Outcome After Decompressive Craniectomy for Middle Cerebral Artery Infarction: Timing of the Intervention

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BACKGROUND: Based on randomized controlled trials (RCTs), clinical guidelines for the treatment of space-occupying hemispheric infarct employ age (≤60 yr) and time elapsed since stroke onset (≤48 h) as decisive criteria whether to perform decompressive craniectomy (DC). However, only few patients in these RCTs underwent DC after 48 h.
OBJECTIVE: To study the association between the timing of DC and (un)favorable outcome in patients with space-occupying middle cerebral artery (MCA) infarct undergoing DC.
METHODS: We performed a single-center cohort study from 2007 to 2017. Unfavorable outcome at 1 yr was defined as a Glasgow outcome scale 1 to 3. Additionally, we systematically reviewed the literature up to November 2018, including studies reporting on the timing of DC and other predictors of outcome. We performed Firth penalized likelihood and random-effects meta-analysis with odds ratio (OR) on unfavorable outcome.
RESULTS: A total of 66 patients were enrolled. A total of 26 (39%) patients achieved favorable and 40 (61%) unfavorable outcomes (13 [20%] died). DC after 48 h since stroke diagnosis did not significantly increase the risk of unfavorable outcome (OR 0.8, 95% CI 0.3-2.3). Also, in the meta-analysis, DC after 48 h of stroke onset was not associated with a higher risk of unfavorable outcome (OR 1.11; 95% CI 0.89-1.38).
CONCLUSION: The outcome of DC performed after 48 h in patients with malignant MCA infarct was not worse than the outcome of DC performed within 48 h. Contrary to current guidelines, we, therefore, advocate not to set a restriction of ≤48 h on the time elapsed since stroke onset in the decision whether to perform DC.

KEY WORDS: Decompressive craniectomy, Ischemic stroke, Outcome, Prognosis, Timing of surgery

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Decompressive craniectomy (DC) in patients with space-occupying hemispheric infarct has been proposed as a way to accommodate the shift of brain tissue and to normalize intracranial pressure, thereby preserving the cerebral blood flow and preventing life-threatening transtentorial herniation and secondary damage.[1] Current international clinical guidelines for the treatment of space-occupying hemispheric infarct are based on 4 European randomized controlled trials (RCTs) comparing DC to conventional therapy and employ both age (≤60 yr) and time elapsed since stroke onset (≤48 hr) as decisive criteria in the decision whether to perform DC.[2-7] However, only few patients in these RCTs underwent DC after 48 h: 11 out of 32 patients in the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial (HAMLET) underwent

ABBREVIATIONS: ACA, anterior cerebral artery; **CT,** computed tomography; **CI,** confidence interval; **DC,** decompressive craniectomy; **DECIMAL,** decompressive craniectomy in malignant middle cerebral artery infarction; **DESTINY,** decompressive surgery for the treatment of malignant infarction of the middle cerebral artery; **GCS,** Glasgow coma scale; **GOS,** Glasgow outcome scale; **HAMLET,** hemicraniectomy after middle cerebral artery infarction with life-threateninglll edema trial; **ICU,** intensive care unit; **MCA,** middle cerebral artery; **mRS,** modified Rankin Scale; **OR,** odds ratio; **PCA,** posterior cerebral artery; **RCTs,** randomized controlled trials

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DC >48 h after stroke onset, whereas all 20 patients in the decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL) trial underwent DC within 36 h of stroke onset and all 66 patients in the decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY)/DESTINY II trials underwent DC within 48 h of onset.[4-7] Remarkably, favorable outcome rates did not differ between the 11 HAMLET patients who underwent DC after 48 h and the 21 HAMLET patients who underwent DC within 48 h (27% vs 24%, respectively).[4] Additionally, several cohort studies comparing subgroups dichotomized by a time point of 48 h elapsed since stroke onset found no difference in outcome.[8-10] Thus far, no meta-analysis comparing DC <48 h vs >48 h after stroke onset has been performed. One could, therefore, question whether the time elapsed since stroke onset should indeed be applied as a decisive criterion in the guidelines. Strict application of exclusion criteria employed by the above-mentioned RCTs may withhold a neurosurgeon from offering a potentially life-saving treatment to a patient suffering from space-occupying hemispheric infarct who is otherwise fit to undergo surgery.

