Neurological Sciences
https://doi.org/10.1007/s10072-021-05218-x

ORIGINAL ARTICLE

Abnormal neurological pupil index is associated with malignant cerebral edema after mechanical thrombectomy in large vessel occlusion patients

Ehsan Dowlati[1] · Kwadwo Sarpong[2] · Stanley Kamande[2] · Austin H. Carroll[2] · Jerome Murray[2] · Alynna Wiley[2] · Brendon Peterson[2] · Jeffrey C. Mai[1,3] · Jason J. Chang[4] · Edward F. Aulisi[3] · Rocco A. Armonda[1,3] · Daniel R. Felbaum[1,3]

Received: 12 January 2021 / Accepted: 23 March 2021

Abstract

Background and objectives Malignant cerebral edema (MCE) is a feared complication in patients suffering from large vessel occlusion. Variables associated with the development of MCE have not been clearly elucidated. Use of pupillometry and the neurological pupil index (NPi) as an objective measure in patients undergoing mechanical thrombectomy (MT) has not been explored. We aim to evaluate variables significantly associated with MCE in patients that undergo MT and hypothesize that abnormal NPi is associated with MCE in this population.

Methods A retrospective analysis of patients with acute ischemic stroke who had undergone MT at our institution between 2017 and 2020 was performed. Baseline and outcome variables were collected, including NPi values from pupillometry readings of patients within 72 h after the MT. Patients were divided into two groups: MCE versus non-MCE group. A univariate and multivariate analysis was performed.

Results Of 284 acute ischemic stroke patients, 64 (22.5%) developed MCE. Mean admission glucose (137 vs. 173; $p < 0.0001$), NIHSS on admission (17 vs. 24; $p < 0.01$), infarct core volume (27.9 vs. 17.9 mL; $p = 0.0036$), TICI score ($p = 0.001$), and number of passes (2.9 vs. 1.8; $p < 0.0001$) were significantly different between the groups. Pupillometry data was present for 64 patients (22.5%). Upon multivariate analysis, abnormal ipsilateral NPi (OR 21.80 95% CI 3.32–286.4; $p = 0.007$) and hemorrhagic conversion were independently associated with MCE.

Conclusion Abnormal NPi and hemorrhagic conversion are significantly associated with MCE in patients following MT. Further investigation is warranted to better define an association between NPi and patient outcomes in this patient population.

Keywords Ischemic stroke · Thrombectomy · Cerebral edema · Pupillary reflex · Pupillometry

Introduction

Acute ischemic stroke (AIS) is one of the leading causes of morbidity and mortality worldwide [1]. Randomized control trials have validated the use of endovascular mechanical thrombectomy (MT) as the gold standard for AIS with intracranial large vessel occlusion (LVO) and early intervention has proven to be effective in predicting good long-term outcomes and recurrence [2, 3].

Although MT offers revascularization as treatment for AIS, patients are still at risk for potential complications including malignant cerebral edema (MCE). MCE is a life-threatening complication that can lead to increased intracranial pressure (ICP), herniation, and even neurological deterioration [4]. Developing MCE has been linked to a number of risk factors such as hyperglycemia, Alberta Stroke Program Early CT

Previous presentation or submissions: Parts of these results were submitted as an abstract to the American Association of Neurological Surgeons Meeting and the Neurosurgical Society of the Virginias in 2021.

✉ Ehsan Dowlati
edowlati@gmail.com

[1] Department of Neurosurgery, MedStar Georgetown University Hospital, 3800 Reservoir Road NW, PHC7, Washington, DC 304-215-3107, USA

[2] Georgetown University School of Medicine, 3900 Reservoir Road NW, Washington, DC, USA

[3] Department of Neurosurgery, MedStar Washington Hospital Center, 110 Irving St. NW, Washington, DC, USA

[4] Department of Critical Care Medicine, MedStar Washington Hospital Center, 110 Irving St. NW, Washington, DC, USA

Published online: 29 March 2021

score (ASPECTS), and dense middle cerebral artery (MCA) sign [5]. Treatment options for such complications are limited to medical management or decompressive hemicraniectomy (DHC) and early treatment can help improve outcomes. Relevant studies on predictive factors that affect patient outcomes after MT or the need for DHC are scarce, and the inter-rater reliability of subjective assessment by neurologists and neurosurgeons remains poor [6]. Thus, studies focusing on identifying robust and objective diagnostic tools in assessing patients who are at risk of developing MCE after MT are warranted.

Studies have implicated pupillary dysfunction to be a good marker for neurological deterioration following onset of a traumatic brain injury (TBI) and AIS [7, 8]. The use of automated objective pupillometers has increased the usefulness of this exam in the neurointensive care setting [9]. Specifically, the neurological pupil index (NPi; ranging 0–5), which is derived from an algorithm that incorporates pupillary size and reactivity, has been an objective measure used to assess oculomotor nerve function [9–11]. Studies demonstrate that a sudden drop in NPi signifies worsening cerebral edema or impending herniation in patients with severe TBI or large hemispheric strokes [8]. Due to these promising findings, serial pupillary light reflex recordings with an automated pupillometer have been reliably used to assess outcomes in multiple disciplines in neurointensive care and other critical care units [12, 13].

In this study, we aim to investigate variables associated with a diagnosis of MCE including the neurological pupil index (NPi) from pupillometry. This is the first study to evaluate NPi as an objective measure for monitoring MCE in AIS patients who have undergone MT for LVO. We hypothesize that abnormal NPi is associated with and may predict MCE in patients that undergo MT.

Methods

Study population

A retrospective review of all adult patients undergoing MT for LVO at our institution was performed between January 2017 and 2020. Patients who had confirmed LVO at the internal carotid artery (ICA) or MCA, first and second segments, were included. Patients were divided into two groups: patients that developed MCE and patients that did not. MCE diagnosis was established radiographically based on CT and/or MRI within 5 days of admission. Our criteria for MCE included the following: hypodensity of greater than half of MCA territory, sulcal effacement, and midline shift greater than 5 mm with obliteration of basal cisterns [14]. This study was approved by our institutional review board.

