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ORIGINAL ARTICLE

Decompressive Hemicraniectomy in Elderly Patients With Space-Occupying Infarction (DECAP): A Prospective Observational Study

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Abstract

Background: Decompressive hemicraniectomy improves survival rates and functional outcome in patients with space-occupying middle cerebral artery (MCA) infarction. We sought to determine clinical outcomes in elderly patients with MCA infarction treated with hemicraniectomy and to identify factors associated with functional outcome.

Methods: We performed a prospective, single-center observational study aiming to include patients aged ≥ 61 years with large MCA infarction treated with hemicraniectomy. The primary endpoint was the functional outcome according to modified Rankin Scale (mRS) score at 6 months after hemicraniectomy. Secondary endpoints included outcome measures at 12 months. A pooled analysis of individual patient data from the single-center cohort and a DESTINY 2 trial subgroup was performed to identify factors associated with functional status at 12 months.

Results: We included 40 MCA infarction patients who underwent hemicraniectomy between 2012 and 2017 at our university hospital (median [IQR] patient age 64 [62–67] years, National Institutes of Health Stroke Scale score 17 [16–21]). The dominant hemisphere was affected in 22/40 patients. Hemicraniectomy was performed within 31 [23–53] h of symptom onset. At 6 months after hemicraniectomy, 6/40 patients (15%) were moderately or moderately severely disabled (mRS score 3 or 4), 19 (47.5%) severely disabled (mRS score 5), and 15 (37.5%) had died. Compared to surgically treated DESTINY 2 patients, the single-center patients less likely exhibited favorable functional outcome at 6 months (mRS scores 0–4; odds ratio 0.239 [95% CI 0.082–0.696]). Case-fatality rate at 12 months was 43%. In a pooled analysis including 79 patients from DECAP and DESTINY 2, no significant associations of baseline and treatment factors with the clinical status at 12 months were observed.

Conclusions: In this single-center cohort of elderly patients with space-occupying MCA infarction and decompressive hemicraniectomy, the probability for survival without severe disability was low. Lethality at 6 and 12 months was comparable to previously reported data from a randomized trial.

Keywords: Stroke, Space-occupying infarction, Decompressive surgery, Hemicraniectomy, Prospective observational study, Pooled analysis

Introduction

Large middle cerebral artery (MCA) infarction occurs in up to 8% of patients with ischemic supra-tentorial stroke, potentially complicated by space-occupying edema, usually developing 2–5 days after stroke onset [1, 2]. Infarction volume is the main predictor for brain edema and

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early clinical deterioration, predominantly caused by brain herniation [3, 4]. In elderly stroke patients with similarly sized infarction, edema appears to occur less frequently versus younger patients, partially due to brain volume decreasing with age [5].

Conservative management of patients with space-occupying MCA infarction comprises pharmacological approaches, hyperventilation and therapeutic hypothermia. No sufficiently powered randomized trials have yet provided evidence supporting their routine clinical use [6–8].

Early decompressive hemicraniectomy (DH) in patients ≤ 60 years with space-occupying MCA infarction considerably reduced mortality while improving chances for lower disability burden versus conservatively treated patients [9, 10]. Small observational studies suggested that DH may likewise prove beneficial for elderly patients [11]. The randomized Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery 2 (DESTINY 2) study included patients ≥ 61 years [12]. In this trial, the surgically treated patients exhibited lower mortality rates at 6 months compared to conservatively treated patients (33% vs. 70%); the chance to survive with moderate disability was low in both groups (modified Rankin Scale [mRS] score 3: 7% vs. 3%), and the risk of severe disability was substantially increased in surgically treated patients (mRS score 5: 28% vs. 13%) [13]. Most patients who survived after DH were moderately severely disabled (mRS score 4), a condition that has been questioned as therapeutic target [14–16], yet found acceptable for most affected patients [17]. DH use in elderly patients varies among clinical centers [18]. Except for the DESTINY 2 trial, there are no prospective studies with large cohorts providing information on long-term, real-world outcomes of elderly patients.

We sought to prospectively evaluate and describe a single-center cohort of elderly patients (aged ≥ 61 years) receiving DH at our at our university stroke center. Outcome measures included functional outcome at 6 and 12 months after stroke, quality of life, and retrospective consent to surgery. A pooled analysis of surgically treated patients from the single-center cohort and DESTINY 2 was performed to identify potential independent predictors for clinical outcome at 12 months.

