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# Decompressive hemicraniectomy in patients with malignant middle cerebral artery infarction: A real-world study

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ABSTRACT

*Background:* Malignant middle cerebral artery infarction (mMCA) is a devastating disease with rates of fatality as high as 80%. Decompressive hemicraniectomy (DHC) reduces mortality, but many survivors inevitably remain severely disabled.

This study aimed to analyze patients with mMCA undergoing DHC or best medical treatment (BMT) baseline characteristics and factors linked to therapeutic choice and determinants of prognosis.

*Methods:* We recorded clinical and radiological features of patients undergoing BMT or DHC. The two groups were compared for epidemiology, clinical presentation, neuroimaging, and prognosis. Regression analysis was performed to identify predictors of surgical treatment and outcome.

*Results:* One hundred twenty-five patients were included (age 67.41 ± 1.39 yo; 65 M). Patients undergoing DHC *(N = 57)* were younger *(DHC 55.71 ± 1.48 yo vs. BMT 77.22 ± 1.38)* and had midline shift *(DHC 96.5% (55/57) vs. BMT 35.3% (24/68),* a larger volume of the affected hemisphere and reduced ventricles volume as compared to BMT.

The chance of surgery depended on age *(Exp(B) = 0.871, $p < 0.001$)*, clinical status at onset *(NIHSS Exp (B) = 0.824, $p = 0.030$)* and volume of the ventricle of the affected hemisphere *(Exp(B) = 0.736, $p = 0.006$)*.

Death rate during admission was significantly lower for DHC *(DHC 15% (6/41) vs BMT 71.7% (38/53), Fisher's test = 30.234, $p < 0.001$)*.

*Conclusion:* Although DHC may cause prolonged hospitalization and long-term disabled patients, it is a lifesaving therapy that should be considered for selected patients with mMCA but perioperative complications and cost-utility should be considered. Patients and families should be correctly counseled about this therapeutic choice and its short- and long-term consequences.

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## 1. Introduction

Stroke due to large vessel occlusion (LVO) is a leading cause of long-term disability and death worldwide [1,2]. Although intravenous thrombolysis and mechanical thrombectomy changed acute stroke treatment [3], most patients remain at risk of large infarction [4] posing them at risk of developing malignant middle cerebral artery infarction (mMCA) [5]. mMCA is the most troublesome and even life-threatening consequence of LVO because it can lead to increased intracranial pressure, inadequate cerebral blood flow, and irreversible tissue injury beyond stroke tissue [6–8]. mMCA occurs in approximately 10% of supratentorial acute ischemic strokes and it is a devastating disease with rates of fatality as high as 80% [6,9–13]. DHC works by avoiding cerebral herniation and reduction of increased intracranial pressure due to brain edema [6–8]. Other pharmacological or physical approaches to reducing edema have been tried [14], but their clinical utility is still under scrutiny [15]. As a consequence, to date, clinicians do not have many alternatives to DHC [6,9–13].

Some trials demonstrated that early decompressive hemicraniectomy (DHC) reduces mortality improving functional outcomes in patients up to 60 years [9–12], but DHC remains a debated therapy among stroke clinicians [12,16] with respect to ideal candidates, optimal timing for surgery, and radiological markers [9–12] [8].

As a result, the clinical application of DHC might not reflect the population studied in clinical trials, and, in the real-world, its use is largely unknown.

Therefore, the aim of this study was: 1) evaluate, in unselected population of stroke patients with mMCA, clinical and radiological features of patients undergoing DHC *vs* Best Medical Therapy (BMT); 2) assess predictors for DHC choice (3) assess predictors for clinical outcome.

## 2. Methods

### 2.1. Data source

This was a retrospective study conducted at the local university high-volume tertiary stroke center. After hospital database reviewing, we included all patients consecutively admitted to the Stroke Unit for ischemic stroke in the anterior cerebral circulation, developing mMCA

The Study was approved by the Institutional Review Board. Inclusion criteria: 1) adult patients (18+ years old); 2) middle cerebral artery ischemic stroke confirmed by multimodal CT; 3) development of mMCA during hospitalization. mMCA was defined as clinical signs of anterior circulation LVO with an NIHSS score > 14, a large space-occupying MCA infarction on brain CT with compression of ventricles or midline shift, and no other obvious cause for neurologic deterioration [17]. All patients were admitted to Stroke Unit and stroke guidelines were followed for all patients [18,19].

Stroke patients were dichotomized in two groups: DHC patients and BMT patients. In DHC group, patients underwent hemicraniectomy and duroplasty without removal of the infarcted tissue. We applied the extended window treatment allowing decompressive DHC within 10 days from stroke onset. The size of the bone flap and opening of the middle cranial fossa was at the discretion of the surgeon. Surgical and postoperative complications were recorded. The bone flap was replaced within 3 months of surgery [20]. BMT included osmotic therapy by intravenous mannitol [21]. National Institute of Health Stroke Scale (NIHSS) score at the admission, NIHSS sub-score of consciousness (NIHSS 1a), Glasgow coma scale (GCS) score and available mRS score at 90 days were recorded [22]. As for hospital policy, all DHC patients were managed in ICU for at least 48 h following surgery. All other patients were managed in the Stroke Unit for the entire duration of their admission.

### 2.2. Image acquisition

All patients underwent multimodal CT imaging, including not enhanced CT (NeCT) and multimodal CT-angiography (mCTA). mCTA was performed at stroke diagnosis followed by NeCT in follow-up

Briefly, CT imaging was performed using a 64-multislice CT (GE MEDICAL SYSTEM Optima CT660 645, GE Healthcare, Milwaukee, Wisconsin).

Acquisition parameters for NeCT were 120 kv and 44mAs, and acquisition duration was 9 s. Acquisition parameters for mCTA were 100 kV and 4 mAs, and acquisition duration was 21 s; after administration of 80 mL of contrast media at 4 mL/s flow, the acquisition was composed of three subsequent phases (separated by an interval of 8 s): the first phase (acquired in the arterial phase) extends from the aortic arch to the vertex, and the next two phases (acquired in the early and late venous phases) from the occipital foramen to the vertex.

### 2.3. Imaging analysis

We extracted quantitative imaging features from brain CT performed within 24 h of stroke onset, prior to DHC and after DHC. We focused on infarct-related hypodensity volume, hemispheric stroke volume and ventricles volume ipsilateral to stroke, as well as midline shift (MLS), uncal herniation.

Volumetric measurements were obtained with a semi-automatic segmentation open-source program called ITK-SNAP (version 2.4.0, Kitware, New York, USA), using the Cavalieri principle [23–25]. For consistency reasons, all quantitative CT analyses were performed by the same radiologist. All measurements were performed twice by the same examiner in two different sittings.

All quantitative measurements of interest (Ischemic stroke volume, CSF ventricles volume, supratentorial hemispheric volume) were computed from manual segmentation performed slice-by-slice.