To address this dilemma, we studied the issue of timing of DC in a cohort of patients with middle cerebral artery (MCA) infarct undergoing DC during the "post-HAMLET" years 2007 to 2017. Additionally, we performed a systematic literature review and meta-analysis of studies reporting on the timing of DC and other predictors of outcome in patients undergoing DC for space-occupying hemispheric infarct.

METHODS

Patient Population

Patients were included in a prospective and consecutive database registering all DC patients in the years 2007 to 2017 (up to 2007, potential DC patients were included in the HAMLET trial, including 9 patients who underwent DC).[4] Patients from this cohort were eligible for the current analysis when previously established baseline criteria and 1-yr follow-up data were available. Formal approval for this observational cohort study was waived off by the institutional ethical review board of our hospital, and patient consent was not required. The authors declare that all supporting data are available within the article (**Table**, **Supplemental Digital Content 1**; **Figure**, **Supplemental Digital Content 2**; and **Text**, **Supplemental Digital Content 3**).

Clinical Management and DC

Upon admission, patients with clinical signs of acute MCA infarct were treated according to a standardized stroke protocol, which closely followed the recommendations for early management of patients with acute ischemic stroke of the European Stroke Organization.[11] In short, patients underwent computed tomography (CT) and CT angiography, and eligible patients received intravenous thrombolysis if the time between onset and confirmation of the infarct was within 4.5 h, with (since 2010) subsequent intra-arterial thrombectomy if a treatable clot was seen on CT angiography within 6 h of onset.[12] After the confirmation of space-occupying hemispheric infarct on follow-up CT, DC was performed when a decrease in consciousness to a Glasgow coma scale (GCS) score of ≤13 for right-sided lesions or an eye and motor score of ≤9 for left-sided lesions occurred, similar to the HAMLET trial study protocol.[4] However, in contrast with the HAMLET protocol, we did not apply a strict time limit of 48 h between stroke onset and DC. Other HAMLET exclusion criteria, such as age >60 yr, hemorrhagic transformation, and involvement of other vascular territories, were not strict decisive criteria as well; the clinical course and overall condition of such patients were discussed by the neurologist and neurosurgeon, and the decision whether to perform DC was taken after the informed consent of the patient and/or relatives.

During DC, a large skin incision was made in the shape of a question mark based at the ear. Then, a bone flap, including the frontal, temporal, and parietal bones, was created with a diameter of at least 120 mm. The craniectomy was extended down to the temporal skull base. The dura was opened widely in a cruciate fashion. The cortical surface was covered with the unapproximated dural flaps and absorbable hemostatic cellulose. Finally, the skin was closed. After surgery, all patients were admitted to the intensive care unit (ICU) for supportive therapy.

Cranioplasty

Patients were discharged to a rehabilitation center/nursing home with a custom-fitted, protective plaster helmet. When there were no signs of persisting brain swelling during the first follow-up visit to the neurosurgical outpatient clinic (usually 12-16 wk after discharge), cranioplasty was scheduled in the following weeks/months.

Data Collection

The following patient-related characteristics were collected: age, sex, presence of comorbidities as stated in the HAMLET trial (ie, history of transient ischemic attack or stroke, ischemic heart disease, atrial fibrillation, hypertension, and diabetes mellitus), GCS scores (E: eyes; M: motor; V: verbal), pupillary light reflexes on admission and pre-DC, CT findings, side of DC, and the time from hospital admission to DC. CT scans pre-DC were analyzed by 2 reviewers to determine the nature of the underlying pathology, the extent of midline shift, brainstem compression (ie, uncal transtentorial herniation or brainstem deviation with obliterated basal cisterns), additional infarct territory, and any associated intracranial injuries. GCS scores and pupillary light reflexes were recorded at the moment of diagnosis and immediately prior to surgery. Outcome at 1-yr postoperatively was derived from the clinician's notes, according to the Glasgow outcome scale (GOS): GOS 1 = death, GOS 2 = persistent vegetative state, GOS 3 = severe disability (conscious but disabled), GOS 4 = moderate disability (disabled but independent), and GOS 5 = good recovery (resumption of normal life even though there may be minor neurological and psychological deficits).[13] In order to report the study accurately and completely, the STROBE guidelines were used.[14]