Methods

Study Design and Patient Selection (DECAP Single-Center Cohort)

DECAP is a prospective, single-center observational study at Dresden University Hospital, Germany, between December 2012 and February 2017 Inclusion criteria were: (i) diagnosis of acute ischemic stroke; (ii) clinically severe MCA syndrome; (iii) non-contrast cerebral computed tomography or magnetic resonance imaging showing infarction > 50% of the MCA territory (with/without ipsilateral anterior cerebral artery [ACA] or posterior cerebral artery [PCA] territory involvement; (iv) aged ≥ 61 years; (v) decompressive hemicraniectomy, performed at Dresden University Hospital; (vi) written informed consent from patient or legal representative.

Study visits were performed before discharge from acute care hospital, at 6 months (± 14 days), and 12 months (± 14 days). All visits after discharge were conducted as pre-specified, structured telephone interviews with the patient or, if the patient was not able to communicate by telephone, with the person most involved in their care. Additionally, at 12 months, a questionnaire was sent to surviving patients, filled in by the care-giver if the patient was unable to write but otherwise sufficiently communicative. Telephone interviews were carried out by an investigator not involved in patient care. The mRS scores were obtained according to the validated Rankin Focused Assessment tool [19].

Patient Data and Imaging Analysis (DECAP Single-Center Cohort)

We obtained individual patient data on stroke symptom onset (if symptom onset was unknown, the time when the patient was last asymptomatic was used), demographics, comorbidities, cardiovascular risk factors and neurological status on admission using the National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), and modified Rankin Scale.

Patient data on in-hospital measures were obtained including clinical course, infarction etiology, and laboratory data; details of decompressive hemicraniectomy including time of surgery and perioperative complications; details of intensive care unit (ICU) treatment including mechanical ventilation, anti-edema therapy, temperature management, tracheostomy; and functional outcome before discharge evaluated by NIHSS, GCS, and mRS.

At follow-up visits (6 and 12 months), we obtained data regarding patient care status, medical conditions, possible complications after hemicraniectomy and/or cranioplasty, and functional status (mRS score). At 12 months, information was gathered on daily living activities and care needs (Barthel index [BI] score), quality of life assessment by patients and carers (EQ-5D, EuroQoL Group 5-Dimension Self-Report Questionnaire), and retrospective consent to intensified stroke treatment including hemicraniectomy.

Individual brain imaging data were evaluated for preoperative localization and extent of ischemic infarction. Post-operative imaging was assessed for infarction size

and hemicraniectomy (maximum outer diameter on transverse scans).

Data management is reported in the online-supplement. Anonymized data of the DECAP cohort that support the findings of this study are available from the corresponding author upon reasonable request.

Decompressive Surgery and Critical Care (DECAP Single-Center Cohort)

Study patients were treated according to current European guidelines for managing acute ischemic stroke. Patients with space-occupying MCA infarction were treated according to our institutional protocol: decompressive surgery and ipsilateral intracranial pressure (ICP) probe insertion performed on patients with clinical signs of large MCA infarction (NIHSS score ≥ 15 (non-dominant hemisphere) or NIHSS score ≥ 20 (dominant hemisphere), impaired consciousness, and imaging revealing infarction of $>50\%$ of the MCA territory. Comorbidities, life expectancy, and other individual characteristics had to be considered by treating physicians. Details of decompressive surgery were reported previously [8]. Cranioplasty was recommended after 3 months using reserved bone or artificial bone flap.

After decompressive surgery, all patients remained sedated, intubated and mechanically ventilated until first post-operative imaging 24 h later (± 12 h). Further details of critical care are reported in the online-supplement.

Outcome Measures (DECAP Single-Center Cohort)

The primary endpoint was clinical outcome determined by mRS score at 6 months, dichotomized between 0–4 and 5–6. These scores range from 0 (no symptoms) to 5 (severe disability), 6 indicating death.

Secondary endpoints included functional outcome at 12 months (mRS), survival at 12 months, extent of supportive care need (BI), quality of life (including EQ-5D), complications associated with decompressive surgery or cranioplasty, and proportion of patients and relatives giving retrospective consent to hemicraniectomy.

Patient Selection for Comparison Group and Pooled Data Analysis

The comparison group consisted of 40 patients aged ≥ 61 years treated with early decompressive surgery within the randomized DESTINY 2 study, part of the Preliminary Analysis Set (PAS) group (DESTINY 2-PAS-DH group) [13]. Further main DESTINY 2 eligibility criteria for inclusion were: (a) symptom onset <48 h before treatment initiation; (b) NIHSS score of ≥ 15 (non-dominant hemisphere) or ≥ 20 (dominant hemisphere) with reduced levels of consciousness; (c) ischemic infarction of at least two thirds of the MCA territory, including the basal ganglia, on brain imaging; (d) preexisting mRS score of 0 or 1; (e) estimated life expectancy ≥ 3 years.