Uncal herniation including medial displacement of the uncus was evaluated visually.

Midline shift was manually measured at the level of the septum pellucidum and expressed in millimeters.

### 2.4. Statistics

Baseline demographics and clinical characteristics were expressed as mean ± SEM for normally distributed continuous variables or as median with interquartile range (IQR) for ordinal variables and continuous variables showing deviation from normality (tested with Shapiro Wilk's). Binary variables were represented as frequency and percentage. Differences between groups (DHC *vs* BMT) were tested with Fisher exact test for binary variables and Mann-Whitney test for continuous variables, as appropriate. The relationship between variables was assessed with Spearman's correlation coefficients. In order to evaluate the determinants of surgical choice and outcome, we applied a binary logistic regression model. As outcome measure, we considered the modified Rankin Scale (mRS) at discharge, dichotomized in survivors (mRS <6) and non-survivors (mRS = 6). Such a dichotomization was performed because mRS frequency distribution was skewed toward the highest value of the scale. Due to the relatively small sample size, we entered in the model the measures that should always be taken into account and some of those which were significantly different between patients undergoing DHC *vs* BMT. Our database presented some missing values; therefore, the sample size was reported step by step for each analysis. Significance level was set at $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences software version 25 (SPSS, Chicago, IL, USA).

## 3. Results

### 3.1. Epidemiological and clinical

Epidemiological and clinical data are summarized in Table 1.

*125* patients were included *(age 67.41 ± 1.39 yo, average ± SEM; 65 M, 63 with right hemispheric stroke, Fig. 1, Panel A). 45.6% (N = 57)* of patients underwent craniotomy. DHC patients were younger *(DHC 55.71 ± 1.48 yo vs BMT 77.22 ± 1.38 (average ± SEM), t = 10.604, df = 123, p < 0.001, Fig. 1, Panel B)*, more often male *(68% (39/57) vs 38% (26/68), Fisher's test = 11.320, p = 0.001, Fig. 1, Panel E)*, and presented with a milder clinical condition at onset *(NIHSS, DHC N = 36, NIHSS = 16 ± 8 vs BMT N = 45, NIHSS = 20 ± 5, Mann-Whitney, Z = 3.082, p = 0.002, Fig. 1, Panel C)* than BMT patients. The level of consciousness, as assessed by GCS score, was better for the surgical group *(DHC N = 34, 12 ± 3 vs BMT N = 44, 11 ± 2, Mann-Whitney, Z = 2.146, p = 0.032, Fig. 1, Panel D)*, but it was not different as assessed by NIHSS1a scores between the two groups *(p > 0.200)*. There was no significant difference between the two groups with respect to the side of the lesion (p > 0.200). Soon after stroke onset, osmotic therapy was administered more often in the DHC group *(DHC 88.2% (30/34) vs 52.17 (24/46), Fisher's test = 11.589, p = 0.001, Fig. 1, Panel G)*. When surgical treatment was performed, it occurred within 10 days from stroke onset *(2 ± 2 days)*. In particular, 33 out of 57 patients (58%) underwent DHC within 48 h from stroke onset. No significant difference was found between early DHC (within 48 h) and extended window treatment (within 10 days) with respect to all epidemiological and clinical variables under investigation.

**Table 1**
Demographic and clinical features of enrolled patients.

| Characteristics | BMT | DHC | *p*-value |
|---|---|---|---|
| N | 68 (54.4%) | 57 (45.6%) | |
| Age *(average ± SEM)* | **77.22 + 1.38** | **55.71 + 1.48** | **p < 0.001** |
| Males | **26/68 (38.23%)** | **39/57 (68.42%)** | **p = 0.001** |
| Lesion in the left hemisphere | 36/68 (52.94%) | 26/57 (45.61%) | p > 0.200 |
| NIHSS at the onset *(median ± IQR)* | **20 ± 5** | **16 ± 8** | **p = 0.002** |
| GCS *(median ± IQR)* | **11 ± 2** | **12 ± 3** | **p = 0.032** |
| NIHSS 1a *(median ± IQR)* | 1 ± 1 | 0 ± 1 | p > 0.200 |
| Early Antiedema therapy | **24/46 (52.17%)** | **30/34 (88.2%)** | **p = 0.001** |
| Death | | | |
| - During hospitalization | **38/53 (71.69%)** | **6/41 (14.63%)** | **p < 0.001** |
| - early death (within 24 h) | 19/68 (27.94%) | | |
| - after 24 h and within admission | **19/34 (55.88%)** | **6/41 (14.63%)** | **p < 0.001** |
| Days to surgery *(days, median ± IQR)* | | 2 ± 2 | |

BMT: Best medical therapy; DHC: Decompressive hemicraniectomy; n: number; SEM: standard error of mean; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; Bold font indicates statistical significance

### 3.2. Neuroradiology

Neuroradiological features are also reported in Table 2 and Figs. 2 and 3.

As compared to BMT, DHC patients almost always presented with midline shift at brain CT performed at the admission in emergency room *(DHC 96.5% (55/57) vs BMT 35.3% (24/68); Fisher's test = 49.931, p < 0.001, Fig. 4, Panel A)*, suggesting that the presence of midline shift is highly related to DHC treatment. This finding was confirmed by the comparison of the degree of midline shift in the two groups, measured in mm *(DHC 2.4 ± 3.75 mm vs BMT 0 ± 2 mm; Mann-Whitney, Z = 5.201, p < 0.001, Fig. 4, Panel D)*. The frequency of uncal herniation did not differ between groups *(DHC 19.6% 11/56 vs*

