur. ***Résultats :*** En fonction des définitions SITS-MOST et NINDS, notre étude a montré respectivement un taux d'HIC de 6,3 % (16/252) et de 10,0 % (25/252). Les taux d'hémorragie asymptomatique et d'hémorragie globale ont été respectivement de 19,4 % (49/252) et de 29,4 % (74/252). Les marqueurs sérologiques qui ont montré une association avec des cas d'hémorragie post-EVT ont été les suivants : faible nombre de lymphocytes (SITS), nombre élevé de neutrophiles (NINDS, hémorragie globale), faible rapport plaquettes/lymphocytes (NINDS) et faible total de globules blancs (NINDS, hémorragie asymptomatique). ***Conclusion :*** Un nombre élevé de neutrophiles, un faible total de globules blancs, un faible nombre de lymphocytes ainsi qu'un faible rapport plaquettes/lymphocytes sont les biomarqueurs sérologiques de base qui ont été associés à des cas d'hémorragie post-TEV. Nos résultats, en particulier l'association entre le diabète sucré et un taux élevé de neutrophiles, confirment les données expérimentales quant au rôle de la thrombo-inflammation dans les transformations hémorragiques consécutives à l'occlusions de larges vaisseaux sanguins.

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Background

Endovascular thrombectomy (EVT) improves 3-month functional outcomes in patients with large vessel acute ischemic stroke.[1] However, 4.4% of patients undergoing EVT still develop symptomatic intracranial hemorrhage (sICH).[2] Real-world studies show even higher sICH rate at 9–16%.[3,4] Post-EVT patients who develop sICH have significantly higher morbidity and mortality.[5] Even asymptomatic intracranial hemorrhage (ICH) in patients undergoing EVT, has been found to decrease the likelihood of attaining an excellent (MRS 0-1) functional outcome.[6]

Given the prognostic implications of post-EVT ICH, identifying factors associated with its occurrence has significant clinical relevance. In particular, we sought to determine if serum biomarkers of neuroinflammation such as neutrophil count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio had any predictive value for ICH after EVT. The goal of this study was to determine factors associated with post-EVT hemorrhage in patients undergoing EVT for large vessel acute ischemic stroke.

Methods

Patient Selection and Study Site

We performed a retrospective review of consecutive patients treated with EVT for acute large vessel ischemic stroke at our institution, a regional stroke center, from March 2011 to April 2020. The inclusion criteria were as follows: age >18 years, diagnosis of acute ischemic stroke with large vessel occlusion (LVO) of the middle cerebral artery (MCA), and/or internal carotid artery (ICA) on computed tomography angiography (CTA), treatment with standard-of-care EVT (stent retriever and/or large bore catheter aspiration), availability of post-EVT head computed tomography (CT), and pre-EVT complete blood counts. Patients with hemorrhage due to vessel perforation were excluded from the study.

The study was approved by the institutional review board. A complete blood count is done for all new acute stroke patients. The hospital uses the Sysmex XN-9000 (Kobe, Japan), a quantitative, multiparameter automated hematology analyzer. The machine uses flow cytometry for cell analysis and sheath flow direct current detection method for counting red blood cells and platelets. Image analysis is also utilized for the differential count

A CTA follows to identify an LVO. Then, the neurovascular team assesses EVT candidacy. Twenty-four hours after EVT, a plain head CT is done to screen for hemorrhage. In cases where it is difficult to delineate HT from contrast staining, a repeat CT is done after another 24 hours to establish a final radiologic diagnosis.

Outcome Measures

The primary outcome of the study is the presence of ICH on the post-EVT scan. We used four definitions[7]: the SITS-MOST criteria (parenchymal hemorrhage >30% of the territory of the infarcted region, with an associated NIHSS worsening of >4 points within 36 hours of stroke onset), the NINDS criteria (any clinical deterioration with any hemorrhage), asymptomatic hemorrhage (no symptoms with any hemorrhage), and overall hemorrhage (includes all types of hemorrhage).

Data Collection

Patient medical records were reviewed by study personnel. We obtained patient demographics, treatment details, and both radiologic and clinical treatment outcomes. All post-EVT cranial scans were again reviewed for the presence of ICH by interventional neuroradiologists.

Statistical Analysis

Methods Overview

Briefly to overview, we identified nonredundant predictors of outcome using backward elimination based on Akaike Information Criteria. We then assessed prediction accuracy using area under the receiver operating curve. To further assess the influence of our predictors, we implemented variable importance ranking from logistic regression models using the drop in Naegelkerke R^2 with the exclusion of each predictor.