Statistical Analyses

Descriptive Statistics and Cohort Comparison (DECAP vs. DESTINY 2-PAS-DH) Primary and secondary outcomes as well as baseline characteristics were analyzed descriptively. Continuous variables were presented as mean (standard deviation) or as median (interquartile range, IQR), categorical variables as absolute and relative frequencies. Differences between the two cohorts were analyzed using the two-sided Mann–Whitney *U*-test or Pearson's Chi-square test (two-sided). Survival rates were visualized using Kaplan–Meier plots for both cohorts.

Pooled Analysis To assess the effects of baseline patient characteristics and other clinical predictors on functional outcome (mRS) at 12 months, data of both cohorts, DECAP and DESTINY 2-PAS-DH, were pooled. A separate univariate logistic regression model for each predictor was applied (for the DECAP cohort only and for both cohorts). The sample size did not allow for multivariate regression model.

Statistical significance was defined as $p<0.05$. Since this was an exploratory trial, no adjustments for multiple comparisons were applied.

All statistical analyses were carried out using the software SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Between December 2012 and February 2017, we included 40 elderly stroke patients with large, space-occupying MCA infarction receiving hemicraniectomy at our center. During the screening period, two more stroke patients ≥ 61 years old were treated with hemicraniectomy who declined study participation.

Patient Characteristics and Treatment (DECAP Single-Center Cohort)

Baseline patient characteristics, including cardiovascular risk factors, clinical status on admission, and baseline imaging data are shown in Table 1. Median patient age was 64 years, and patients were clinically severely impaired on hospital admission (median NIHSS score: 17). The dominant hemisphere was affected in 22/40 (55%), and additional ipsilateral ischemic infarction was observed by baseline imaging in 10 (ACA territory) and 3 (PCA territory) of 40 patients, respectively. Atrial fibrillation was present in 43%. DH was performed 31 h

(median) after stroke symptom onset, with a maximum of 139 h. Median diameter of hemicraniectomy was 132 mm and all patients received an ICP probe. Table 2 presents ICU treatments, complications and outcome measures. Osmotherapy was applied in 23/40 (58%) patients and controlled therapeutic hypothermia in 9/40 (23%). Tracheostomy was performed in 17/40 (43%). Pneumonia was the most common complication (22/40, 55%). Median ICU treatment duration was 22 days.

Outcome Measures (DECAP Single-Center Cohort)

Primary Endpoint

Figure 1 depicts functional outcomes according to mRS at 6 months. Of the 25 surviving patients, most were severely disabled (mRS score: 5, 19 patients). Three patients were moderately severely disabled (mRS score 4) or had moderate impairment (mRS score 3), respectively.

Secondary Endpoints

Outcome measures for secondary endpoints are shown in Table 3. Functional outcomes according to mRS at 12 months are depicted in Fig. 1. The case-fatality rate was 43% (17/40 patients), with surviving patients mostly severely disabled (mRS score 5; 14/40 patients). Median BI score (range 0–100) at 12 months was 12.5, indicating high-grade dependency.

Survival estimates for the 12 month-observational period are depicted in Fig. 2. Nearly 50% of patients died within 14 days after stroke onset (8 of 17 deceased patients), mainly due to cerebral herniation. Causes of deaths were (a) cerebral herniation ($n=8$), intracerebral hemorrhage ($n=1$), severe sepsis ($n=3$), pneumonia ($n=2$) and respiratory insufficiency ($n=1$); for two patients, no specific cause of death was documented.