Data Analysis

A favorable outcome was defined as GOS 4 and 5 and unfavorable outcome as GOS 1 to 3. The Shapiro-Wilk test was used to test continuous variables for normal distribution; if the Shapiro-Wilk test was >0.9, a variable was considered normally distributed; otherwise, the variable was considered not normally distributed. Means (±standard deviation, SD) were used for normally distributed continuous variables and medians (interquartile range, 25%-75%) were used for not normally distributed continuous variables. Univariate statistical analysis was

performed to identify differences between patients undergoing DC within 48 h and those undergoing DC after 48 h of stroke diagnosis: the 2-tailed *t*-test (for comparisons of normally distributed continuous variables), Mann-Whitney *U* test (for comparisons of not normally distributed continuous variables), Fisher's exact test (for analysis of 2 × 2 tables), and chi-square test (for analysis of N × 2 contingency tables) were done when appropriate. Firth's penalized likelihood approach was used to determine the association between the timing of DC and unfavorable outcome. Results with a $P < .05$ were considered statistically significant. IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, New York) was used for calculations.

Systematic Literature Review

A (nonpreregistered) literature search of the PubMed database (National Library of Medicine) up to November 2018 was conducted in order to find RCTs and cohort studies reporting on prognostic factors of unfavorable outcome after DC. The following keywords were used: decompressive craniectomy, hemicraniectomy, or decompression and craniectomy in combination with middle cerebral artery infarct. Only publications written in English were included. No publication date or publication status restrictions were imposed. The studies had to report prognostic factors on outcome after DC in patients of any age with MCA infarct. The outcome description could be through GOS, modified Rankin Scale (mRS), or Barthel index on any time. Non-RCT studies were excluded when less than 20 patients were presented. Prognostic factors on unfavorable outcome, reported in included studies, are summarized in Table.

Meta-Analysis

Considering the factor "time elapsed since stroke onset," meta-analysis was conducted according to a random-effects model (DerSimonian and Laird method). Studies initially included in the systematic review of the literature were selected for meta-analysis when (1) timing of DC could be dichotomized by a time point of 48 h since stroke onset, and (2) outcome data were reported or extractable according to mRS 0 to 3/GOS 4 to 5 (favorable) vs mRS 4 to 6/GOS 1 to 3 (unfavorable). The outcome data of the current cohort were also included in the meta-analysis. Heterogeneity was calculated through χ^2-based Q test with $P > .05$. Meta-analysis was performed using Review Manager (The Cochrane Collaboration).[15] Funnel plots were analyzed for publication bias. The PRISMA guidelines were used in order to report the systematic review and meta-analysis accurately and completely.[16]

RESULTS

Patient Population

A total of 66 consecutive patients underwent DC for space-occupying MCA infarct, of whom 23 (35%) after 48 h elapsed since stroke diagnosis. Overall, 26 (39%) patients survived favorably, 27 (41%) survived unfavorably (all GOS 3), and 13 (20%) died. Out of those 13 patients who died, 1 patient died despite 80 d of maximal treatment and 12 patients died following withdrawal of mechanical ventilation on median postoperative day 3.5 (IQR 3-5) because of presumed poor prognosis based on poor GCS scores (8 patients with E1M1Vtube, 3 with E1M2Vtube, and 1 with E1M3Vtube).

Timing of DC

The characteristics of the patients, dichotomized by timing of DC since stroke diagnosis, are presented in Table. DC after 48 h since admission was not associated with unfavorable outcome at 1-yr follow-up (OR 0.8, 95% CI 0.3-2.3, $P = .62$).