Data collection

Baseline characteristic variables were collected including age, sex, NIHSS on admission, baseline modified Rankin Score (mRS), admission glucose, body mass index (BMI), comorbidities (hypertension, diabetes, heart failure, and kidney disease), tissue plasminogen activator (tPA) administration, occlusion site, and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification for etiology. Procedural variables analyzed included time from last known normal to reperfusion, number of passes of the retriever or aspirator, and modified Thrombolysis in Cerebral Infarction (mTICI) score, which were all recorded during the time of the procedure. Radiographic data was collected including ASPECTS when CT was available, infarct core volume and perfusion mismatch (difference in volume between infarct penumbra and core volume) when perfusion study was available, and presence of hemorrhagic conversion as defined by intraparenchymal hemorrhage Type 2 (PH2) occupying 30% or more of the infarcted tissue [15].

Automated pupillometer (NPi-200 Pupillometer System, NeurOptics, Inc.) data for patients were collected when available. Determination of pupillometry used was based on neurosurgeon and neurointensivist preference. When recorded, NPi values were measured once every hour. Recordings from within 72 h after MT were used for analysis. The NPi was the primary measure analyzed from the pupillometry data given its clinical relevance. Finally, outcome measures were also collected including need for hyperosmolar therapy or decompressive hemicraniectomy, length of stay (LOS), in-hospital complication, discharge disposition, NIHSS at discharge, and functional outcome as mRS at 3-month follow-up.

Statistical analysis

Baseline characteristics and outcome variables were classified as categorical or continuous variables. The univariate analysis was performed using Fisher's exact test and Mann-Whitney *U* tests. A multivariate analysis was performed using a binomial logistic regression with MCE as the dependent variable to analyze the impact of confounders including age, gender, glucose level, occluded vessel site, NIHSS at admission, number of passes, revascularization time, TICI score, hemorrhagic conversion, and NPi status. Statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). For the statistical analyses, we used the generalhoslem, stats, precrec R packages [16]. Odds ratios (OR) were calculated with a 95% confidence interval (CI) and significance was determined by *p*-value less than 0.05.

Results

Baseline characteristics

A total of 284 patients (mean age 65.4 years; 48.2% male) were included in the study. Fifty-one (18.0%) were diagnosed with an ICA occlusion, 186 (65.5%) with an M1 occlusion, and 47 (16.5%) with an M2 occlusion. Median baseline mRS was 0 [IQR 0–1] and median admission NIHSS was 17 [IQR 13–22]; 150 (52.8%) patients received intravenous tPA prior to MT. Mean time from last known normal to recanalization was 8.4 ± 4.7 h. Forty-three (15.1%) patients experienced hemorrhagic conversion of their stroke territory and 64 (22.5%) were diagnosed with MCE on CT or MRI within 5 days of AIS onset.

Compared to non-MCE patients (n = 220), MCE patients (n = 64) were less likely to be male (35.9% vs. 51.8%, p = 0.0320). They were more likely to have had an ICA occlusion (35.9% vs. 12.7%; $p < 0.0001$) compared to MCA occlusion (Fig. 1a). Mean infarct core volume was significantly higher in MCE patients (27.9 vs. 17.9 mL; $p = 0.0036$). MCE patients had a higher rate of diabetes (57.8% vs. 31.8%; $p < 0.0001$) and higher blood glucose level on admission (173 vs. 137; $p < 0.0001$). Median admission NIHSS was significantly higher in MCE patients (24 vs. 17; $p = 0.0021$). Stroke TOAST etiology, ASPECTS, and perfusion mismatch volume did not significantly differ (Table 1).

Procedurally, mean time from last known normal to recanalization was 8.40 h for the non-MCE patients and 8.63 h for the MCE patients. TICI score distribution was significantly different between the two groups, with 89.1% of non-MCE patients achieving a TICI 2B or 3 score versus 70.3% of MCE patients ($p < 0.0001$; Fig. 1b). MCE patients also underwent greater number of passes on average (1.8 vs. 2.9; $p < 0.0001$). MCE patients were more likely to have hemorrhagic conversion (35.9% vs. 9.1%; $p < 0.0001$) (Table 1).

Outcome measures

Compared to the non-MCE group, the MCE group had greater LOS (16.3 vs. 9.2 days; p = 0.0279). Forty-three (67.2%) MCE patients underwent a decompressive hemicraniectomy due to refractory medical treatment compared to no patients in the non-MCE group ($p < 0.0001$). They also were treated with hyperosmolar therapy at a higher rate (96.9% vs. 15.0%; $p < 0.0001$). Median NIHSS at discharge was 24 for the MCE patients while it was 7 for the non-MCE patients ($p < 0.0001$). MCE patients were more likely to have an in-hospital complication during their stay (84.4% vs. 58.7%; $p < 0.0001$). Most common complications included respiratory failure followed by infection (pneumonia, urinary tract infection, etc.). Mortality rates were worse in MCE patients with 51.6% facing mortality compared to 8.6% in the non-MCE group ($p < 0.0001$). Additionally, significantly less patients in the MCE group went home after discharge compared to non-MCE patients (3.1% vs. 27.7%; $p < 0.0001$). In terms of functional outcomes, mRS scores for all patients were obtained at 3 months follow-up and significantly higher proportion of patients in the non-MCE were independent with an mRS of 0–2 compared to MCE group (52.3% vs. 6.3%; $p < 0.0001$) (Table 2).

Pupillometry results

Twenty-nine (13.2%) patients from the non-MCE group and 35 (54.7%) MCE patients underwent automated pupillometry within 72 h after MT. Mean number of data time points available for non-MCE and MCE patients was 27.5 and 23.5 data points, respectively. NPi values were averaged for the ipsilateral side (e.g., right NPi values were used when there was a right MCA vessel occlusion) and compared (4.12 in non-MCE group vs. 2.46 in MCE group; $p < 0.0001$). Ipsilateral NPi averages were dichotomized to normal versus abnormal using 3.0 as cut-off, similar to previous studies [17, 18]