At 12 months after hemicraniectomy, surviving patients ($n=23$) were cared for at home ($n=13$), nursing homes ($n=7$), or other institutions ($n=1$; $n=2$ missing). Persistent tracheostoma was still required in 6

Table 2 Treatment of DECAP patients

	DECAP *N* = 40
Hemicraniectomy size (mm)	132.0 (124.5, 138.5)
Intercranial pressure probe	40 (100.0%)
Osmotherapy	23 (57.5%)
Hypothermia	9 (22.5%)
Tracheostomy	17 (42.5%)
Duration until tracheostomy (days)	11.0 (8.0, 15.0)
Pneumonia	22 (55.0%)
Sepsis	4 (10.0%)
Venous thrombosis	1 (2.5%)
Cardiac arrhythmia	6 (15.0%)
Renal failure (renal replacement therapy)	6 (15.0%)
ICU duration (days)	22.0 (14.5, 26.0)
Lethality at hospital discharge	10 (25.0%)
NIHSS score at hospital discharge ($N=22$)	24.0 (18.0, 29.0)
GCS score at hospital discharge ($N=30$)	10.0 (9.0, 12.0)

GCS Glasgow Coma Scale, *ICU* intensive care unit, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale; Median (IQR) or *N* (%)

Table 1 Demographic and clinical characteristics of DECAP and DESTINY 2-PAS-DH patients

	DECAP *N* = 40	DESTINY 2-PAS-DH *N* = 40	*p* value*
Age (years)	64.0 (62.0, 67.0)	70.0 (67.0, 73.0)	< .001
Gender, female	17 (42.5%)	20 (50.0%)	0.501
Atrial fibrillation	17 (42.5%)	–	–
Arterial hypertension	32 (80.0%)	–	–
Current smoker	10 (25.0%)	–	–
Hyperlipidemia	9 (22.5%)	–	–
Diabetes mellitus	13 (32.5%)	–	–
NIHSS score at admission	17.0 (16.0, 21.0)	20.0 (18.0, 22.0)	0.008
GCS score at admission	11.0 (3.0, 13.0)	13.0 (9.0, 14.0)	0.034
Dominant hemisphere affected	22 (55.0%)	14 (35.0%)	0.097
ACA infarction ipsilateral	10 (25.0%)	9 (22.5%)	0.793
PCA infarction ipsilateral	3 (7.5%)	1 (2.5%)	0.305
Time to surgery (h)	30.8 (22.8, 53.4)	28.3 (24.0, 38.6)	0.399

ACA anterior cerebral artery, *GCS* Glasgow Coma Scale, *IQR* interquartile range, *NIHSS* National Institutes of Health Stroke Scale, *PCA* posterior cerebral artery, *SD* standard deviation; Median (IQR) or *N* (%)

*Categorical variables: Chi-square test/continuous variables: Wilcoxon signed-rank test