Cranioplasty

In 47 out of 53 surviving patients, cranioplasty was performed after a mean of 167 ± 76 d. In 7 (15%) patients, complications occurred: 4 suffered from an epidural hematoma (requiring surgical evacuation in 2), 2 suffered from autolysis of the autologous bone graft (requiring bone graft removal in 1 with replacement of a patient specific implant), and 1 suffered from autologous bone graft infection (requiring bone graft removal).

Systematic Literature Review

The PubMed search yielded 245 studies, of which 207 were excluded, because titles and abstracts did not meet the inclusion criteria. By reading full-text, the remaining 38 studies were assessed for eligibility. A total of 13 studies were excluded because they did not analyze patient characteristics for predictors of unfavorable outcome. From the reference lists of the remaining 25 studies, 1 additional study that met the inclusion criteria was identified. Thus, in total, 26 studies reporting on 3135 patients were included[8-10,17-39] (Figure 1). The favorable outcome rate among the studies ranged from 14% to 48%. **Table**, **Supplemental Digital Content 1** summarizes the most frequently noted clinical characteristics in the available literature that may influence outcome: patient's age, time between stroke onset and DC, side of infarct, brainstem compression on CT scan, ischemic involvement of the anterior cerebral artery (ACA) or posterior cerebral artery (PCA), extent of pre-DC midline shift, pre-DC GCS scores, and pupillary abnormalities. Whether a characteristic was significantly associated with unfavorable outcome is shown in **Table**, **Supplemental Digital Content 1** per study (including the current cohort).

Meta-Analysis

A total of 7 studies reporting on 1508 patients were included in the meta-analysis, together with the 66 patients of the current cohort (Figure 1).[4,9,10,22,31,37,40] Figure 2 presents the forest plot reporting unfavorable outcome rates (mRS 4-6 or GOS 1-3) dichotomized by timing of DC (<48 h vs ≥48 h elapsed since stroke onset). DC after 48 h of stroke onset was not associated with a higher risk of unfavorable outcome (OR 1.1; 95% CI 0.89-1.38). The funnel plot showed a low publication bias regarding unfavorable outcome in patients sorted by timing of DC (**Figure**, **Supplemental Digital Content 2**).

DISCUSSION

We reviewed the long-term clinical outcome of patients with MCA infarct in whom we performed DC during the

TABLE. Baseline Characteristics of 66 Space-Occupying MCA Infarction Patients Undergoing DC Categorized by Timing of DC

Characteristics	Outcome		*P* value*
	DC <48 h	DC ≥48 h	
N (male)	43 (30)	23 (13)	
Age, years, mean ± SD	47.3 ± 11.3	52.3 ± 11.8	.097
Comorbidities			
History of TIA or stroke, n (%)	2 (5)	0	
Ischemic heart disease, n (%)	4 (9)	1 (4)	
Atrial fibrillation, n (%)	5 (12)	1 (4)	
Hypertension, n (%)	16 (37)	4 (17)	
Diabetes, n (%)	6 (14)	1 (4)	
One or more comorbidities, n (%)	24 (56)	6 (26)	.037
Neurological condition on admission			
Intubated, n (%)	1 (2)	2 (9)	
GCS score in nonintubated patients, mean ± SD	12.3 ± 2.1	12.1 ± 2.5	
Intubated or GCS score ≤8, n (%)	3 (7)	5 (22)	
Pupillary light reflexes on admission			
Normal, n (%)	42 (98)	23 (100)	
Unilaterally absent, n (%)	1 (2)	0	
Midline shift before DC, mm, mean	8.5 ± 4.9	11.5 ± 3.8	.013
Brainstem compression, n (%)	27 (63)	19 (83)	
Left-sided DC, n (%)	15 (35)	13 (57)	
Involvement of ACA or PCA	10 (23)	5 (22)	
Neurological condition pre-DC			
Intubated, n (%)	12 (28)	5 (22)	
GCS score in nonintubated patients, mean ± SD	8.8 ± 2.6	8.4 ± 3.0	
Intubated or GCS score ≤8, n (%)	28 (65)	16 (70)	
Pupillary light reflexes pre-DC			
Normal, n (%)	30 (70)	19 (83)	
Unilaterally absent, n (%)	7 (16)	1 (4)	
Bilaterally absent, n (%)	6 (14)	3 (13)	
Time between DC and stroke onset, hours, median (IQR)	21.7 (17-39)	61 (52-75)	<.001
Unfavorable outcome	27 (63)	13 (57)	
GOS 1 (death)	9 (21)	4 (17)	
GOS 3	18 (42)	9 (39)	

