RESEARCH ARTICLE

Parenchymal Hemorrhage Rate Is Associated with Time to Reperfusion and Outcome

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Objective: Despite a 90% reperfusion rate, only 50% of patients with anterior circulation large vessel occlusion-related acute ischemic stroke (LVO-AIS) have a functional recovery at 3 months. Parenchymal hematoma (PH) is a predictor of poor outcome after endovascular treatment (EVT). We aim to investigate the relationship between the delay from onset to reperfusion, the occurrence of PH, and functional outcome.
Methods: The Endovascular Treatment in Ischemic Stroke (ETIS) registry is an ongoing prospective observational study. Data were analyzed from the subgroup of patients who underwent a successful EVT defined by a modified Thrombolysis in Cerebral Infarction (mTICI) score 2b-3. We assessed the factors associated with PH, (ie, PH1 or PH2 grade according to the European Collaborative Acute Stroke Study 2 (ECASS) classification of hemorrhagic transformation), then evaluated the relationships between PH, delay from onset to reperfusion, and functional recovery defined by a modified Rankin Scale (mRS) of 0–2.
Results: We analyzed 2,919 patients with an LVO-related AIS who underwent a successful EVT. Overall, 13.3% of the participant experienced a PH. The rate of PH increased by 2.5% (95% CI 1.5%–3.6%, $p < 0.001$) for every additional hour of onset to reperfusion delay and was, by comparison with the other study patients, consistently associated with a lower rate of functional recovery 19.7% (95% CI 11.6%–27.7%, $p < 0.001$) irrespective of time from onset to reperfusion.
Interpretation: Our results demonstrate that PH rate is associated with the delay from onset to reperfusion and participates in the relationship between time to reperfusion and outcome. Time is Bleeding.

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Endovascular treatment (EVT) is highly effective in patients with anterior large vessel occlusion related to acute ischemic stroke (LVO-AIS).[1] However, despite a 90% reperfusion rate, less than 50% of the patients will achieve a functional recovery at 3 months. Symptomatic intracerebral hemorrhage (sICH) and less commonly parenchymal hematoma (PH) have been proposed as safety endpoints in randomized controlled trials (RCTs) testing EVT versus the best medical treatment of LVO-AIS.[1,2] The occurrence of PH is an independent predictor

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of poor outcome after successful endovascular reperfusion in the early and late time window.[3,4] Blood pressure control and intravenous thrombolysis (IVT) have been typically associated with hemorrhagic transformation (HT).[5,6] However, recent randomized controlled trials (RCTs) results failed to show a significant benefit of withholding IVT before or proposing an intensive blood pressure control after endovascular reperfusion.[7,8] Experimental studies demonstrated in animal models that HT may result from the so-called "no-reflow" phenomenon: a thrombo-inflammatory process in the venular microcirculation despite LVO reperfusion. Its severity and persistence result in blood–brain barrier (BBB) leakage and subsequent HT.[9–11] Ongoing RCTs are testing periprocedural antithrombotic medication to improve microvascular reperfusion by preventing no-reflow and, thus, mitigating the risk of reperfusion hemorrhage. This positive effect can be counterbalanced by the increased risk of HT favored by antithrombotic treatment, as recently illustrated by the results of the MR-CLEAN-MED study.[12] If typically accepted, little is known about the relationship between the rate of PH and the delay from onset to endovascular reperfusion and its impact on clinical outcome. In other words, would the relationship between time to reperfusion and outcome not only be related to infarct progression but also to an increased rate of PH? With this as a background, we aim to investigate in a large prospective clinical practice registry the relationships between the occurrence of PH, the delay between onset and endovascular reperfusion, and functional outcome.

Methods

Study Design and Data Sources

We used data from the Endovascular Treatment in Ischemic Stroke (ETIS) registry (ClinicalTrials.gov Identifier: NCT03776877), an ongoing, prospective multicenter observational registry. This registry is composed by 21 French comprehensive stroke centers. It is pooling individual data of consecutive adult patients treated by EVT for an LVO-AIS. All data of the ETIS registry are collected, analyzed, stored, and accessed locally according to the recommendations of the "Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de santé." IRB ETIS number was: 2018–09 and IDRCB number: 2017-A03457-46.

Written informed consent was obtained from all the patients or their legal representatives.