Predictive Models

The following variables were considered for the models: age, sex, comorbid conditions (atrial fibrillation, congestive heart failure, hypertension, diabetes, coronary artery disease, hyperlipidemia) NIHSS score at presentation, prior anticoagulation, prior antiplatelet use, prior ischemic stroke, prior hemorrhagic stroke, treatment with intravenous or intraarterial thrombolysis, time from symptom onset to reperfusion, degree of recanalization, use of general anesthesia, ASPECTS score on admission, exact location of clot, total number of thrombectomy passes, and serum biomarkers (WBC count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio). We applied logistic regression models for predictions and to assess variable correlation with clinical outcome. For model selection, we will use Akaike information criterion with backward elimination to optimize the balance of model complexity against goodness of fit.[8] Predictions will be undertaken with threefold cross-validation to avoid overfitting.[9] This method has been found superior in terms of discriminatory ability, calibration, and overall accuracy to the split-sample method by the comparative study of Steyerberg et al.[10] Predictive performance of the different models described below will be assessed by computing the AUC and compared using DeLong's test.[11]

Variable Importance Ranking

We used the Nagelkerke R^2 value,[12] a measure for goodness of fit, to rank variable importance. Nagelkerke R^2 numerically

expresses the percentage of variability attributed to a predictor. The ranking of variables was extracted from the drop in the Nagelkerke R^2 value that occurs in response to excluding variables of interest from the model. We used this ranking to identify the most influential variables and include them to create a more simplistic model with fewer variables. There are recognized limitations for "pseudo" R^2 methods: (1) they can be argued to give artificially high R^2 scores that may suggest the model fits better than it really does, and (2) there are a variety of "pseudo" R^2 measures to choose from, each of which interprets the model differently and therefore gives different results. In our study, we used the same modality of R^2 value to assess the change in model fit rather than focus on the numeric value, a technique that has been applied in past papers.[13,14]

Statistical Software

Statistical analysis and modeling were carried out in R,[15] an open-source software environment for statistical programming and graphics (https://www.r-project.org/). Receiver operating curve analysis was done using the "pROC" package.[16] Threshold optimization was performed using packages "pROC" and "SDMTools"[17] AUCs were compared using DeLong's test.[11] Nagelkerke R^2 was implemented using the "fmsb" package.[18]

Ethics Approval

The study was approved by our institutional research ethics board (18-397). The retrospective nature of the study precluded informed consent from the patients.

Results

Patient Characteristics

A total of 335 acute stroke patients underwent EVT, of which 252 patients met the inclusion criteria (See Online Supplement Figure 1). The baseline characteristics of the patients are summarized in Table 1.

Table 1: Baseline characteristics and treatment outcomes

Baseline characteristics	
Age, mean (range)	67.1 (31–95)
Female n (%)	120 (47.6)
Atrial fibrillation n (%)	89 (35.3)
Congestive heart failure n (%)	28 (11.1)
Diabetes n (%)	56 (22.2)
Coronary artery disease n (%)	52 (20.6)
Hyperlipidemia n (%)	101 (40.0)
Prior anticoagulants n (%)	48 (19.0)
Prior antiplatelets n (%)	75 (29.8)
Prior ischemic stroke n (%)	39 (15.5)
Prior hemorrhagic stroke n (%)	4 (1.6)
Location of clot, n (%)	
Tandem	55 (21.8)
ICA	21 (8.3)
M1	142 (56.3)
M2	34 (13.5)
NIHSS on admission, mean (range)	15.0.0 (1–30)
ASPECTS on admission, mean (range)	8.0 (2–10)
Procedural details	
Intravenous tPA, n (%)	144 (57.1)
Intra-arterial tPA, n (%)	8 (3.2)
General Anesthesia n (%)	16 (6.3)
Onset to perfusion	363 (93–1629)
<360 min n (%)	123 (48.8)
≥360 min n (%)	80 (31.7)
Failed n (%)	49 (19.4)
Cell counts mean (SD)	
Total white blood cell count	9.67 (3.40)
Neutrophil	7.11 (3.51)
Lymphocyte	1.71 (1.07)
Platelet	231.06 (77.03)
Neutrophil/lymohocyte ratio	6.45 (10.16)
Platelet/lymohocyte	181.75 (162.56)
Treatment outcomes	
Recanalization (TICI), n (%)	
0–2a	44 (17.4)
>2b	208 (82.5)
Post-EVT hemorrhage n (%)	
SICH SITS definition	16 (6.3)
SICH NINDS definition	25 (10.0)
Asymptomatic ICH	49 (19.4)
Overall ICH	74 (29.4)

Predictive Models

On logistic regression modeling, we yielded 5, 6, 7, and 6 variables significantly associated with occurrence of post-EVT intracerebral hemorrhage as described by SITS, NINDS, asymptomatic, and overall ICH definitions (Table 2) respectively. Consistent predictors across the four models were the lower white blood cell (WBC) or lymphocyte count, and number of passes. Significance values and odds ratios are summarized in Table 2.