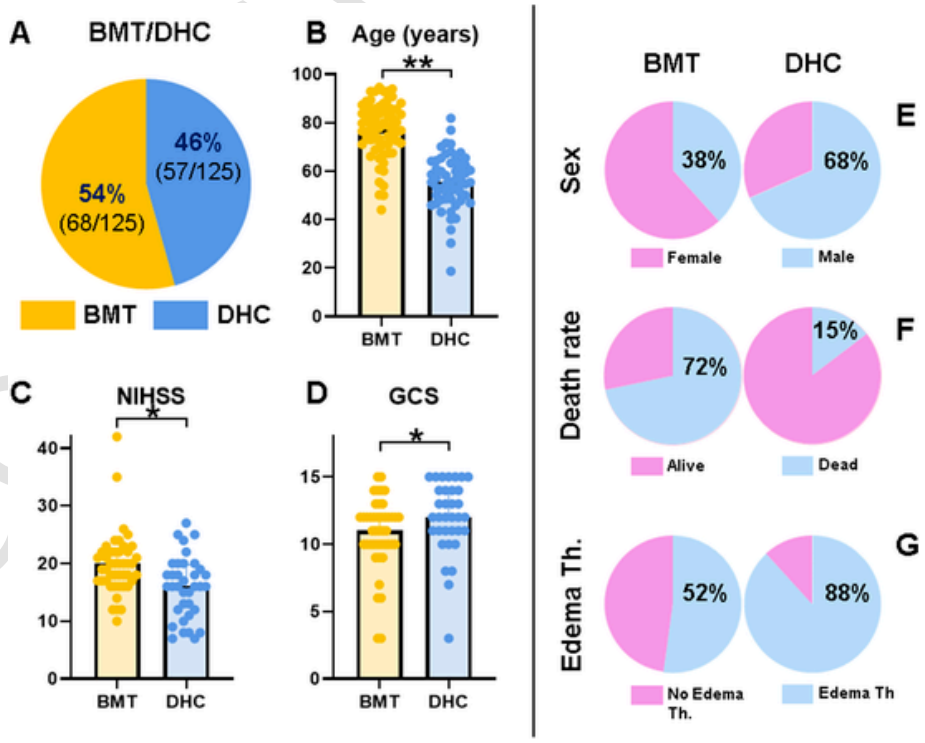


**Fig. 1.** Epidemiological and clinical features.
*Panel A*, proportion of patients undergoing BMT and DHC. *Panel B*, age was significantly lower in the DHC group. *Panel C*, NIHSS was significantly lower in the DHC group. *Panel D*, GCS was higher for the DHC group. *Panel E*, patients undergoing DHC were more often male. *Panel F*, death rate was higher in the BMT group. *Panel G*, edema therapy was administered more often in the DHC group. * denotes $p < 0.05$, ** denotes $p < 0.001$.

**Table 2**
Neuroradiological features.

| Characteristics | BMT | DHC | p-value |
|---|---|---|---|
| Midline shift *(frequency)* | **24/68 (35.29%)** | **55/57 (96.49%)** | **p < 0.001** |
| Uncal herniation *(frequency)* | 7/68 (10.29%) | 11/55 (19.64%) | p = 0.200 |
| Degree of midline shift *(mm, median ± IQR)* | **0 ± 2** | **2.4 ± 3.75** | **p < 0.001** |
| Lesion Volume *($mm^3$, median ± IQR)* | **152.0 ± 1.4** | **189.7 ± 2.4** | **p > 0.200** |
| Volume Affected Hemisphere *($mm^3$, median ± IQR)* | **538.0 ± 66.9** | **581.1 ± 91.9** | **p = 0.002** |
| Volume ventricle affected hemisphere *($mm^3$, median ± IQR)* | **13.9 ± 7.45** | **4.07 ± 6.39** | **p < 0.001** |
| FU CT scan *(days, median ± IQR)* | **3 ± 2** | **2 ± 2** | **p < 0.001** |
| FU Degree of midline shift *(FU – admission, mm, median ± IQR)* | 5 ± 6.75 | 7.5 ± 5.88 | p > 0.200 |
| FU Lesion Volume *(FU – admission, $mm^3$, median ± IQR)* | 0.50 ± 1.28 | 0.96 ± 1.12 | *p* > 0.05 |
| FU Volume Affected Hemisphere *(FU – admission, $mm^3$, median ± IQR)* | 0.28 ± 0.40 | 0.24 ± 0.23 | p > 0.200 |
| FU Volume ventricle affected hemisphere *(FU – admission, $mm^3$, median ± IQR)* | −4.19 ± 6.96 | −2.71 ± 6.40 | *p* > 0.200 |

BMT: Best medical therapy; DHC: Decompressive hemicraniectomy; SEM: standard error of mean; IQR: interquartile range; FU: Follow-up; Bold font indicates statistical significance.

*BMT 10.3% (7/68), Fisher's test, p = 0.200,* Fig. 4 *Panel B).* The volume of the lesion measured in cubic centimeters did not differ between groups *(DHC 189.7 ± 2.4 vs BMT 152.0 ± 1.4, Mann-Whitney, p > 0.200,* Fig. 4, *Panel D),* whereas the volume of the affected hemisphere was significantly higher and the volume of the ventricles of the affected side significantly smaller in the DHC group *(Volume affected hemisphere (cc) DHC 581.1 ± 91.9 vs BMT 538.0 ± 66.9, Mann-Whitney, Z = 3.173, p = 0.002; Volume ventricle affected hemisphere (cc) DHC 4.07 ± 6.39 vs BMT 13.9 ± 7.45 Mann-Whitney, Z = 7.246, p < 0.001,* Fig. 4, *Panel D).*

Patients underwent a follow-up CT scan after 2 ± 3 days, significantly earlier for DHC patients *(DHC 2 ± 2 vs BMT 3 ± 2, Mann-Whitney, Z = 4.658, p < 0.001,* Fig. 4 *Panel C).* The greater the edema and midline shift at the first CT scan, the earlier was the follow-up performed *(Spearman's Rho N = 104 with number of days prior to follow-up as dependent variable: Stroke Volume Rho = −0.300, p = 0.002; Volume Affected Hemisphere Rho = −0.163, p = 0.099; Volume ventricle affected hemisphere Rho = 0.464, p < 0.001; Midline Shift Rho = −0.379, p < 0.001).*

The follow-up CT scan overall showed a greater degree of edema (Mann-Whitney test $p < 0.05$ consistently for midline shift, stroke volume, affected hemisphere volume and volume of the ventricles of the affected side), but not significantly different for DHC and BMT *(*Fig. 4, *Panel E).* Finally, in the DHC group there was no significant relationship between the neuroradiological features and their evolution (follow-up CT scan) and the time of surgical treatment (Spearman's Rho, $p > 0.200$ consistently). Most patients undergoing surgery received 4 CT scans: at admission, FU scan, before surgery and after surgery. The longitudinal variation of neuroradiological features is reported in Supplementary Figure.

### 3.3. Predictors of surgical treatment

We performed a logistic regression to investigate the factors impacting on the medical choice to perform DHC. Our sample size did not allow to consider all possible variables and some factors were correlated to each other. Our experimental setup allowed however to provide preliminary data on factors that might impact on the therapeutic choice. We opted for entering only those factors deemed most relevant from an epidemiological/clinical/radiological perspective: age, sex, clinical sta-