*Two-tailed *t*-test for means, Mann-Whitney *U* test for medians, Fisher's exact test for binary variables, and chi-square test for ordinal variables (pupillary light reflexes pre-DC).
DC: decompressive craniectomy; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; h: hours; IQR: interquartile range; N: number of patients; TIA: transient ischemic attack.

"post-HAMLET" years 2007 to 2017 and performed a systematic literature review and meta-analysis. Compared to the outcome results of the pooled analysis of the 3 European RCTs, a comparable favorable outcome rate was seen in the current cohort.[4] DC >48 h after stroke onset was not a predictor of unfavorable outcome.

Timing of DC

Patients with space-occupying hemispheric infarct generally deteriorate after 48 h of edema formation, and death usually occurs within 72 h to 96 h.[41] Mori et al[42] found that early DC (before the onset of brain herniation, ie, prophylactic DC) significantly improved outcome compared with late DC (after the appearance of clinical and radiological findings of brain herniation). However, these results should be interpreted with caution, because Frank et al[42] found that only 26 out of 40 eligible patients with large MCA territory strokes deteriorated significantly, suggesting that numerous patients in the study by Mori et al[5-7] might have received unnecessary surgery. Since Mori et al[43-45], many subsequent studies solely focused on patients undergoing DC within 48 h of stroke onset. Even more, clinical guidelines advise to perform DC for space-occupying infarct only within 48 h of stroke onset.[2,3] As stated in the introduction, these guidelines were mainly based on the results of RCTs comparing DC to conventional therapy, but only few patients underwent DC after >48 h.[4-6] Also, in the hemicraniectomy and durotomy upon deterioration from infarction-related swelling trial, similar to the HAMLET trial, favorable outcome rates did not statistically differ between the 8 patients who underwent DC after 48 h and the 6 patients who underwent DC within 48 h: 25%