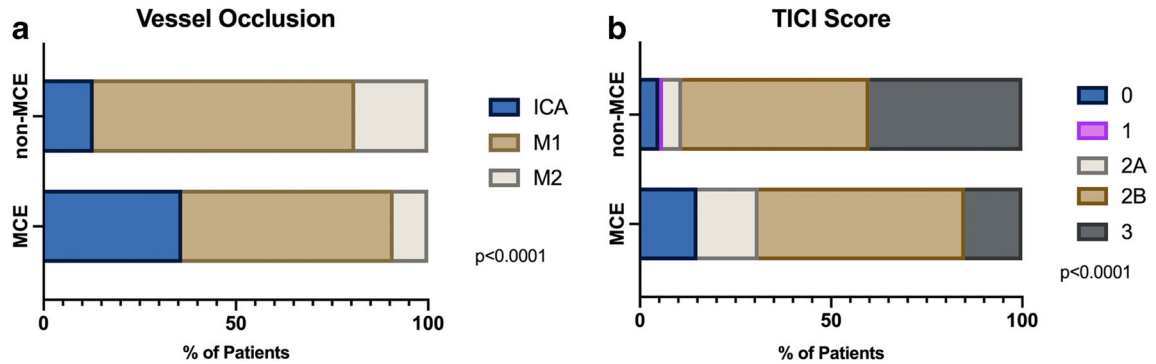

Fig. 1 **a** Proportion of patients with location of occlusion at internal carotid artery (ICA), middle cerebral artery, segment 1 (M1), and segment 2 (M2) is significantly different between patients with and without malignant cerebral edema (MCE) ($p < 0.0001$). **b** Proportion of patients corresponding to TICI score after mechanical thrombectomy is significantly different between patients with and without malignant cerebral edema (MCE) ($p < 0.0001$)

Table 1 Comparison of baseline and procedural characteristics between mechanical thrombectomy patients diagnosed with malignant cerebral edema (MCE) and those with no MCE

Variable	No MCE (n = 220)	MCE (n = 64)	*p*-value
Mean age	65.03 ± 15.5	66.56 ± 14.9	0.5210
Male sex	114 (51.8%)	23 (35.9%)	**0.0320**
Vessel occlusion			**< 0.0001**
Internal carotid artery	28 (12.7%)	23 (35.9%)	
Middle cerebral artery, M1 segment	151 (68.6%)	35 (54.7%)	
Middle cerebral artery, M2 segment	41 (18.6%)	6 (9.4%)	
TOAST stroke etiology			0.8002
1-Large artery atherosclerosis	68 (30.9%)	24 (37.5%)	
2-Small vessel disease	10 (4.5%)	1 (1.6%)	
3-Cardioembolism	104 (47.3%)	30 (46.9%)	
4-Other determined etiology	21 (9.5%)	5 (7.8%)	
5-Undetermined etiology	17 (7.3%)	4 (6.3%)	
Median ASPECTS [IQR]	9 [8–10]	9 [8–10]	0.2170
Mean admission glucose	137.4 ± 52.6	173.0 ± 78.0	**< 0.0001**
Mean body mass index	29.0 ± 7.2	28.8 ± 6.6	0.9200
Comorbidities			0.1157
Hypertension	176 (80.0%)	56 (87.5%)	0.2010
Diabetes mellitus	70 (31.8%)	37 (57.8%)	**< 0.0001**
End-stage/chronic kidney disease	26 (11.8%)	9 (14.1%)	0.6670
Heart failure/atrial fibrillation	83 (37.7%)	22 (34.4%)	0.6610
Baseline mRS			0.8388
0–1	189 (85.9%)	56 (87.5%)	
2–5	31 (14.1%)	8 (12.5%)	
Median admission NIHSS [IQR]	17 [11–23]	22 [17–24]	**0.0021**
Received tPA	114 (51.8%)	36 (56.3%)	0.5711
Mean infarct core volume (mL)	17.9 ± 34.3	27.9 ± 30.4	**0.0036**
Mean perfusion mismatch (mL)	109.2 ± 78.4	112.8 ± 73.3	0.8811
Mean revascularization time (hours)	8.4 ± 4.8	8.63 ± 4.9	0.5628
TICI score			**< 0.0001**
0	11 (5.0%)	9 (14.1%)	
1	1 (0.5%)	0 (0.0%)	
2A	12 (5.5%)	10 (15.6%)	
2B	110 (50.0%)	35 (54.7%)	
3	86 (39.1%)	10 (15.6%)	
Mean no. of passes	1.82 ± 0.9	2.88 ± 1.3	**< 0.0001**
Hemorrhagic conversion	20 (9.1%)	23 (35.9%)	**< 0.0001**

Bold values denote statistical significance, p values < 0.05

ASPECTS, Alberta stroke program early CT score; *mRS*, modified Rankin Scale; *NIHSS*, National Institute of Health Stroke Scale; *tPA*, tissue plasminogen activator; *TICI*, thrombolysis in cerebral infarction

Table 2 Comparison of outcomes between mechanical thrombectomy patients diagnosed with malignant cerebral edema (MCE) and those with no MCE

Variable	No MCE (n = 220)	MCE (n = 64)	*p*-value
Decompressive hemicraniectomy	0 (0.0%)	43 (67.2%)	**< 0.0001**
Hyperosmolar therapy	33 (15.0%)	62 (96.9%)	**< 0.0001**
Mean length of stay (days)	9.2 ± 8.5	16.3 ± 14.5	**0.0279**
Median discharge NIHSS [IQR]	7 [3–13]	24 [16–30]	**< 0.0001**
In-hospital complication	91 (58.7%)	54 (84.4%)	**< 0.0001**
Disposition			**< 0.0001**
Home	61 (27.7%)	2 (3.1%)	
Acute rehab	110 (50.0%)	15 (23.4%)	
Skilled nursing facility	25 (11.4%)	7 (10.9%)	
Long-term care	5 (2.3%)	7 (10.9%)	
Death/hospice	19 (8.6%)	33 (51.6%)	
mRS at 3 months			**< 0.0001**
0–2	115 (52.3%)	4 (6.3%)	
3–6	104 (47.7%)	60 (93.7%)	

Bold values denote statistical significance, p values < 0.05

NIHSS, National Institute of Health Stroke Scale; *mRS*, modified Rankins Score

(10.3% abnormal in non-MCE group vs. 57.1% abnormal in MCE group; $p < 0.0001$). Further, patients were dichotomized into two groups: those having any single ipsilateral NPi recording of less than 3.0 and those without any recordings of less than 3.0. All three comparisons between the MCE and non-MCE patients showed significant difference after Bonferroni correction (Table 3). An example of the timeline of two patients in the MCE group undergoing pupillometry change is shown in Fig. 2.

A multivariate logistic regression analysis was completed to determine independent predictors of MCE. Hemorrhagic conversion (OR 7.31 95% CI 1.48–46.2; $p = 0.022$) and abnormal ipsilateral NPi (OR 21.80 95% CI 3.32–286.4; $p = 0.007$) were the variables independently associated with MCE, when controlling for other baseline variables (Table 4; Fig. 3).