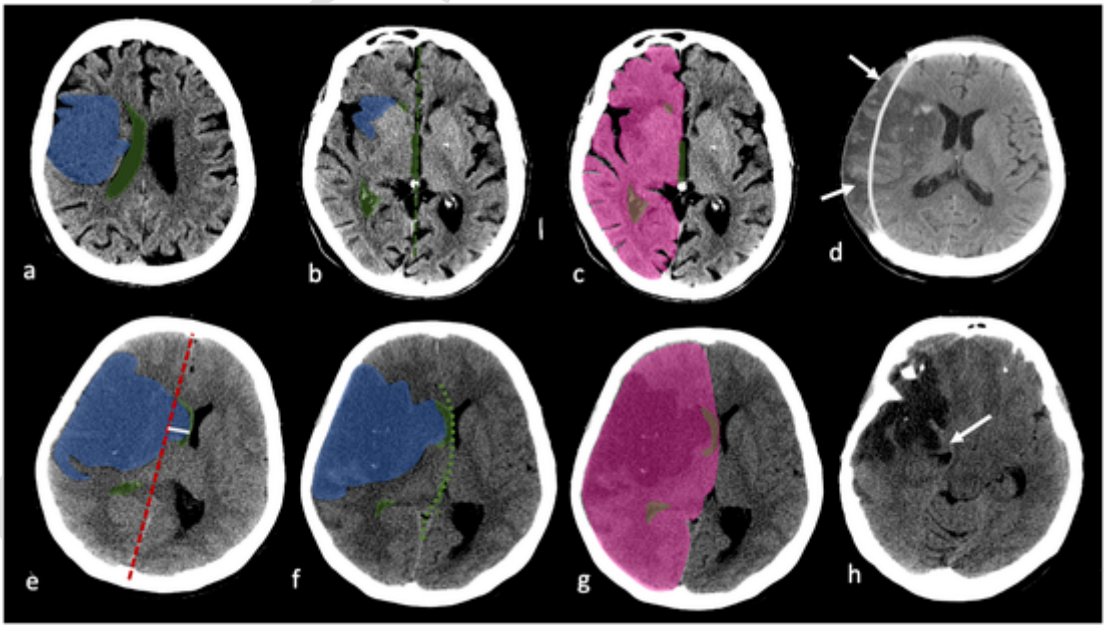


**Fig. 2.** Quantitative CT measures in two representative patients with mMCA. Patient with mMCA underwent to DHC (*Panels a-b-c-d*); patient with mMCA under BMT (*Panels e-f-g-h*). Ischemic stroke volume -related hypodensity is represented in blue shared area (*Panels a, b, e, f*). Supratentorial CSF ventricles volumes (lateral and third ventricles) ipsilateral to stroke are represented in green shared area (*Panels a-b-c-e-f*); only half of third ventricle was included in the ipsilateral supratentorial ventricles volume. Total supratentorial hemispheric volume is represented in pink shared area, it includes brain tissue volume contained within the hemisphere ipsilateral to stroke; hemispheric lateral and third ventricles were excluded (*Panels c-g*). Uncal herniation is represented by medial displacement of the uncus (*white arrow in h*). Midline shift was measured at the level of the septum pellucidum (*Panel e*). The size of the bone flap was measured from an imaginary line connecting the craniectomy edges on axial postoperative CT scan (*white arrows in d*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

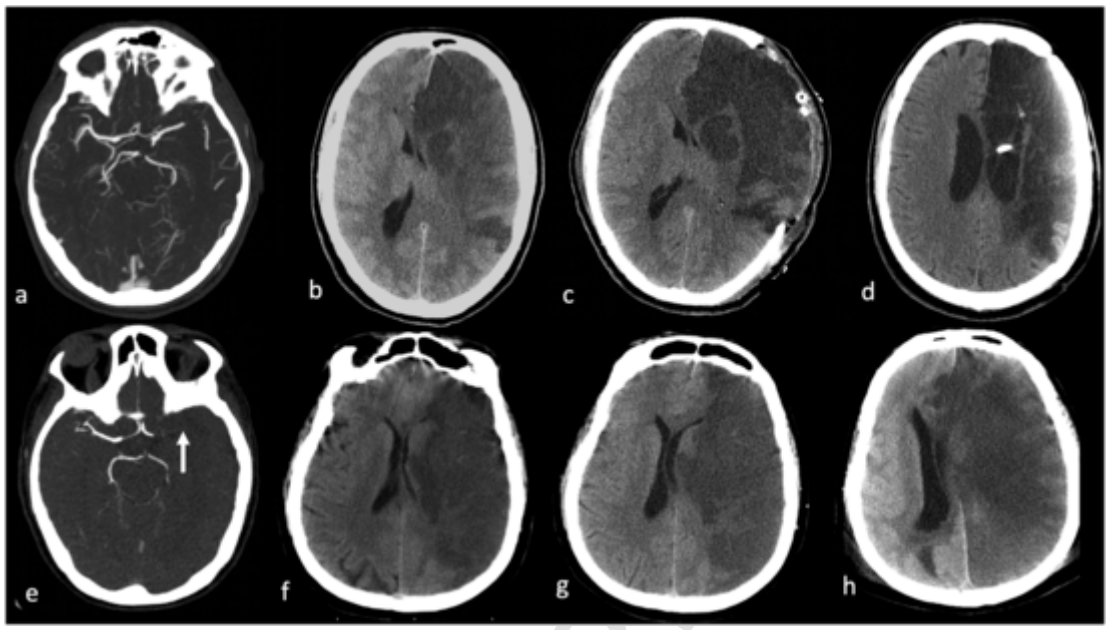


**Fig. 3.** Brain CT follow-up in two representative patients with mMCA. Enhanced CT (Panels a-e); un-enhanced CT (Panels b-c-d-f-g-h).
Patient with mMCA stroke underwent DHC (upper panels).CT performed at 24 h: left fronto-parieto-temporal stroke with cortical swelling, shift of midline structures and mass effect on the ventricular system (*Panel b*). Note occlusion of left mMCA (*Panel a*). CT performed at 48 h: right fronto-temporo-parietal craniectomy, increased parenchymal swelling with parenchymal herniation through the craniotomy operculum; the shift of the structures of the midline is unchanged (*Panel c*).CT performed at 4 months: craniotomy operculum repositioned and evolution of mMCA stroke in the gliotic-malacic stage with passive dilation of the ventricular system and cortical necrosis (*Panel d*).Patient *with mMCA under BMT (lower panels).*CT performed at 24 h: left fronto-parieto-temporal stroke with cortical swelling, midline structures shift and mass effect on the ventricular system (*Panel f*). Note occlusion of left mMCA (*Panel e*).CT performed at 48 h: increased parenchymal swelling and shift of the midline structures (*Panel g*).CT performed at 5 days: Further increase of parenchymal swelling with subfalcine herniation and increased midline structures shift and mass effect on the ventricular system (*Panel h*); the patient died 1 day later.

tus at onset (NIHSS), midline shift (mm), and volume of the ventricle of the affected hemisphere. The model was overall statistically significant *($X^2(5) = 68.042$, $p < 0.001$)*. The explained variance was *76.8% (Nagelkerke $R^2$)* and the rate of good classification was 86.3%. While gender and the amount of midline shift did not significantly change the likelihood of undergoing surgery, the chance of undergoing surgery depended on age *(Exp(B) = 0.871, $p < 0.001$)*, clinical status at onset *(NIHSS Exp(B) = 0.824, $p = 0.030$)* and volume of the ventricle of the affected hemisphere *(Exp(B) = 0.736, $p = 0.006$)*. In other words, the probability of DHC was higher for patients who were younger (for each year of age the probability of having surgery reduced by *12.9%*), less severe (for each NIHSS point increase the probability of having surgery reduced by *17.6%*) and had small ventricles of the affected hemisphere (so that ventricles larger by 1 cc reduced the risk of having surgery by *26.4%*). Note that while no significant effect of the amount of shift was found here, the presence of any shift was highly related to surgical treatment, as virtually all operated patients had a midline shift.