Centers and Patients

Detailed materials have been previously described.[13] For this analysis, we used the following inclusion criteria: known time of symptom onset, intracranial proximal arterial occlusion in the anterior circulation (tandem or intracranial carotid artery [ICA, ICA-T] or M1 segment of the middle cerebral artery), and a successful EVT defined by a modified Thrombolysis in Cerebral Infarction (mTICI) score 2b-3 at the end of the procedure. Collateral score was assessed on the first run of the angiography before EVT. The analyzed data concerned patients treated with EVT between January 01, 2015, and Dec 31, 2021, in 21 centers.

Outcomes

Neuroimaging criteria were evaluated by one neuroradiologist (>10 years of experience) of each center, blinded to the procedure results and clinical outcome. Brain imaging (CT or magnetic resonance imaging) was performed systematically 24 hours after MT.

HT was evaluated according to the European Collaborative Acute Stroke Study-2 (ECASS) classification.[14] sICH was defined by a Type 2 parenchymal hemorrhage with deterioration in National Institutes of Health Stroke Scale score of 4 points or death.

Functional outcome was assessed using the modified Rankin Scale (mRS) performed by certified investigators during a routinely scheduled clinical visit or a standardized telephone interview.

Study End Points

PH was defined by either a PH1 or 2 grade on ECASS-2 classification. Exploratory analyses also evaluated sICH, PH2, and any ICH. Delay from onset to reperfusion; was calculated by the delay between the time of symptom onset and the end of the MT procedure. Functional recovery was defined by an mRS 0–2 at 3 months.

Statistical Analysis

Quantitative variables are expressed by the mean (SD) for normally distributed parameters or median (interquartile range [IQR]) otherwise. Categorical variables are expressed as numbers (percentages). The patients were divided into two groups; PH (i.e., PH1 + PH2) vs. the others (HI1, HI2, and no hemorrhage). Baseline characteristics were compared between groups using the analysis of variance (ANOVA) test for Gaussian continuous variables, Kruskal-Wallis test for non-Gaussian continuous variables, or $\chi 2$ test (or Fisher' exact test when the expected cell frequency was <5) for categorical variables, as appropriate. To identify predictors of PH, multiple regression models were fitted using the Akaike and Bayesian information criterion (AIC and BIC, respectively).[15]

The effect of PH on functional outcome, was assessed visually as an ordinal logistic regression analysis could not be used because of violation of the proportional

odds assumption. As a secondary outcome we dichotomized mRS (mRS 0–2 vs 3–6) and compared the different types of HT (HI1, HI2, PH1, PH2) and PH by pairs using mixed logistic regression with center as random effect and listwise deletion for missing data. Adjustment for potential confounders included age, systolic blood pressure at presentation, diabetes, blood glucose, imaging type at admission, NIHSS and ASPECTS, total number of passes and intravenous thrombolysis. Effects are presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were conducted at a two-tailed α level of 0.05. The data were analyzed using STATA ver. 17.

Results

Among 4,946 patients collected in the ETIS registry from January 2015 to December 2021, 2,919 were enrolled in this study. Reasons for exclusion (age < 18 years; MT not realized, no reperfusion was achieved, ECASS status not addressed at day 1, subarachnoid hemorrhage only, intraventricular hemorrhage only or remote hemorrhage only) are summarized on Fig 1.

Among the patient enrolled in the study 1,185 (47%) experienced an HT and 301 (15%) a PH. On univariate analysis, the occurrence of PH was associated with sex ($p < 0.001$), hypertension ($p < 0.001$), hypercholesterolemia ($p = 0.001$), diabetes ($p = 0.001$), coronaropathy ($p = 0.041$), initial systolic blood pressure ($p = 0.011$), initial diastolic blood pressure ($p = 0.008$), glycemia ($p < 0.001$), initial NIHSS ($p < 0.001$), initial ASPECTS ($p < 0.001$), clot burden score ($p = 0.008$), collateral grade ($p < 0.001$) admission mode ($p < 0.001$) IV thrombolysis ($p = 0.036$), general anesthesia ($p = 0.018$), thrombectomy strategy ($p < 0.001$) and time from onset to reperfusion ($p < 0.001$) (Supporting Information Table S1, which is available online).