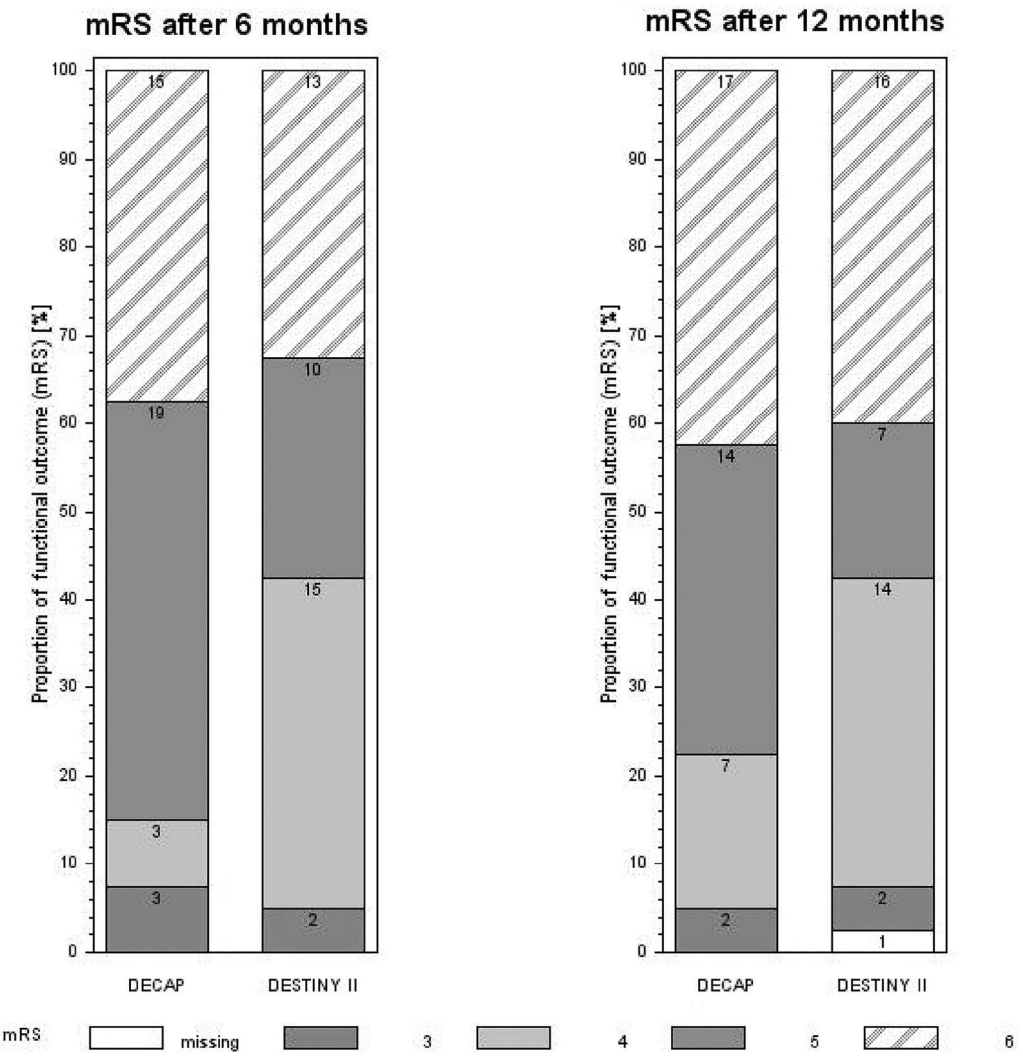

Fig. 1 Functional outcome of DECAP and DESTINY 2—patients (PAS-DH subgroup treated with hemicraniectomy) at 6 months and 12 months after hemicraniectomy

and a percutaneous feeding in 12/23 surviving patients; no patients were mechanically ventilated at 12 months.

Median time from hemicraniectomy to cranioplasty was 107 days. Hemicraniectomy- or cranioplasty-related complications, evaluated on hospital discharge for all patients and at 12 months after hemicraniectomy for survivors, were observed in seven patients (osteolysis: $n=5$, local infection: $n=1$, space-occupying hematoma: $n=1$).

Quality of life, according to the visual-analogue scale (range 0 [no quality of life]–100 [high quality of life]), was rated with median of 30. Surviving patients were mainly confined to bed, unable to wash and dress, and frequently reported pain or discomfort (online-supplement, Table I).

Retrospective consent to hemicraniectomy was given by 14/23 surviving patients. Three gave no retrospective consent, five were unable to communicate sufficiently, and for one no evaluation was available.

Subgroup analyses (mRS 0–4 vs. 5–6 at 12 months) of the DECAP cohort are reported in the supplemental material (Table II). The dominant hemisphere was equally affected in patients of both subgroups. All patients of the DECAP cohort treated with hypothermia had a poor functional outcome (mRS 5–6) at 12 months.

Accordingly, univariate analyses revealed an association of hypothermia with functional outcome at 12 months in the DECAP cohort, although not statistically significant. Osmotherapy and time to decompressive surgery were

Table 3 Outcome measures at 6 and 12 months (DECAP and DESTINY 2-PAS-DH cohorts)

	DECAP *N* = 40	DESTINY 2-PAS-DH *N* = 40	*p* value*
mRS score after 6 months, *N*	40	40	
Moderate disability (mRS 3)	3 (7.5%)	2 (5.0%)	0.011
Moderately severe disability (mRS 4)	3 (7.5%)	15 (37.5%)	
Severe disability (mRS 5)	19 (47.5%)	10 (25.0%)	
Death (mRS 6)	15 (37.5%)	13 (32.5%)	
Median (IQR)	5.0 (5.0, 6.0)	5.0 (4.0, 6.0)	0.124
mRS score after 12 months, *N*	40	39	
Moderate disability (mRS 3)	2 (5.0%)	2 (5.1%)	0.196
Moderately severe disability (mRS 4)	7 (17.5%)	14 (35.9%)	
Severe disability (mRS 5)	14 (35.0%)	7 (17.9%)	
Death (mRS 6)	17 (42.5%)	16 (41.0%)	
Median (IQR)	5.0 (5.0, 6.0)	5.0 (4.0, 6.0)	0.380
mRS score after 12 months, *N*	40	39	
mRS score 5–6	31 (77.5%)	23 (59.0%)	0.077
mRS score 0–4	9 (22.5%)	16 (41.0%)	
Symptom onset to death (days)	20.0 (7.0, 81.0)	80.5 (17.5, 160.5)	0.090
Early deaths (≤ 14 days)	8 (47.1%)	3 (18.8%)	0.085
Barthel index after 12 months, *N*	18	23	
Median (IQR)	12.5 (0.0, 25.0)	15.0 (10.0, 30.0)	0.443
EQ-5D VAS after 12 months, *N*	14	18	
Median (IQR)	30.0 (20.0, 40.0)	49.0 (30.0, 60.0)	0.072
Time to cranioplasty (days), *N*	24	25	
Median (IQR)	106.5 (95.0, 115.0)	126.0 (102.0, 190.0)	0.073
Complications of hemicraniectomy/cranioplasty, survivors**	7 (33.3%)	8 (34.8%)	NA