ROC analysis showed that midline shift could differentiate between DHC and BMT groups (AUC 0.78–95%CI 0.69–0.88) with of cut-off value of 5 mm (sensitivity 25% specificity 86%).

### 3.4. Prognosis

Death rate during admission was significantly lower for DHC than BMT *(DHC 15% (6/41) vs BMT 71.7% (38/53), Fisher's test = 30.234, $p < 0.001$)*. Note that 19 patients died during the first 24 h from admission (classified as early deaths). None of these patients underwent DHC. Even taking aside these patients, the death rate remained higher in the BMT group *(55.9% (19/34), Fischer's test 14.231, $p < 0.001$)*. After excluding patients who died over the course of the admission, the follow-up mRS at three months was available for 44 patients *(29 DHC and 15 BME)*. DHC patients showed a significantly better outcome, but results should be taken with caution given the small sample size (DHC 4 ± 1 *vs* BMT 5 ± 0, *Mann-Whitney, $Z = 2.569$, $p = 0.010$)*.

In order to assess the predictors of outcome, we built a binary logistic regression model with binarized mRS at discharge (dead or alive) as dependent variable and the following predictors: age, sex, NIHSS at onset, therapy (DHC *vs* BMT), midline shift (mm), volume of the ventricle of the affected hemisphere (cc). The model ($N = 78$) was overall significant (Wald-Chi-square = 36.504, df = 6, $p < 0.001$), with an explained variance of 49.9% (Nagelkerke R Square) and an overall classification rate of 79.9%. The only variables in the equations which significantly change the risk of death were age (Exp(B) = 1.077, p = 0.010) and therapy (Exp(B) = 0.146, $p = 0.034$). In other words, for each year of age, the risk of death increased by 7.7%, whereas all other factors being constant, the risk of death decreased by 96.6% with DHC. Especially this latter result should be taken with caution, as there could be a classification bias of the patients who received medical therapy only and died within the first day. These patients belong to the medical therapy, but at least some of them could undergo surgery if only time permitted. The same model after excluding these subjects, although underpowered, was statistically significant $N = 65$, Wald-Chi-Square = 22.506, $p < 0.001$, with a 40.2% of explained variance (Nagelkerke R Square) and an overall classification rate of 78.5%. In this case the therapeutic approach (BMT *vs* DHC) did not significantly impact on the outcome ($p > 0.200$), while the only significant factor was the patient's age (Exp(B) = 1.087, $p = 0.020$), meaning that for each additional year of age the risk of death increased by 8.7%, being all other factors kept constant.

## 4. Discussion

We investigated baseline clinical and radiological characteristics of stroke patients developing mMCA in order to understand determinants

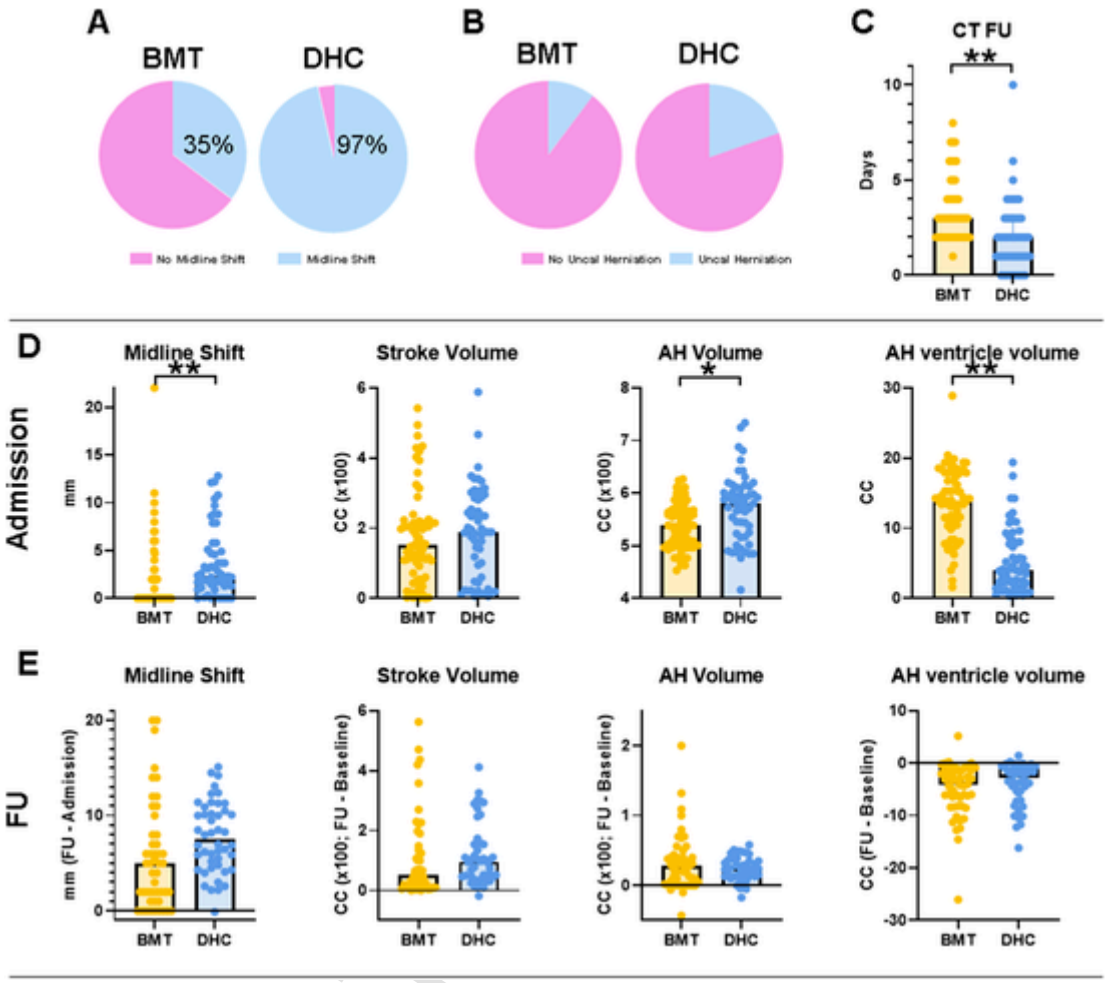


**Fig. 4.** *Panel A,* frequency of midline shift in the two groups. *Panel B,* frequency of uncal herniation in the two groups. *Panel C,* Follow-up CT was performed earlier in the DHC group. *Panel D and E* show the radiological features for the two groups at admission and follow-up CT scan, respectively. * denotes $p < 0.05$, ** denotes $p < 0.001$.

for surgical or medical choice and their effects on outcome in an unselected stroke population.