Discussion

The current study presents the potential diagnostic and prognostic value of certain variables for patients undergoing MT that develop MCE. Specifically, abnormal NPi and hemorrhagic conversion were independently associated with MCE. MCE patients also had worse outcomes as measured by LOS, discharge NIHSS, complications, disposition, and 3-month mRS.

Baseline characteristics in MT patients

MT has been shown by multiple studies to be superior to medical management for LVO AIS. A meta-analyses of randomized control trials found that MT can increase the odds for better functional outcomes by 50% with better health-related quality of life, and cognitive function after 90 days [19, 20]. Despite these findings, there are several factors that are associated with complications and worse outcomes in AIS, within and outside the setting of MT.

Baseline characteristic differences such as age and sex have been explored in previous studies. One study indicates that females are less likely to regain functional independence after 90 days post-stroke measured by mRS. These differences were found to persist even after MT treatment [21]. Our study similarly demonstrated that females predominated the MCE group (64.1% vs. 35.9%; $p = 0.0320$). In contrast, in many animal models of ischemic stroke, estrogen has been shown to play a neuro-protective role, reducing histological damage, area of infarction, and subsequent cerebral edema [22, 23]. In humans, one series involving the administration of estrogen to post-menopausal women also demonstrated cognitive benefit and reduced burden of AIS [24]. The average female patient was 69.4 years of age in our study and thus menopausal with a paucity of estrogen. Finally, we found no difference in age between the two cohorts, although age has been a risk factor for complicated AIS as older patients often had an increased number of comorbidities resulting in poor outcomes regardless of MT [25].

Admission hyperglycemia during AIS is associated with poorer outcomes, such as higher mortality, poorer neurological and functional results, and lower treatment effects of MT [26, 27]. Our results show that MT patients with MCE were more likely to have elevated admission glucose and have a history of diabetes mellitus. Overall, these findings highlight the importance of recognizing baseline variables that may act as possible risk factor in AIS complications and further investigate its role in MCE.

Other factors such as larger vessel occlusion, including ICA, are commonly associated with increased odds for mortality [28]. This is, again, validated by our results showing increased proportion of ICA occlusion in the MCE group (Fig. 1a), although stroke etiology and ASPECTS score did not significantly differ. Overall, these parameters, such as sex, age, admission glucose, and vessel occlusion, were included in our multivariate analysis to control for these variables and none are independently significant in predicting MCE post-MT in our patients.

Procedural variables in MT patients

Certain procedural parameters have been shown to predict functional outcomes and complications after MT for LVO. Specifically, the utilization of fewer clot retrieval passes has been correlated with improved functional outcomes [29, 30]. In one series, patients fully recanalized (TICI 3) in one pass had significantly better 24-h early neurological improvements and 3-month mRS outcomes. This "first pass effect" was

Table 3 Pupillometry results within first 72 h after mechanical thrombectomy in patients with malignant cerebral edema (MCE) and those with no MCE

Variable	No MCE (n = 29)	MCE (n = 35)	*p*-value
Average pupillometry time points	27.5 ± 21.4	23.5 ± 22.3	0.5934
Ipsilateral average NPi	4.12 ± 1.3	2.46 ± 1.9	**< 0.0001**
Ipsilateral average NPi < 3.0	3 (10.3%)	20 (57.1%)	**< 0.0001**
Single abnormal NPi (< 3.0)	4 (13.8%)	25 (71.4%)	**< 0.0001**