Predictive Performance

AUCs were 0.69 (95% CI: 0.55–0.83), 0.78 (95% CI: 0.69–0.86), 0.69 (95% CI: 0.61–0.77), and 0.72 (95% CI: 0.65– 0.79) for the SITS, NINDS, asymptomatic, and overall hemorrhages, respectively. These values reflect only fair diagnostic accuracy of the models. Predictions were carried out using threefold cross-validation approach to avoid model overfitting. Using DeLong's test, there were no significant differences between all combinations of ROC curves.

Importance Ranking of Outcome Predictors

Based on the drop in Nagelkerke R^2 values, a pseudo-R^2 value used to describe goodness of model fit, we ranked the influence of each variable on the outcome of interest. While there was some overlap in significant predictors between models, the highest-ranking variables were distinct for each model as summarized in Table 3.

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Table 2: Table summary of confidence intervals, odds ratios, and significance levels for the post EVT intracerebral hemorrhage definitions

	Variable	OR	2.50%	97.50%	p
SITS	Diabetes mellitus	2.51	0.79	7.39	0.10
	IV tPA	2.73	0.90	9.95	0.09
	ASPECTS	0.72	0.52	1.00	0.05
	Number of passes	1.63	0.97	2.63	0.05
	Lymphocyte	0.63	0.29	1.15	0.21
NINDS	Diabetes mellitus	2.49	0.90	6.60	0.07
	IV tPA	4.00	1.46	13.01	0.01
	Number of passes	1.72	1.14	2.57	0.01
	Total WBC	0.52	0.31	0.80	0.01
	Neutrophil	2.00	1.30	3.40	0.01
	Platelet-to-lymphocyte ratio	1.00	0.99	1.00	0.22
Asymptomatic hemorrhage	Prior anticoagulants	0.39	0.13	1.02	0.07
	NIHSS score	1.07	1.01	1.15	0.04
	Onset to perfusion: <360 min	Reference			
	Onset to perfusion: ≥360 min	3.72	1.66	8.60	0.00
	Onset to perfusion: failed	1.35	0.48	3.66	0.56
	IV tPA	0.40	0.19	0.83	0.02
	Location of clot: tandem	Reference			
	Location of clot: ICA	3.23	0.64	16.51	0.15
	Location of clot: M1	4.66	1.59	17.41	0.01
	Location of clot: M2	8.54	2.24	38.64	0.00
	Number of passes	1.32	0.91	1.90	0.14
	Total WBC	0.84	0.73	0.94	0.01
Overall hemorrhage	CHF	0.39	0.11	1.09	0.09
	Diabetes mellitus	2.72	1.34	5.56	0.01
	ASPECTS	0.77	0.65	0.93	0.01
	Number of passes	1.64	1.22	2.23	0.00
	Total WBC	0.64	0.47	0.83	0.00
	Neutrophil	1.44	1.11	1.90	0.01

Discussion

Our study demonstrates a 6.3% (SITS) and 10.0% (NINDS) sICH rate, as well as a 19.4% asymptomatic and 29.4% overall hemorrhage rate. Serologic markers that demonstrated association with post-EVT hemorrhage were: low lymphocyte count (SITS), high neutrophil count (NINDS, overall hemorrhage), low platelet-to-lymphocyte ratio (NINDS), and low total WBC (NINDS, asymptomatic hemorrhage). Other factors that showed previous association with post EVT hemorrhage were also seen in our study: diabetes mellitus,[19] higher number of passes,[4,19] onset to perfusion time,[4,20] lower ASPECTS,[6,21] and intravenous thrombolysis.[19,22] The neutrophil-to-lymphocyte ratio has previously been associated with early neurological deterioration,[23] post-thrombolysis hemorrhagic transformation,[24] and poor outcomes in acute ischemic stroke patients.[25] However, it was not associated with post-EVT hemorrhage in our study using any of the definitions.