Some trials aimed to address this clinical issue (DECIMAL [11], DESTINY [10], HAMLET [26]) [12]. These trials demonstrated that, in patients who develop mMCA aged up to 60 years, early DHC reduces mortality and improves functional outcome [9–12]. The survivors usually experience severe dependency [9–12]. However, the choice of candidates and timing for DHC is still a matter of debate [26,27] due to their peculiar risk factors profile compared to older patients [28] and their wider life expectancy [29].

Cerebral edema after acute infarction ranges between 2 and 5 days: while 68% of patients exhibit clinical deterioration within 48 h of symptom onset, almost one-third of patients experience worsening of sensorium after 48 h [30]. Previous studies reported that mMCA can develop in 3 ways: a rapid and fulminant course (within 24–36 h), a gradually progressive course (over several days), or an initially worsening course followed by a plateau and resolution (about a week) [6,31].

The original randomized controlled clinical trials that established the efficacy of DHC after mMCA were neither designed nor powered to evaluate the optimal timing of intervention.

Target populations of the available trials were limited by strict enrolling criteria, and they were not representative of the real-world. Real-world data in common clinical practice are puzzling and only a few studies focused on clinical and radiological features of patients with mMCA undergoing DHC [32]. Because of the time frame used as enrollment criteria, the initial pooled analysis was restricted to patients treated within 48 h [9–11]; therefore, subsequent guidelines recommended intervention be pursued within 2 days of the onset of stroke symptoms [31].

The relationship between days to surgery and the outcome is certainly puzzling. Although mMCA is described to peak 2 to 5 days after its onset, it may vary among patients. In fact, in our real-world population, some patients underwent DHC within 10 days and determinants for this late development of mMCA are not entirely understood [33].

As for the outcome, the DESTINY study [10] and a pooled analysis of three European randomized controlled trials [12] showed that DHC reduced 30-day mortality, but 53% patients had poor functional outcomes after 6plus months of follow-up, with no significant difference *vs.* BMT. Other studies showed that timely DHC increased survival with good outcomes and decreased survival with disability [34]. Therefore, the evidence provided by clinical trials is conflicting and not confirmed in daily clinical practice. As per clinical trials, only young patients should undergo DHC, but in the real world, it is not infrequent that DHC is deemed the only rescue chance for older patients suffering from mMCA [5]. A population-based epidemiological study in North America demonstrated that applying the strict eligibility criteria of the pooled analysis of the European hemicraniectomy trials [12] would grant DHC eligibility to only 0.3% of cases [35]. If, on the one hand, the clinical trials have demonstrated the benefit of DHC, their strict eligibility criteria may have limited DHC application in real-world [10,27].

The DESTINY II trial enrolled patients with a median age of 70 years. It was stopped early, as a significant benefit of DHC became

clear. Still, survivors had a relevant burden of disability, with 32% of patients having mRS score of 4 and 19% mRS score of 5 at the one-year follow-up visit [16]. These results revealed that, in selected populations, early DHC after mMCA remains one of the most crucial treatment strategies for severe ischemic stroke patients ineligible for acute stroke treatment or in whom these treatments had been ineffective.

Our data showed that DHC patients were younger and more often male than patients treated by medical therapy. Moreover, they showed both better neurological condition and

level of consciousness, assessed by GCS. GCS score was higher in the DHC group than in BMT, but this difference was not observed considering the NIHSS1a score. This finding is conceivably due to a "floor effect" due to limited items in the NIHSS1a sub-score that did not allow to appraise differences between groups.

Antiedema therapy was administered more often in the DHC group; this was most likely related to the higher radiological degree of brain edema in the DHC group.

Some risk factors for mMCA development can be measured early on imaging because the semiquantitative and indirect radiologic evaluation of brain swelling, such as midline shift, develops relatively late in the edema cascade compared to the water accumulation [36]. Interestingly, early radiological data showed that almost all DHC patients had midline shifts compared to BMT, but uncal herniation and lesion volume did not differ between groups. This data suggests that midline shift, but not uncal herniation or lesion volume, is highly related to DHC treatment choice. On the other hand, the volume of the affected hemisphere was significantly higher and the volume of the ventricles of the affected side significantly smaller in the DHC group. A previous study evaluated the effect of midline shift on DHC results and authors found that smaller post-DHC midline shift was associated with smaller pre-DHC midline brain shift and greater transcalvarial brain herniation [37].

Follow-up CT scans were performed significantly earlier for patients undergone DHC than BMT and it was due to the aim of evaluating the trend in cerebral edema progression. In fact, follow-up CT scan showed a greater degree of edema. It is commonly observed in all stroke patients because of vasogenic edema phase [6] and it was not different between DHC and BMT group.

In agreement with previous studies [9–12], we found that the probability of DHC was higher for those patients who were younger, less severe and had more ventricle compression revealed of the affected hemisphere compared to patients treated with only BMT.

Our real-world data demonstrate that DHC was offered in our center to almost half of the patients presenting mMCA, therefore far higher than what could have been expected from the clinical trials. DHC proposal was offered also to patients who would have been excluded by clinical trials (*i.e.* elder patients). Overall, our data suggest that the decision to proceed to DHC resulted from a team effort (neurologist, neuro-radiologist and neurosurgeon) who valued a combination of epidemiological, clinical and radiological features and both patient and family consultation. Our study also highlights the relevance of careful neuroradiological evaluation. Quantitative assessment of CT features might be challenging especially in an emergency setting, but it might provide useful information whenever the analytical tools will be automatic and fast [38,39].

We also attempted to characterize cut-off values of midline shift which are more likely to lead to DHC but sensitivity and specificity do not appear sufficient for a clinical application and the qualitative evaluation seems to prevail up to date in our center.

DHC had lower death rate compared to medical treatment. The pooled analysis of DESTINY [10], DECIMAL [11], and HAMLET [9] revealed a significant benefit independent to the involvement of the dominant hemisphere and aphasia [12]. Accordingly, in our population decision for DHC or medical treatment was independent by hemisphere involvement.

DHC patients showed a significant better outcome during hospitalization with lower death rate and the main determinant was age, although stroke patients show also other risk factors conditioning clinical outcome [40,41].

We also found patients in DHC group showed lower mortality compared with patients in BMT group. Thus, despite a larger involvement in early brain CT scans, DHC patients showed better outcome than BMT patients. In fact, the extension of the lesion may be an indirect cause of death when patients are not treated [6].

Previous data reported stroke recovery generally follows a nonlinear pattern with the highest rate of recovery in the first weeks but limited improvements after 6 months whereas DHC may have long-lasting improvements [33] and recovery may be observed also after 3 years [42]. We did not have long-term follow-up data but currently available outcome scales such as mRS may be inadequate for chronic long-term assessment [5].