Bold values denote statistical significance, p values < 0.05

NPi, neurological pupil index

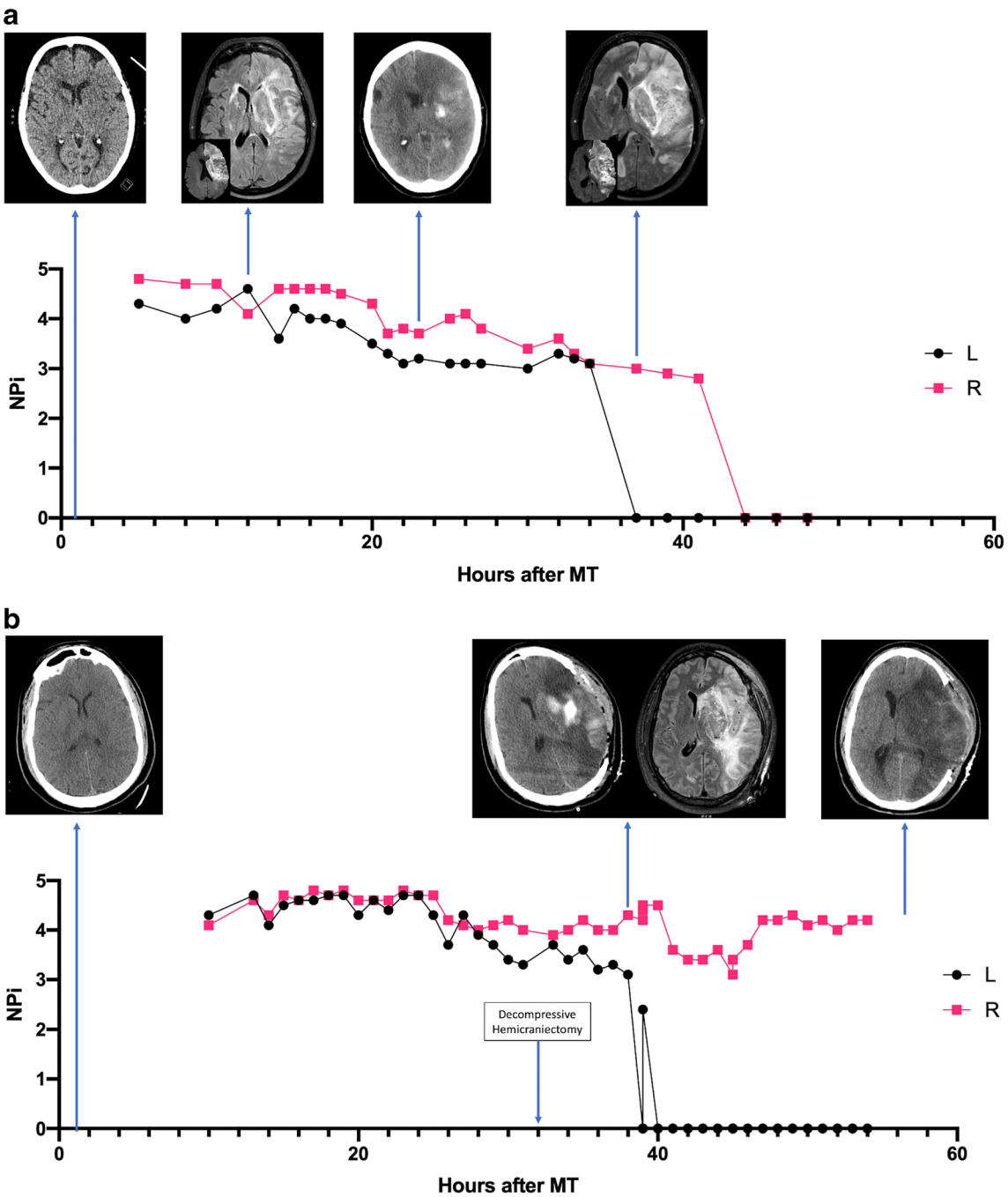

Fig. 2 **a** 79-year-old female with left middle cerebral artery (MCA) occlusion that underwent mechanical thrombectomy 16 h after last known normal. She had an infarct core volume of 9 mL and perfusion mismatch of 39 mL. A TICI 2B recanalization was achieved after two passes with stent retriever. She was monitored with automated pupillometry and NPi values over time are noted with relevant CT and MRIs. She had a steady and continuous drop in NPi of both sides with a sharp decline on the left at 35 h post-thrombectomy followed by a significant drop on the right side at 43 h. Family had declined surgical intervention and patient passed on hospital day 3. **b** 44-year-old male presenting with left MCA occlusion and underwent mechanical thrombectomy 8 h after last known normal. CT showed an ASPECT score of 9. Thrombectomy achieved a TICI 2A recanalization after four passes with stent retriever. He was monitored with automated pupillometry and NPi values over time are noted with relevant CT and MRI. He had a mild decline in left NPi from 4.8 to 3.3 at which point decision was made to surgically intervene. Patient underwent hemorrhagic conversion of their stroke territory and their left NPi continued to drop to 0. Patient was discharged on hospital day 25 to acute rehab with an mRS of 4

postulated to occur due to significantly reduced early infarct core growth [31]. Another study has shown that after five passes, the probability of successful recanalization declines significantly [30]. As expected, the degree of recanalization signified by an increasing TICI score has also been correlated with improved functional outcomes [32].

Table 4 Multivariate logistic regression of predictive variables for patients with malignant cerebral edema (MCE) versus non-MCE patients using the 64 patients with available pupillometry data

Variable	OR	95% CI	*p*-value
Age	1.03	0.98–1.09	0.203
Male sex	0.80	0.15–4.12	0.783
Admission glucose	1.63	0.98–1.02	0.493
Admission NIHSS	0.99	0.88–1.16	0.407
Infarct core volume	1.03	0.99–1.08	0.134
ICA occlusion	1.48	0.29–8.14	0.639
Revascularization time	1.88	0.73–1.05	0.212
TICI 2B or 3	4.89	0.29–160.3	0.298
Hemorrhagic conversion	7.31	1.48–46.2	**0.022**
Abnormal ipsilateral NPi < 3.0	21.80	3.32–286.4	**0.007**

Bold values denote statistical significance, p values < 0.05

OR, odds ratio; *CI*, confidence interval; *NIHSS*, National Institute of Health Stroke Scale; *ICA*, internal carotid artery; *TICI*, thrombolysis in cerebral infarction; *NPi*, neurological pupil index

While the relationship between the number of passes and degree of recanalization to functional outcomes is clear, less data is available to inform the ability of number of passes and TICI score to reliably predict the development of MCE. Our study examines these variables as prognostic determinants of MCE after thrombectomy. In contrast to our findings, Tracol et al. demonstrated that time to MT and infarct volume were independent predictors of MCE, while TICI score was not [33]. In Sabben et al., patients undergoing MT were also analyzed for predictors of MCE, patients with TICI scores ≥ 2B developed significantly less MCE ($p < 0.05$) [34]. In another retrospective series of 98 patients (35.7% MCE), neither increased clot retrieval attempts nor TICI score predicted MCE [35]. In contrast, our data demonstrated an association between increased number of passes (mean 2.9 vs. 1.8; $p < 0.0001$) and poorer TICI score ($p < 0.0001$) with the development of MCE on bivariate analysis. However, the difference between 2.9 and 1.8 passes may not be clinically significant and the threshold for poor outcome may be higher, as one study suggests this number to be more than three passes [36].

Utility of pupillometry

Our results show that NPi as well as hemorrhagic conversion is independently associated with MCE in MT patients. Presence of hemorrhagic conversion has been shown to be