According to the AIC/BIC information criterion, independent predictors of PH HT were systolic blood pressure at presentation (1.01 95% CI 1.004–1.01, $p = 0.001$), diabetes (OR 1.67 95% CI 1.08–2.57, $p = 0.02$), blood glucose (OR 1.06 95% CI 1.007–1.12, $p = 0.026$), initial NIHSS (OR 1.04 95% CI 1.01–1.08, $p = 0.002$), initial ASPECTS (OR 0.84 95% CI 0.78–0.91, $p = 0.001$), total number of

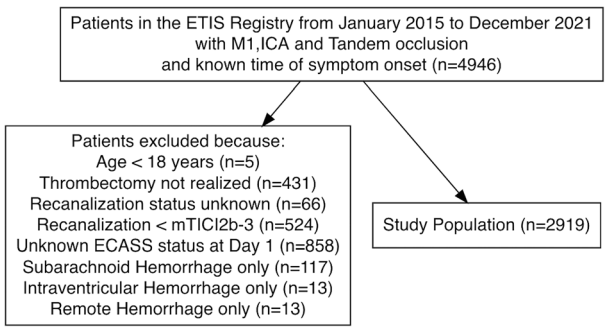

FIGURE 1: Patient flow chart.

TABLE. Predictors of PH Hemorrhagic Transformation According to the AIC/BIC Criterion

	Odds Ratio (95% CI)	*p*-value
SBP at presentation	1.01 (1.004–1.01)	0.001
Diabetes	1.67 (1.08–2.57)	0.002
Blood glucose	1.06 (1.007–1.12)	0.026
NIHSS	1.04 (1.01–1.08)	0.002
ASPECTS	0.84 (0.78–0.91)	0.018
Initial imaging with CT	(OR 1.77 95% CI 1.14–2.74)	0.01
Total number of passes ≤ 2	0.63 (0.44–0.92)	0.009
Time from onset to reperfusion	1.002 (1.001–1.003)	<0.001

Abbreviations: AIC/BIC, Akaike and Bayesian information criterion; ASPECTS: Alberta Stroke Program Early CT Scan Score; CI, confidence interval; NIHSS: National Institute of Health Stroke Scale; PH, parenchymal hematoma; SBP: systolic blood pressure; SDP: diastolic blood pressure.

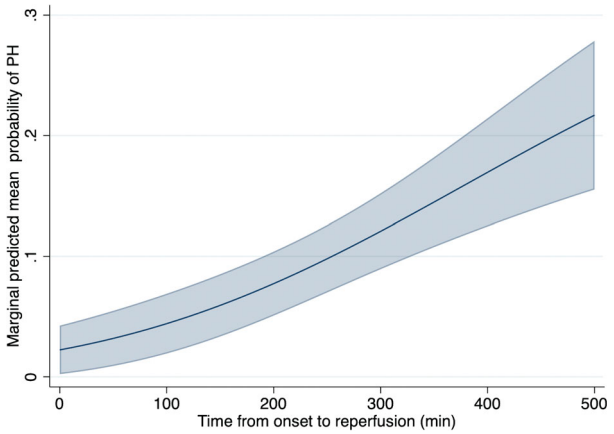

FIGURE 2: Relationship between the probability of parenchymal hemorrhage (PH) and the Delay between onset to reperfusion. After adjustment for age, systolic blood pressure at presentation, diabetes, blood glucose, National Institute of Health Stroke Scale (NIHSS) and Alberta Stroke Program Early CT Scan Score (ASPECTS) at admission, total number of passes less or equal to two, initial imaging type, intravenous thrombolysis, the mean marginal probability of a PH hemorrhagic transformation increases by 2.5% (95% CI 1.5%–3.6%, $p < 0.001$) for every additional hour of reperfusion delay. [Color figure can be viewed at www.annalsofneurology.org]