As for the timing for surgery, in our real-world study surgery was usually performed within 48 h from stroke onset, but some patients underwent surgery up to 10 days after stroke. While previous studies have described late DHC, they also demonstrated a negative effect on prognosis [10,12] [9]. We did not find any significant epidemiological/clinical/neuroradiological difference between patients undergoing early DHC (within 48 h) and extended window treatment (within 10 days), although these results should be taken with caution due to the small sample size. In real-world, clinicians may face with the dilemma of pursuing DHC before significant neurological deterioration from mass effect has transpired, or performing DHC outside of the recommended interval [43]. However, inappropriate patient selection and overutilization of surgery are suboptimal, as decompressive craniectomy carries a risk of additional perioperative complications, including infection and reoperation [43]. Furthermore, patients undergoing DHC require twice a surgical approach. DHC is the first step of the surgery and autologous or synthetic cranioplasty is the second step [44]; thus, surgery-related complications should be carefully considered.

Another key point is the cost-utility of DHC *versus* medical treatment in the management of mMCA in terms of healthcare and economic resources. Only a few studies explored this topic, concluding that surgery would not be considered cost effective by normal standards at this point in time, although this topic raises some ethical considerations [29]. Observational studies suggest that 69% of survivors and families of malignant MCA treated with DHC would undergo the same treatment again [45]. This supports the utilization of a patient/family-centered approach to decision-making, including thorough education about therapeutic options and associated outcomes [46].

Our data confirm that patients who undergo DHC have a better outcome in terms of mortality, but sequelae may be heavy because patients are commonly bedridden and totally dependent.

We confirmed that the two most relevant outcome factors are age and therapy: elder patients have a higher risk to die, as expected; conversely, when all other variables are kept constant, DHC may be a game-changer in the management of patients with mMCA.

In conclusion, DHC is to be considered as a life-saving measure and patients who undergo DHC show improved survival but neurological outcomes in terms of independency or functional recovery are poor. On this basis, needing more effective pharmacological treatments, DHC might be suggested in some patients, mainly younger, without comorbidities and with a longer life expectancy but the selection should be on a case-by-case basis, taking into account mainly patients' will and familiar context who should be correctly counseled.

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## Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