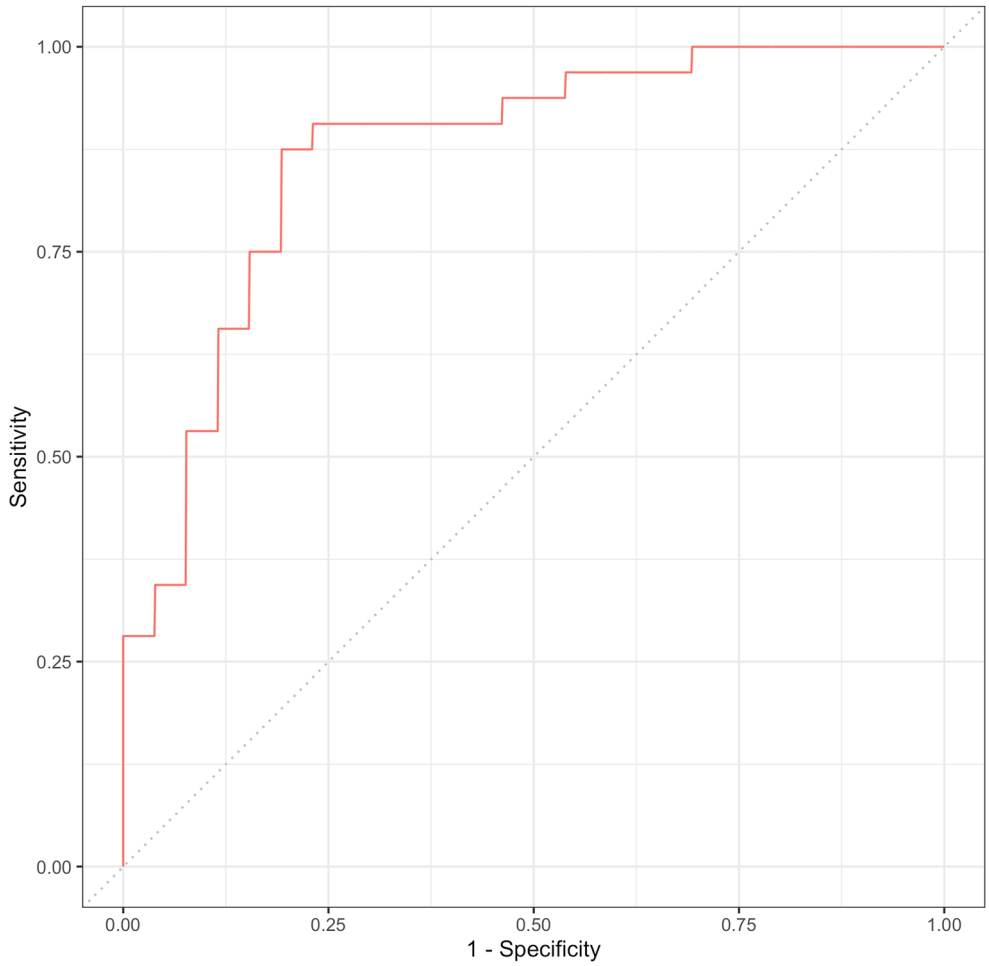

Fig. 3 Receiver operating characteristic curve analysis of multivariate regression model involving hemorrhagic conversion and abnormal neurological pupil index demonstrating discriminative ability in predicting malignant cerebral edema. Area under the curve = 0.870 [95% CI 0.735 to 0.945]; $p < 0.0001$

associated with worse outcomes and can be directly explained by the mass effect and additional cerebral edema that follows [37]. In terms of pupillary measurements, monitoring of pupil size, shape, symmetry, and light reflex can have both prognostic and diagnostic benefit [38]. Previous studies have detailed the importance of the pupillary light reflex as a factor that can indicate conditions associated with herniation and increased intracranial pressure [9, 38].

The most studied use of automated pupillometry and NPi has been in the setting of severe TBI, used to monitor the efficacy of interventions to prevent secondary neurological injury. In a study by Ong et al., NPi was found to improve significantly within 2 h after osmotic therapy was applied. This study concluded that NPi data could be used to regulate doses and timing [39]. Jahns et al. studied pupillometry in the setting of increased ICP following TBI and found that with sustained elevated ICP elevations, NPi became abnormal compared to baseline (4.2 vs. 2.8; $p < 0.0001$). In addition, NPi was lower in patients who had poorer outcomes [18]. Changes in ICP detected by NPi have also been shown to precede transtentorial herniation [40]. El Ahmadieh et al. found that patients following TBI with an NPi < 3.0 had more instances of mass effect and increased ICP requiring a greater need for surgical intervention [17].

These findings parallel the ones in our study and demonstrate the usefulness of NPi monitoring for critical patients. Abnormal trending NPi may alert physicians to initiate hyperosmolar therapy or consider operative interventions in the form of DHC. This is especially important in AIS where early intervention for MCE is life-saving. A majority of patients in the MCE group (67.2%) required and underwent DHC due to failure of medical therapy. This proportion would have been higher if it included patients who were offered a DHC but refused based on goals of care discussion and family decision-making.

Furthermore, non-MCE patients had lower mRS scores (0–2) and were more independent compared to the MCE group in our study (52.3% vs. 6.3%; $p < 0.0001$) (Table 2). This is inline with another recent study showing that patients with MCE after MT have worse functional outcomes at follow-up [41]. These results further highlight the need for the discovery and use of early predictors of MCE, including hourly objective NPi measurements, to optimize management and lower complication and mortality rates in AIS patients.

Use of automated pupillometry and NPi monitoring goes beyond the neurocritical care setting. It has been studied in cardiopulmonary settings [12] as well as anesthesia care, especially with opioid usage [13, 42]. The easy use and non-invasive nature makes adding pupillometry readings to critically ill patients advantageous. Additionally, it provides an objective measure with higher reliability than physician measured recordings [43]. Furthermore, NPi is not affected by commonly used analgesics and sedatives used in the ICU such as fentanyl and propofol [42].

Limitations

Limitations in this study include the retrospective study design. All patients were derived from a single institution and this limits the sample size available as well as the generalizability of the outcomes. Only patients undergoing MT were included, thus the results may not be applicable to AIS patients that were medically managed or patients with hemorrhagic strokes. Although more commonly used in intensive care settings across the United States, pupillometry technology is not available at all institutions which may hinder the utility of such technique and reproducibility of the study. More importantly, NPi data was gathered in only 23% of our total stroke population based on intensivist preference. In particular, pupillometry data was only obtained in 29 of the 220 patients that did not develop MCE, likely due to a perceived improved prognosis in these patients. Follow-up studies would have to impose pupillometry measurements on all patients suffering from LVO regardless of perceived prognosis by clinicians in order to avoid Type 1 error.

Conclusion

Our study demonstrates that MCE is independently associated with abnormal ipsilateral NPi and hemorrhagic conversion in patients undergoing MT for LVO. There is potential value in use of pupillometry in this at-risk population to monitor for MCE. This can be used to supplement but not replace serial neurologic exams and radiographic follow-up and provides a rapid, non-invasive, and objective method of assessment. Further prospective studies are warranted to evaluate the relationship between abnormal NPi and MCE.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was approved by our institutional review board.

Informed consent Informed consent was waived given retrospective nature of the study.