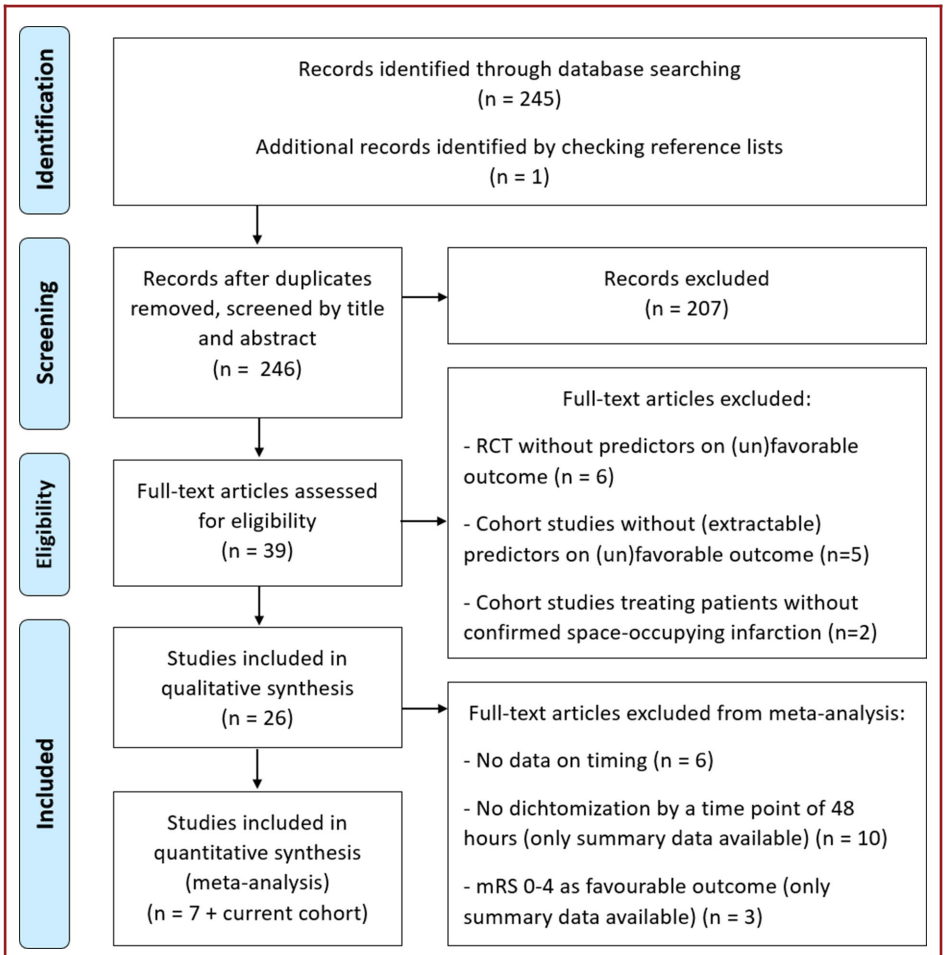

FIGURE 1. *PRISMA flow diagram of PubMed search until November 2018.*

vs 33%, respectively. The current study shows that both in our post-HAMLET cohort and in the vast majority of published cohort studies, time elapsed between stroke onset and DC does not influence outcome.[8-10,20,22-24,26,27,30,32,34,37,38] Of course, this finding may be related to the limited power of most of these studies ($N \leq 71$). The large retrospective analysis of 1301 patients by Dasenbrock et al[10] did find a correlation between a delay of >72 h and unfavorable outcome, but not for a delay of >48 h. Moreover, the correlation between a delay of >72 h and unfavorable outcome was not observed in the 932 out of 1301 patients without a diagnosis of herniation. These results suggest that the occurrence of clinical deterioration influences outcome rather than time between stroke onset and DC. Therefore, we advocate to not set a restriction of ≤48 h on time elapsed since stroke onset in the decision whether to perform DC. Instead, patients should be intensively controlled in the first days of stroke onset so that delay time to DC is minimized when neurological deterioration occurs.

Future Perspectives

In the era of evidence-based medicine, conducting RCTs is considered critical to test common therapies and to define international clinical guidelines. However, inclusion and exclusion criteria of RCTs are not necessarily prognostic factors and should, therefore, not be "automatically" incorporated into clinical guidelines. To ultimately study the timing issue of DC in malignant MCA infarction, a properly designed RCT should be performed. However, an RCT comparing DC to conservative treatment in patients developing life-threatening neurological deterioration after 48 h of stroke onset may be considered unethical for patients in whom a considerable percentage showed favorable outcome following DC in previous cohort studies. Alternatively, a noninferiority trial comparing DC ≤48 h to DC >48 h would require large numbers of patients (estimated at >250 patients per group). The previous RCTs (HAMLET, DECIMAL, and DESTINY) included only 38 to 112 patients, so it is unlikely that the neurosurgical community will undertake such a noninferiority trial.[4-7]