## References

[1] G.A. Roth, D. Abate, K.H. Abate, et al., Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017, Lancet 392 (2018) 1736–1788, https://doi.org/10.1016/S0140-6736(18)32203-7.
[2] J.F. Meschia, C. Bushnell, B. Boden-Albala, et al., Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (2014) 3754–3832, https://doi.org/10.1161/STR.0000000000000046.
[3] O.A. Berkhemer, P.S.S. Fransen, D. Beumer, et al., A randomized trial of intraarterial treatment for acute ischemic stroke, N. Engl. J. Med. 372 (2015) 11–20, https://doi.org/10.1056/NEJMoa1411587.
[4] G. Peng, C. Huang, W. Chen, et al., Risk factors for decompressive craniectomy after endovascular treatment in acute ischemic stroke, Neurosurg. Rev. (2019), https://doi.org/10.1007/s10143-019-01167-4.
[5] T. Beez, C. Munoz-Bendix, H.-J. Steiger, K. Beseoglu, Decompressive craniectomy for acute ischemic stroke, Crit. Care 23 (2019), https://doi.org/10.1186/s13054-019-2490-x.
[6] W. Hacke, S. Schwab, M. Horn, et al., "Malignant" middle cerebral artery territory infarction: clinical course and prognostic signs, Arch. Neurol. 53 (1996) 309–315, https://doi.org/10.1001/archneur.1996.00550040037012.
[7] D.E. Moulin, R. Lo, J. Chiang, H.J. Barnett, Prognosis in middle cerebral artery occlusion, Stroke 16 (1985) 282–284, https://doi.org/10.1161/01.str.16.2.282.
[8] S.-B. Jeon, Y. Koh, H.A. Choi, K. Lee, Critical care for patients with massive ischemic stroke, J Stroke 16 (2014) 146–160, https://doi.org/10.5853/jos.2014.16.3.146.
[9] J. Hofmeijer, L.J. Kappelle, A. Algra, et al., Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [HAMLET]): a multicentre, open, randomised trial, Lancet Neurol. 8 (2009) 326–333, https://doi.org/10.1016/S1474-4422(09)70047-X.
[10] E. Jüttler, S. Schwab, P. Schmiedek, et al., Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): a randomized, controlled trial, Stroke 38 (2007) 2518–2525, https://doi.org/10.1161/STROKEAHA.107.485649.
[11] K. Vahedi, E. Vicaut, J. Mateo, et al., Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL trial), Stroke 38 (2007) 2506–2517, https://doi.org/10.1161/STROKEAHA.107.485235.
[12] K. Vahedi, J. Hofmeijer, E. Juettler, et al., Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials, Lancet Neurol. 6 (2007) 215–222, https://doi.org/10.1016/S1474-4422(07)70036-4.
[13] T. Heinsius, J. Bogousslavsky, G. Van Melle, Large infarcts in the middle cerebral artery territory. Etiology and outcome patterns, Neurology 50 (1998) 341–350, https://doi.org/10.1212/wnl.50.2.341.
[14] V. Di Lazzaro, P. Profice, M. Dileone, et al., Delayed hypothermia in malignant ischaemic stroke, Neurol. Sci. 33 (2012) 661–664, https://doi.org/10.1007/s10072-011-0824-9.
[15] W.T. Kimberly, M.B. Bevers, R. von Kummer, et al., Effect of IV glyburide on adjudicated edema endpoints in the GAMES-RP trial, Neurology 91 (2018) e2163–e2169, https://doi.org/10.1212/WNL.0000000000006618.
[16] E. Jüttler, A. Unterberg, J. Woitzik, et al., Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke, N. Engl. J. Med. 370 (2014) 1091–1100, https://doi.org/10.1056/NEJMoa1311367.
[17] G. Thomalla, F. Hartmann, E. Juettler, et al., Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study, Ann. Neurol. 68 (2010) 435–445, https://doi.org/10.1002/ana.22125.
[18] D. Inzitari, G. Carlucci, Italian stroke guidelines (SPREAD): evidence and clinical practice, Neurol. Sci. 27 (Suppl. 3) (2006) S225–S227, https://doi.org/10.1007/s10072-006-0622-y.
[19] E.C. Jauch, J.L. Saver, H.P. Adams, et al., Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 44 (2013) 870–947, https://doi.org/10.1161/STR.0b013e318284056a.
[20] K. Jo, S.S. Bajgur, H. Kim, et al., A simple prediction score system for malignant brain edema progression in large hemispheric infarction, PLoS One 12 (2017) e0171425, https://doi.org/10.1371/journal.pone.0171425.
[21] M.T. Torbey, J. Bösel, D.H. Rhoney, et al., Evidence-based guidelines for the management of large hemispheric infarction, Neurocrit. Care. 22 (2015) 146–164.
[22] J.C. Van Swieten, P.J. Koudstaal, M.C. Visser, et al., Interobserver agreement for the assessment of handicap in stroke patients, Stroke 19 (1988) 604–607, https://doi.org/10.1161/01.STR.19.5.604.
[23] I.J. Abecassis, C.C. Young, D.J. Caldwell, et al., The Kempe incision for decompressive craniectomy, craniotomy, and cranioplasty in traumatic brain injury and stroke, J. Neurosurg. 1–10 (2021), https://doi.org/10.3171/2020.11.JNS203567.
[24] Y. Yu, F.-L. Zhang, Y.-M. Qu, et al., Intracranial calcification is predictive for hemorrhagic transformation and prognosis after intravenous thrombolysis in non-cardioembolic stroke patients, J. Atheroscler. Thromb. 28 (2021) 356–364, https://doi.org/10.5551/jat.55889.
[25] Y.-Q. Zhou, G.-H. Son, Y.-Q. Shi, et al., Quantitative segmentation analysis of the radiological changes by using ITK-SNAP: risk assessment of the severity and recurrence of medication-related osteonecrosis of the jaw, Int. J. Med. Sci. 18 (2021) 2209–2216, https://doi.org/10.7150/ijms.56408.
[26] J. Hofmeijer, G.J. Amelink, A. Algra, et al., Hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial (HAMLET). Protocol for a randomised controlled trial of decompressive surgery in space-occupying hemispheric infarction, Trials 7 (2006) 29, https://doi.org/10.1186/1745-6215-7-29.
[27] E. Jüttler, A. Unterberg, J. Woitzik, et al., Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke, N. Engl. J. Med. 370 (2014) 1091–1100, https://doi.org/10.1056/NEJMoa1311367.
[28] R. Renna, F. Pilato, P. Profice, et al., Risk factor and etiology analysis of ischemic stroke in young adult patients, J. Stroke Cerebrovasc. Dis. 23 (2014) e221–e227, https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.10.008.
[29] A. Bhattacharyya, A. Tahir, A. Chandrashekar, et al., A cost-utility analysis of decompressive hemicraniectomy versus medical treatment in the management of space-occupying brain oedema post middle cerebral artery infarction, Eur. J. Neurol. 26 (2019) 313–e19, https://doi.org/10.1111/ene.13814.
[30] A.I. Qureshi, J.I. Suarez, A.M. Yahia, et al., Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review, Crit. Care Med. 31 (2003) 272–277, https://doi.org/10.1097/00003246-200301000-00043.
[31] E.F.M. Wijdicks, K.N. Sheth, B.S. Carter, et al., Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (2014) 1222–1238, https://doi.org/10.1161/01.str.0000441965.15164.d6.
[32] I.L. Maier, D. Behme, M. Schnieder, et al., Early computed tomography-based scores to predict decompressive hemicraniectomy after endovascular therapy in acute ischemic stroke, PLoS One 12 (2017) e0173737, https://doi.org/10.1371/journal.pone.0173737.
[33] F. Kastrau, M. Wolter, W. Huber, F. Block, Recovery from aphasia after Hemicraniectomy for infarction of the speech-dominant hemisphere, Stroke 36 (2005) 825–829, https://doi.org/10.1161/01.STR.0000157595.93115.70.
[34] T.-K. Lin, S.-M. Chen, Y.-C. Huang, et al., The outcome predictors of malignant large infarction and the functional outcome of survivors following decompressive Craniectomy, World Neurosurg 93 (2016) 133–138, https://doi.org/10.1016/j.wneu.2016.06.005.
[35] R. Rahme, R. Curry, D. Kleindorfer, et al., How often are patients with ischemic stroke eligible for decompressive hemicraniectomy? Stroke 43 (2012) 550–552, https://doi.org/10.1161/STROKEAHA.111.635185.
[36] J. Shi, H. Wu, Z. Dong, et al., Automated quantitative lesion water uptake in acute stroke is a predictor of malignant cerebral edema, Eur. Radiol. (2022), https://doi.org/10.1007/s00330-021-08443-2.
[37] A. Bruno, N. Paletta, U. Verma, et al., Limiting brain shift in malignant hemispheric infarction by decompressive Craniectomy, J. Stroke Cerebrovasc. Dis. 30 (2021) 105830, https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105830.
[38] T. Verdolotti, F. Pilato, S. Cottonaro, et al., ColorViz, a new and rapid tool for assessing collateral circulation during stroke, Brain Sci 10 (2020) E882, https://doi.org/10.3390/brainsci10110882.
[39] F. Pilato, T. Verdolotti, R. Calandrelli, et al., Color-coded multiphase computed tomography angiography may predict outcome in anterior circulation acute ischemic stroke, J. Neurol. Sci. 430 (2021) 119989, https://doi.org/10.1016/j.jns.2021.119989.
[40] F. Pilato, P. Profice, M. Dileone, et al., Stroke in critically ill patients, Minerva Anestesiol. 75 (2009) 245–250.
[41] F. Pilato, S. Silva, I. Valente, et al., Predicting factors of functional outcome in patients with acute ischemic stroke admitted to neuro-intensive care unit-a prospective cohort study, Brain Sci 10 (2020) E911, https://doi.org/10.3390/brainsci10120911.
[42] M. Geurts, H.B. van der Worp, L.J. Kappelle, et al., Surgical decompression for space-occupying cerebral infarction: outcomes at 3 years in the randomized HAMLET trial, Stroke 44 (2013) 2506–2508, https://doi.org/10.1161/STROKEAHA.113.002014.
[43] H.H. Dasenbrock, F.C. Robertson, H. Vaitkevicius, et al., Timing of decompressive Hemicraniectomy for stroke: a Nationwide inpatient sample analysis, Stroke 48 (2017) 704–711, https://doi.org/10.1161/STROKEAHA.116.014727.
[44] E. Dowlati, K.B.D. Pasko, E.A. Molina, et al., Decompressive hemicraniectomy and cranioplasty using subcutaneously preserved autologous bone flaps versus synthetic implants: perioperative outcomes and cost analysis, J. Neurosurg. 1–8 (2022), https://doi.org/10.3171/2022.3.JNS212637.
[45] R. Gupta, E.S. Connolly, S. Mayer, M.S.V. Elkind, Hemicraniectomy for massive middle cerebral artery territory infarction, Stroke 35 (2004) 539–543, https://doi.org/10.1161/01.STR.0000109772.64650.18.
[46] K. Rumalla, M. Ottenhausen, P. Kan, J.-K. Burkhardt, Recent Nationwide impact of mechanical thrombectomy on decompressive Hemicraniectomy for acute

ischemic stroke, Stroke 50 (2019) 2133–2139, https://doi.org/10.1161/STROKEAHA.119.025063.