References

1. GBD 2016 Lifetime Risk of Stroke Collaborators, Feigin VL, Nguyen G et al (2018) Global, Regional, and country-specific lifetime risks of stroke, 1990 and 2016. N Engl J Med 379:2429–2437. https://doi.org/10.1056/NEJMoa1804492
2. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJH, van Walderveen MAA, Staals J, Hofmeijer J, van

Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PLM, van Rooij WJJ, van den Berg JSP, van Hasselt BAAM, Aerden LAM, Dallinga RJ, Visser MC, Bot JCJ, Vroomen PC, Eshghi O, Schreuder THCML, Heijboer RJJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers MES, Jenniskens SFM, Beenen LFM, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YBWEM, van der Lugt A, van Oostenbrugge RJ, Majoie CBLM, Dippel DWJ (2015) A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 372:11–20. https://doi.org/10.1056/NEJMoa1411587

3. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 387:1723–1731. https://doi.org/10.1016/S0140-6736(16)00163-X
4. Jadhav AP, Molyneaux BJ, Hill MD, Jovin TG (2018) Care of the post-thrombectomy patient. Stroke 49:2801–2807. https://doi.org/10.1161/STROKEAHA.118.021640
5. Shimoyama T, Kimura K, Uemura J, Yamashita S, Saji N, Shibazaki K, Iguchi Y (2014) The DASH score: a simple score to assess risk for development of malignant middle cerebral artery infarction. J Neurol Sci 338:102–106. https://doi.org/10.1016/j.jns.2013.12.024
6. Olson DM, Zomorodi M, Britz GW et al (2013) Continuous cerebral spinal fluid drainage associated with complications in patients admitted with subarachnoid hemorrhage. J Neurosurg 119:974–980. https://doi.org/10.3171/2013.6.JNS122403
7. Chen JW, Gombart ZJ, Rogers S, Gardiner SK, Cecil S, Bullock RM (2011) Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the Neurological Pupil index. Surg Neurol Int 2. https://doi.org/10.4103/2152-7806.82248
8. Kim TJ, Park S-H, Jeong H-B, Ha EJ, Cho WS, Kang HS, Kim JE, Ko SB (2020) Neurological Pupil index as an indicator of neurological worsening in large hemispheric strokes. Neurocrit Care 33:575–581. https://doi.org/10.1007/s12028-020-00936-0
9. Emelifeonwu JA, Reid K, Rhodes JK, Myles L (2018) Saved by the pupillometer!–a role for pupillometry in the acute assessment of patients with traumatic brain injuries? Brain Inj 32:675–677. https://doi.org/10.1080/02699052.2018.1429021
10. Papangelou A, Zink EK, Chang W-TW, Frattalone A, Gergen D, Gottschalk A, Geocadin RG (2018) Automated pupillometry and detection of clinical transtentorial brain herniation: a case series. Mil Med 183:e113–e121. https://doi.org/10.1093/milmed/usx018
11. Zafar SF, Suarez JI (2014) Automated pupillometer for monitoring the critically ill patient: a critical appraisal. J Crit Care 29:599–603. https://doi.org/10.1016/j.jcrc.2014.01.012
12. Riker RR, Sawyer ME, Fischman VG, May T, Lord C, Eldridge A, Seder DB (2020) Neurological Pupil index and pupillary light reflex by pupillometry predict outcome early after cardiac arrest. Neurocrit Care 32:152–161. https://doi.org/10.1007/s12028-019-00717-4
13. Murillo R, Crucilla C, Schmittner J, Hotchkiss E, Pickworth WB (2004) Pupillometry in the detection of concomitant drug use in opioid-maintained patients. Methods Find Exp Clin Pharmacol 26:271–275
14. Kimberly WT, Dutra BG, Boers AMM, Alves HCBR, Berkhemer OA, van den Berg L, Sheth KN, Roos YBWEM, van der Lugt A, Beenen LFM, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ, Lingsma HF, Marquering H, Majoie CBLM, for the MR CLEAN Investigators (2018) Association of reperfusion with brain edema in patients with acute ischemic stroke. JAMA Neurol 75:453–461. https://doi.org/10.1001/jamaneurol.2017.5162
15. von Kummer R, Broderick JP, Campbell BCV et al (2015) The Heidelberg bleeding classification. Stroke 46:2981–2986. https://doi.org/10.1161/STROKEAHA.115.010049
16. R Core Team (2020) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
17. El Ahmadieh TY, Bedros NM, Stutzman SE et al (2020) Automated pupillometry as a triage and assessment tool in patients with traumatic brain injury. World Neurosurg 145:e163–e169. https://doi.org/10.1016/j.wneu.2020.09.152
18. Jahns F-P, Miroz JP, Messerer M, Daniel RT, Taccone FS, Eckert P, Oddo M (2019) Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. Crit Care 23:155. https://doi.org/10.1186/s13054-019-2436-3
19. Chen C-J, Ding D, Starke RM, Mehndiratta P, Crowley RW, Liu KC, Southerland AM, Worrall BB (2015) Endovascular vs medical management of acute ischemic stroke. Neurology 85:1980–1990. https://doi.org/10.1212/WNL.0000000000002176
20. Lambrinos A, Schaink AK, Dhalla I, Krings T, Casaubon LK, Sikich N, Lum C, Bharatha A, Pereira VM, Stotts G, Saposnik G, Kelloway L, Xie X, Hill MD (2016) Mechanical thrombectomy in acute ischemic stroke: a systematic review. Can J Neurol Sci 43:455–460. https://doi.org/10.1017/cjn.2016.30
21. Madsen TE, DeCroce-Movson E, Hemendinger M, McTaggart RA, Yaghi S, Cutting S, Furie KL, Saad A, Siket MS, Jayaraman MV (2019) Sex differences in 90-day outcomes after mechanical thrombectomy for acute ischemic stroke. J Neurointerv Surg 11:221–225. https://doi.org/10.1136/neurintsurg-2018-014050
22. Hurn PD, Brass LM (2003) Estrogen and stroke: a balanced analysis. Stroke 34:338–341. https://doi.org/10.1161/01.str.0000054051.88378.25
23. Zhang YQ, Shi J, Rajakumar G, Day AL, Simpkins JW (1998) Effects of gender and estradiol treatment on focal brain ischemia. Brain Res 784:321–324. https://doi.org/10.1016/s0006-8993(97)00502-7
24. Schmidt R, Fazekas F, Reinhart B, Kapeller P, Fazekas G, Offenbacher H, Eber B, Schumacher M, Freidl W (1996) Estrogen replacement therapy in older women: a neuropsychological and brain MRI study. J Am Geriatr Soc 44:1307–1313. https://doi.org/10.1111/j.1532-5415.1996.tb01400.x
25. Navis A, Garcia-Santibanez R, Skliut M (2019) Epidemiology and outcomes of ischemic stroke and transient ischemic attack in the adult and geriatric population. J Stroke Cerebrovasc Dis 28:84–89. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.013
26. Chamorro Á, Brown S, Amaro S, Hill MD, Muir KW, Dippel DWJ, van Zwam W, Butcher K, Ford GA, den Hertog HM, Mitchell PJ, Demchuk AM, Majoie CBLM, Bracard S, Sibon I, Jadhav AP, Lara-Rodriguez B, van der Lugt A, Osei E, Renú A, Richard S, Rodriguez-Luna D, Donnan GA, Dixit A, Almekhlafi M, Deltour S, Epstein J, Guillon B, Bakchine S, Gomis M, du Mesnil de Rochemont R, Lopes D, Reddy V, Rudel G, Roos YBWEM, Bonafe A, Diener HC, Berkhemer OA, Cloud GC, Davis SM, van Oostenbrugge R, Guillemin F, Goyal M, Campbell BCV, Menon BK, for the HERMES Collaborators (2019) Glucose modifies the effect of endovascular thrombectomy in patients with acute stroke. Stroke 50:690–696. https://doi.org/10.1161/STROKEAHA.118.023769
27. Lau L-H, Lew J, Borschmann K, Thijs V, Ekinci EI (2019) Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review. J Diabetes Investig 10:780–792. https://doi.org/10.1111/jdi.12932