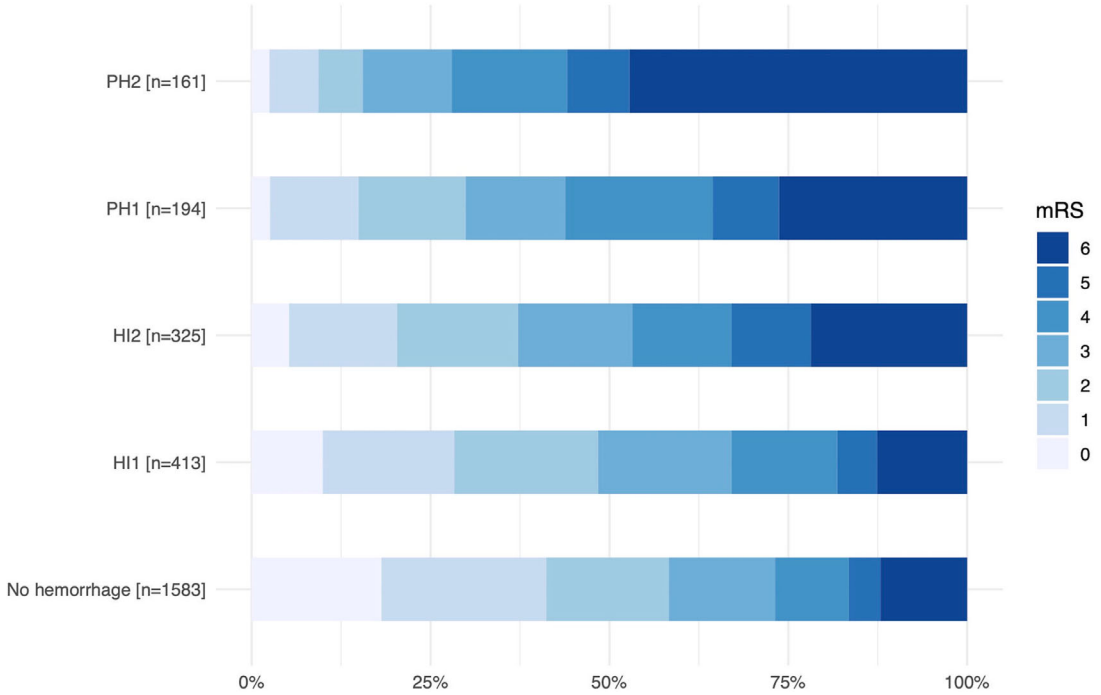

FIGURE 3: Distribution of modified Rankin Scale (mRS) according to ECASS-2 grade. Hemorrhagic infarction (HI 1 et 2), parenchymal hemorrhage (PH 1 et 2). The odds of good functional recovery (mRS 0–2) were decreased for the HI1 compared to the no hemorrhagic transformation group (odds ratio [OR] 0.67; 95% confidence interval [C]I 0.54–0.84, $p < 0.001$), the HI2 compared to the HI1 group (OR 0.59 95% CI 0.43–0.80, $p = 0.001$), the PH2 compared to the PH1 group (OR 0.42; 95% CI 0.24–0.72, $p = 0.002$), while there was a statistical tendency for decreasd odds of good functional recovery (mRS 0–2) in the HI2 compared to the HI1 group (OR 0.68; 95% 0.46–1.01, $p = 0.06$).

passes less or equal to two (OR 0.63 95% CI 0.44–0.92, $p = 0.018$), initial imaging with CT (OR 1.77 95% CI 1.14–2.74, $p = 0.01$), and time from onset to reperfusion (OR 1.002 95% CI 1.001–1.003, $p < 0.001$) (Table). The mean marginal probability of PH increased by 2.5% (95% CI 1.5%–3.6%, $p < 0.001$) for every additional hour delay of reperfusion (Fig 2). In addition, the mean marginal probabilities of sICH; PH2 and any ICH increased respectively by 1.6% (95% CI 0.7%–2.4%, $p < 0.001$); 1.1% (95% CI 0.3%–1.9%, $p = 0.004$) and 4.8% (95% CI 3.3%–6.3%, $p < 0.001$) for every additional hour delay of reperfusion (Supporting Information Figs S1–S3).

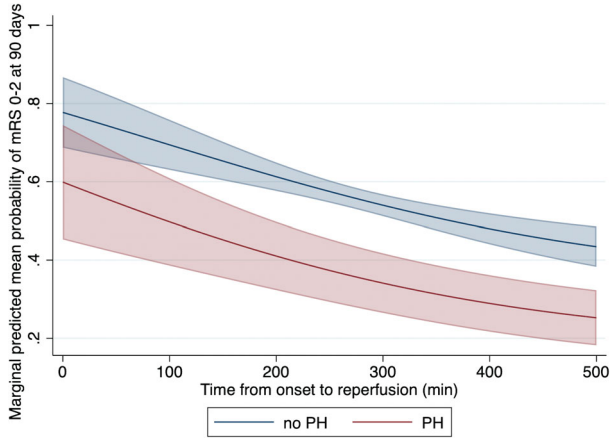

FIGURE 4: Relationship between the occurrence of parenchymal hemorrhage (PH; Blue no PH; Red – PH hemorrhagic transformation), the delay from onset reperfusion, and functional recovery (mRS 0–2). After adjustment for age, systolic blood pressure, National Institute of Health Stroke Scale (NIHSS), Alberta Stroke Program Early CT Scan Score (ASPECTS), diabetes, blood glucose, number of passes less or equal to two and intravenous thrombolysis, the mean marginal probability of functional recovery (mRS 0–2) diminishes by an average of 19.7% (95% CI 11.6%–27.7%, $p < 0.001$) for every additional hour of reperfusion delay.