Blood–brain barrier disruption induced by the inflammatory response to acute ischemic stroke may play a role in post-EVT hemorrhage. Neutrophils are a source of matrix metalloproteinase (MMP)-9, which play a direct role in degrading tight junction proteins. Conceivably, higher neutrophil counts may lead to higher levels of MMP-9, potentially translating to a higher risk of HT.[26] The role of neutrophils is emphasized further by decrease in ischemic volume in rats undergoing middle cerebral artery occlusion after the administration of anti-neutrophil antibodies compared with those with a normal complement of neutrophils.[27] These pathomechanisms may underlie a recent finding that high neutrophil count predicts poor clinical outcomes despite recanalization in patients with large vessel occlusion.[28]

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Table 3: Variable importance ranking

	Variable	Nagelkerke	Drop	Rank
SITS	ASPECTS	0.080	0.039	1
	Number of passes	0.084	0.035	2
	IV tPA	0.087	0.032	3
	Diabetes mellitus	0.093	0.025	4
	Lymphocytes	0.098	0.021	5
NINDS	Neutrophils	0.138	0.083	1
	Total WBC count	0.144	0.076	2
	IV tPA	0.163	0.057	3
	Number of passes	0.171	0.049	4
	Diabetes mellitus	0.197	0.023	5
	Platelet to lymphocyte ratio	0.201	0.020	6
Asymptomatic hemorrhage	Location of clot	0.170	0.065	1
	Onset to perfusion	0.175	0.060	2
	Total WBC count	0.182	0.053	3
	IV tPA	0.202	0.033	4
	NIHSS score	0.209	0.025	5
	Prior anticoagulants	0.215	0.020	6
	Number of passes	0.223	0.012	7
Overall hemorrhage	Total WBC count	0.156	0.059	1
	Number of passes	0.162	0.054	2
	Neutrophils	0.176	0.039	3
	ASPECTS	0.176	0.039	4
	Diabetes mellitus	0.178	0.038	5
	CHF	0.200	0.016	6

Large cohorts of patients undergoing intravenous thrombolysis[29] and endovascular thrombectomy[4] also demonstrated an increased risk of hemorrhagic transformation in patients with higher neutrophil counts and ratios. Circulating neutrophil transcriptomes have also been demonstrated to correlate with the presence of unruptured intracranial aneurysms.[30–32]

Diabetes has been associated with post EVT hemorrhage in past studies.[19,22] Chronic hyperglycemia in diabetic mice undergoing MCA occlusion has been demonstrated to aggravate HT by inciting mitochondrial dysfunction leading to endothelial cell death.[33] Classically, HT had been attributed to free radical damage from reperfusion injury. However, similar to our findings, a large multicenter study demonstrated that reperfusion status did not correlate with HT after EVT.[21] More recent basic science research has focused on downstream microvascular thromboinflammation (DMT), a phenomenon characterized by leukocyte margination (mostly neutrophils) and thrombosis in the venules after proximal large vessel occlusion. DMT by inducing vascular leakage may account for microhemorrhages and incomplete reperfusion despite large vessel recanalization.[34]

Hyperglycemia has been demonstrated to precipitate infarct growth and HT by exacerbating DMT through preactivating neutrophils in rats undergoing experimental large vessel occlusion.[35] Earlier studies noted that diabetic rats had a more robust neutrophil–endothelial cell interaction compared with nondiabetic ones in the setting of large vessel ischemia reperfusion injury models.[36] This interplay between diabetes and neutrophils may be the pathomechanism behind the association of both factors with post-EVT ICH in our study.

Higher WBC count has already been associated with less hematoma expansion in spontaneous ICH.[37] However, its association with less post-EVT hemorrhage has not yet been described elsewhere. A higher platelet lymphocyte ratio has been associated with poorer clinical outcomes in patients undergoing thrombolysis and endovascular therapy[38,39]; counterintuitively, our study demonstrates that a lower ratio is associated with sICH (NINDS). Similarly, the association of lower lymphocyte to our outcome of interest (SITS) is also a new finding.

Limitations of our study include its retrospective nature, lack of a core laboratory, and low sample size. Next, perfusion imaging and MRI data were not included in the analysis. The model also needs validation using a different large independent cohort. Furthermore, the models obtained by the study only have moderate accuracy. Lastly, the paper is exploratory in nature. It is a proof of concept of the association of serology markers to post-EVT hemorrhage.

Conclusion

Higher neutrophil counts, low WBC counts, low lymphocyte counts, and low platelet-to-lymphoycyte ratio were baseline

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serology biomarkers that were associated with post-EVT hemorrhage. Our findings, particularly the association of diabetes mellitus and high neutrophil count with post-EVT hemorrhage, support experimental data on the role of thromboinflammation in hemorrhagic transformation of large vessel occlusions. Larger stroke registries with data on inflammatory biomarkers are necessary to confirm our findings.

Conflict of Interest

The authors have no conflicts of interest to declare.

Statement of Authorship

All authors fulfilled the following ICMJE criteria for authorship; substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Statement

The full dataset of the study is available upon reasonable request.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.197.

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