28. Smith WS, Lev MH, English JD, Camargo EC, Chou M, Johnston SC, Gonzalez G, Schaefer PW, Dillon WP, Koroshetz WJ, Furie KL (2009) Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 40:3834–3840. https://doi.org/10.1161/STROKEAHA.109.561787
29. Nikoubashman O, Dekeyzer S, Riabikin A, Keulers A, Reich A, Mpotsaris A, Wiesmann M (2019) True first-pass effect. Stroke 50:2140–2146. https://doi.org/10.1161/STROKEAHA.119.025148
30. Seker F, Pfaff J, Wolf M, Ringleb PA, Nagel S, Schönenberger S, Herweh C, Möhlenbruch MA, Bendszus M, Pham M (2017) Correlation of thrombectomy maneuver count with recanalization success and clinical outcome in patients with ischemic stroke. AJNR Am J Neuroradiol 38:1368–1371. https://doi.org/10.3174/ajnr.A5212
31. Ben Hassen W, Tordjman M, Boulouis G, Bretzner M, Bricout N, Legrand L, Benzakoun J, Edjlali M, Seners P, Cordonnier C, Oppenheim C, Turc G, Henon H, Naggara O (2020) Benefit of first-pass complete reperfusion in thrombectomy is mediated by limited infarct growth. Eur J Neurol 28:124–131. https://doi.org/10.1111/ene.14490
32. Kaesmacher J, Maegerlein C, Zibold F, Wunderlich S, Zimmer C, Friedrich B (2018) Improving mTICI2b reperfusion to mTICI2c/3 reperfusions: a retrospective observational study assessing technical feasibility, safety and clinical efficacy. Eur Radiol 28:274–282. https://doi.org/10.1007/s00330-017-4928-3
33. Tracol C, Vannier S, Hurel C, Tuffier S, Eugene F, le Reste PJ (2020) Predictors of malignant middle cerebral artery infarction after mechanical thrombectomy. Rev Neurol (Paris) 176:619–625. https://doi.org/10.1016/j.neurol.2020.01.352
34. Sabben C, Desilles JP, Charbonneau F, Savatovsky J, Morvan E, Obadia A, Raynouard I, Fela F, Escalard S, Redjem H, Smajda S, Ciccio G, Blanc R, Fahed R, le Guerinel C, Engrand N, Ben Maacha M, Labreuche J, Mazighi M, Piotin M, Obadia M (2020) Early successful reperfusion after endovascular therapy reduces malignant middle cerebral artery infarction occurrence in young patients with large diffusion-weighted imaging lesions. Eur J Neurol 27:1988–1995. https://doi.org/10.1111/ene.14330
35. Davoli A, Motta C, Koch G, Diomedi M, Napolitano S, Giordano A, Panella M, Morosetti D, Fabiano S, Floris R, Gandini R, Sallustio F (2018) Pretreatment predictors of malignant evolution in patients with ischemic stroke undergoing mechanical thrombectomy. J Neurointerv Surg 10:340–344. https://doi.org/10.1136/neurintsurg-2017-013224
36. Shi Z, Guo S, Zheng S, Min J, Geng Y (2020) Number of stent retriever passes associated with clinical outcome after mechanical thrombectomy in acute ischemic stroke. J Stroke Cerebrovasc Dis 29:105199. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105199
37. Soomro J, Zhu L, Savitz SI, Sarraj A (2020) Predictors of acute neurological worsening after endovascular thrombectomy. Interv Neurol 8:172–179. https://doi.org/10.1159/000499973
38. Bower MM, Sweidan AJ, Xu JC, Stern-Neze S, Yu W, Groysman LI (2019) Quantitative pupillometry in the intensive care unit. J Intensive Care Med:885066619881124. https://doi.org/10.1177/0885066619881124
39. Ong C, Hutch M, Barra M, Kim A, Zafar S, Smirnakis S (2019) Effects of osmotic therapy on pupil reactivity: quantification using pupillometry in critically ill neurologic patients. Neurocrit Care 30:307–315. https://doi.org/10.1007/s12028-018-0620-y
40. Lussier BL, Olson DM, Aiyagari V (2019) Automated pupillometry in neurocritical care: research and practice. Curr Neurol Neurosci Rep 19:71. https://doi.org/10.1007/s11910-019-0994-z
41. Huang X, Yang Q, Shi X, Xu X, Ge L, Ding X, Zhou Z (2019) Predictors of malignant brain edema after mechanical thrombectomy for acute ischemic stroke. J Neurointerv Surg 11:994–998. https://doi.org/10.1136/neurintsurg-2018-014650
42. Shirozu K, Setoguchi H, Tokuda K, Karashima Y, Ikeda M, Kubo M, Nakamura K, Hoka S (2017) The effects of anesthetic agents on pupillary function during general anesthesia using the automated infrared quantitative pupillometer. J Clin Monit Comput 31:291–296. https://doi.org/10.1007/s10877-016-9839-3
43. Olson DM, Stutzman S, Saju C et al (2016) Interrater reliability of pupillary assessments. Neurocrit Care 24:251–257. https://doi.org/10.1007/s12028-015-0182-1