The mRS distribution according to individual HT subtypes is shown in Fig 3. After adjustment, PH diminished the mean marginal probability of having a good outcome by 19.7% (95% CI 11.6%–27.7%, $p < 0.001$). This effect remained stable irrespective of the onset to reperfusion time delay (Fig 4).

Discussion

In this study, we assessed the association of the delay from onset to reperfusion with PH and outcome of LVO-AIS patients who underwent endovascular reperfusion in current clinical practice. Our results confirm that PH and delay from onset to reperfusion were related, and both impacted the functional outcome of LVO-AIS patients who underwent endovascular reperfusion.

We previously reported in a smaller dataset of the ETIS registry a strong relationship between the occurrence of PH and poor functional outcome.[13] One of the specificity of the current study is that it focused on the subgroup of patients who underwent a successful EVT. The rate of PH was consistent with previous studies (15%).[6] Age, NIHSS, ASPECTS, initial imaging with CT, and procedure duration were associated with PH. Interestingly, delay from onset to reperfusion was also a strong independent predictor of the occurrence of PH and the occurrence of PH was associated at each time point with a consistent 19.7% (95% CI 11.6%–27.7%, $p < 0.001$) decreased mean marginal probability of functional recovery after a successful EVT. Another large national clinical practice registry, the MR CLEAN registry,[16] confirmed that the delay from onset to reperfusion was associated with outcome but failed to demonstrate an association with the occurrence of sICH. We did confirm in our dataset a relationship between delay from onset to reperfusion and the occurrence of sICH as well as any HT or PH2 (Supporting Information Figs S1–S3). The MR CLEAN MED study has been stopped prematurely for safety reasons.[12] In this RCT, the patients treated by EVT allocated to a moderate dose of periprocedural unfractionated heparin had a higher rate of sICH and worse outcome than those who did not receive unfractionated heparin. But unfractionated heparin was also associated with an increased recanalization rate and subgroup analyses showed that the point estimate of the treatment effect of unfractionated heparin was beneficial in patients with an onset to reperfusion time shorter than 195 minutes. This finding suggests a relationship between heparin-associated benefit (increased reperfusion), hemorrhagic risk, and delay from onset to reperfusion.

We have recently demonstrated in a prospective cohort study of patients treated by EVT after a median delay of 4.5 hours after onset and regardless of perfusion imaging profile, that the absence of salvageable ischemic tissue on pretreatment imaging as well as the occurrence of HT were both independent predictors of poor functional outcome after reperfusion.[3] We also found a relationship between HT and outcome in the treatment arm of the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE-3) study in which endovascular reperfusion was achieved after a median delay of 13 hours.[4] Interestingly in the early time window dataset, the rate of PH was 30% versus 16% in the treatment arm of the DEFUSE-3 trial. This discrepancy might be explained by another critical predictor of PH: a different imaging selection. In the early time window study, a low ASPECTS score was not an exclusion criterion, and investigators were blinded to the results of perfusion imaging. In DEFUSE-3, patients were selected based on the presence of a small to moderate core and a large salvageable ischemic tissue on baseline imaging.

As a consequence, baseline core lesion volume was almost twice larger in the early time window cohort by comparison with the DEFUSE-3 treatment arm, which may explain the observed difference. Our results also demonstrate a strong relationship between PH and low ASPECTS, and sICH rates were higher in the MT arm in a recent RCT testing EVT vs. best medical management in patients with a low ASPECTS within 6 hours after onset.[17] They also suggest that initial imaging by CT was by comparison with MRI associated with an higher rate of PH after adjustment on ASPECTS. The results of ongoing RCTs testing EVT in patients with low ASPECTS in a 0–24 hours time window, regardless of the imaging modality, will be of particular interest to assess the relative effect of low ASPECTS and the delay from onset to reperfusion on the PH risk and its impact on functional recovery.[18,19]

Overall, our results underline the importance of an expedited transfer of patients with suspected LVO-AIS to the cath lab to reduce the delay from onset to reperfusion, encouraging the use mobile stroke unit and the completion of RCT testing direct transfer to the angio suite.[20,21]

Our study suffers from several limitations inherent to its design. First, as it is a clinical practice study, information re-baseline imaging profiles were limited to ASPECTS estimated by various imaging modalities. Therefore we cannot isolate from our dataset any other significant reliable imaging biomarker. Studies investigating objective core lesion volume, mismatch, and other advanced imaging biomarkers of the risk of HT are ongoing on other datasets. Second, our study focused on PH. This choice was guided by our experience in the previous BP-Target study, where HI1 and HI2 diagnosis remained challenging due to contrast extravasation and differential diagnosis required an extra follow-up imaging at 3 days.[7] We, therefore, focused on PH in this proof of concept paper. Nonetheless our results confirm that delay from onset to reperfusion was associated with the occurrence of any ICH (Supporting Information Figs 1-3).