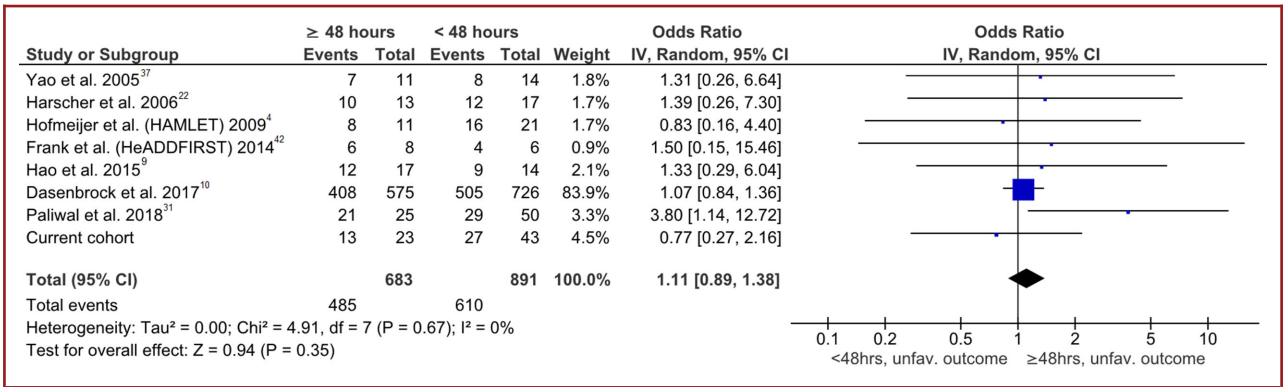

FIGURE 2. *Forest plot presenting odds ratio's for unfavorable outcome (event) after decompressive craniectomy for DC after 48 h of stroke onset.*

With the currently available level of evidence, we advocate not to set a restriction of ≤48 h on the time elapsed since stroke onset in the decision whether to perform DC.[2,3]

Limitations of the Study

The present retrospective study has several limitations. First, we did not report data on patients with space-occupying hemispheric infarct in whom the neurologist and neurosurgeon decided not to perform DC. The current cohort, therefore, represents a selection of stroke patients who were judged to have good chances of favoring from surgery. Second, we calculated the delay time between the time of admission and time of DC, whereas most published studies calculated the time between stroke onset and DC. We choose this approach because the exact time of stroke onset was difficult to determine in many patients (especially in patients suffering from wake-up stroke). Third, a limitation in our analysis of predictors of unfavorable outcome may have been the tendency to restrict treatment selectively in patients with certain characteristics presumed to predict unfavorable outcome.[46,47] Self-fulfilling prophecies may cause erroneous causal relations, because signs "known" to be related to unfavorable outcome itself lead to restriction of treatment and restriction of treatment to unfavorable outcome. Fourth, we considered only a GOS score of 4 or 5 as favorable outcome, because it corresponds to independence in activities of daily living. In the literature, however, there were studies that also considered an mRS score of 4 as favorable outcome, corresponding to patients who were unable to walk or attend their own bodily needs unassisted.[8,26,30,33,38] Indeed, a systematic review of the literature reporting on outcome from a DC patient's perspective by Rahme et al[48] concluded that the vast majority of patients were satisfied with life and did not regret having undergone DC despite high rates of physical disability and depression. Additionally, Van Middelaar et al[49] found that, in retrospect, the vast majority of patients would choose again for DC after space-occupying MCA infarct, even though 44% of them had mRS score of ≥4. Fifth, because of the small sample size, Firth's penalized likelihood approach was used, but only univariate; therefore, there was no correction for the effects of other confounding factors. Sixth, the favorable outcome rate among the 26 studies included in the systematic review varied considerably. Finally, we included mostly small series in the meta-analysis, which are of poorer quality data. One could therefore interpret the conclusions of this study as explorative. On the other hand, in almost all available RCTs no study patients were treated after 48 h.[5-7,43,44] Therefore, we present the best available level of evidence considering this subject.

CONCLUSION

Outcome of DC in patients with malignant MCA infarct performed after 48 h was not worse than outcome of DC within 48 h. Contrary to the current guidelines, we therefore advocate not to set a restriction of ≤48 h on the time elapsed since stroke onset in the decision whether to perform DC.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. **Table**. The influence of clinical characteristics on outcome: literature findings and current cohort. *Time elapsed since stroke onset, current cohort: delay time calculated between stroke admission, and DC; BI: Barthel index; DC: decompressive craniectomy; FU: follow-up in months; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; hrs: time elapsed in hours; mRS: modified Rankin Scale; N: number of patients; NIS-SOM: Nationwide Inpatient Sample SAH Outcome Measure; OR: odds ratio; P-OS: prospective observational cohort study; RCT: randomized controlled trial; R-OS: retrospective observational cohort study; Yrs: patient's age in years.

Supplemental Digital Content 2. **Figure.** Funnel plot of comparison: unfavorable outcome rate in patients with time elapsed since stroke onset ≥48 h vs <48 h.

Supplemental Digital Content 3. **Text.** References of Supplemental Digital Content 1.