In conclusion, our findings confirm in a large clinical practice prospective registry that the PH rate increases with the delay from onset to reperfusion and is associated with functional outcome. Time is not only penumbral salvage, Time is also bleeding.

Acknowledgments

On behalf of the ETIS investigators (cf Appendix).

Authors Contribution

JMO, SF, MM and BG contributed to the conception and design of the study; All authors contributed to the acquisition and analysis of data; JMO, SF, MM and BG contributed to drafting the text or preparing the figures.

Potential Conflict of Interest

Nothing to report.

References

1. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723–1731.
2. Jovin TG, Nogueira RG, Lansberg MG, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. Lancet 2022;399:249–258.
3. Olivot JM, Heit JJ, Mazighi M, et al. What predicts poor outcome after successful thrombectomy in early time window? J Neurointerv Surg 2021; neurintsurg-2021-017946.
4. Heit JJ, Mlynash M, Christensen S, et al. What predicts poor outcome after successful thrombectomy in late time windows? J Neurointerv Surg 2021;13:421–425.
5. Whiteley WN, Emberson J, Lees KR, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol 2016;15:925–933.
6. Maier B, Desilles JP, Mazighi M. Intracranial hemorrhage after reperfusion therapies in acute ischemic stroke patients. Front Neurol 2020;11:599908.
7. Mazighi M, Richard S, Lapergue B, et al. Safety and efficacy of intensive blood pressure lowering after successful endovascular therapy in acute ischaemic stroke (BP-TARGET): a multicentre, open-label, randomised controlled trial. Lancet Neurol 2021;20:265–274.
8. Turc G, Tsivgoulis G, Audebert HJ, et al. European stroke organisation—European Society for Minimally Invasive Neurological Therapy expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion. Eur Stroke J 2022;7:I–XXVI.
9. Desilles JP, Syvannarath V, Ollivier V, et al. Exacerbation of thromboinflammation by hyperglycemia precipitates cerebral infarct growth and hemorrhagic transformation. Stroke 2017;48:1932–1940.
10. Ng FC, Churilov L, Yassi N, et al. Microvascular dysfunction in blood-brain barrier disruption and hypoperfusion within the infarct post-treatment are associated with cerebral edema. Stroke 2022;53:1597–1605.
11. Mishra NK, Leigh R, Campbell BCV. Editorial: intracranial bleeding after reperfusion therapy in acute ischemic stroke. Front Neurol 2021;12:745993.
12. van der Steen W, van de Graaf RA, Chalos V, et al. Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial. Lancet 2022;399:1059–1069.
13. Boisseau W, Fahed R, Lapergue B, et al. Predictors of parenchymal hematoma after mechanical Thrombectomy: a multicenter study. Stroke 2019;50:2364–2370.
14. Hacke W, Kaste M, Fieschi C, et al. 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 1998;352:1245–1251.
15. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. Sociol Methods Res 2004;33:261–304.
16. Mulder M, Jansen IGH, Goldhoorn RB, et al. Time to endovascular treatment and outcome in acute ischemic stroke: MR CLEAN registry results. Circulation 2018;138:232–240.
17. Yoshimura S, Sakai N, Yamagami H, et al. Endovascular therapy for acute stroke with a large ischemic region. N Engl J Med 2022;386:1303–1313.
18. Sarraj A, Pizzo E, Lobotesis K, et al. Endovascular thrombectomy in patients with large core ischemic stroke: a cost-effectiveness analysis from the SELECT study. J Neurointerv Surg 2021;13:875–882.
19. Bendszus M, Bonekamp S, Berge E, et al. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. Int J Stroke 2019;14:87–93.
20. Grotta JC, Yamal JM, Parker SA, et al. Prospective, multicenter, controlled trial of Mobile stroke units. N Engl J Med 2021;385:971–981.
21. Riou-Comte N, Zhu F, Cherifi A, et al. Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicentre randomised controlled DIRECT ANGIO trial protocol. BMJ Open 2021;11:e040522.