EQ-5D EuroQoL group 5-dimension self-report questionnaire, *mRS* modified Rankin Scale, *NA* not applicable, *VAS* visual-analogue scale [range from 0 (worst quality of life) to 100 (best quality of life)]

*Categorical variables: Chi-square test/continuous variables: Wilcoxon signed-rank test

**DECAP: *N* = 21, DESTINY 2-PAS-DH: *N* = 23

non-significantly associated with better functional outcome (Supplemental material, Table III).

Comparison of DECAP and DESTINY 2-PAS-DH Cohorts

Table 1 shows selected baseline characteristics for the DECAP single-center cohort and DESTINY 2-PAS-DH cohort. DECAP patients, compared to DESTINY 2-PAS-DH patients, were significantly younger (median age: 64 vs. 70 years, $p < 0.01$), with the dominant hemisphere more frequently affected (55% vs. 35%, $p = 0.097$). Time from symptom onset to surgery was comparable in both cohorts (median time: 31 vs. 28 h, $p = 0.399$).

Outcome at 6 and 12 months for both cohorts is depicted in Table 3. After 6 months, DECAP patients were significantly more severely affected according to the mRS score than the DESTINY 2-PAS-DH patients ($p = 0.011$). Mortality at 6 months was comparable in both cohorts (38% vs. 33%), and again 1 year after hemicraniectomy, with 43% (DECAP) and 41% (DESTINY 2-PAS-DH), respectively (Fig. 2). A moderate or moderately severe impairment (mRS score 3 or 4) was observed in 23% (9/40) of DECAP patients, thus less frequently than for the reference cohort (41%, 16/39) ($p = 0.077$). The DECAP patients died earlier, mainly within the first 2 weeks, while patients of comparator cohort more frequently died later in the observational period. Patients of the DESTINY 2 cohort rated their quality of life higher at 12 months (median visual-analogue scale score 49 vs. 30, $p = 0.072$).

If both cohorts were compared for survival chances without severe impairment (mRS 0–4) at 6 months, univariate logistic regression revealed an odds ratio of 0.239 for DECAP patients (95% CI 0.082–0.696; $p = 0.009$). For survival without severe impairment after 12 months, an odds ratio of 0.417 (95% CI 0.157–1.111; $p = 0.08$) was found for the DECAP cohort.

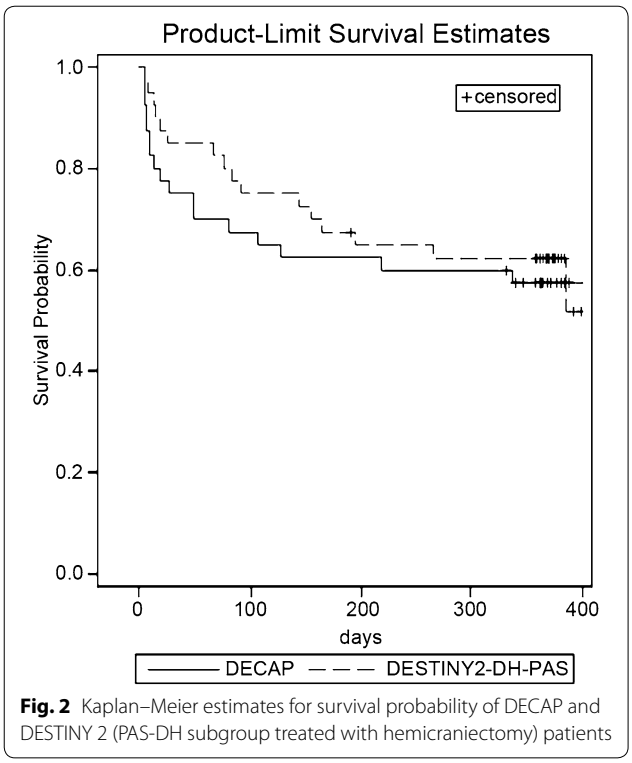

Fig. 2 Kaplan–Meier estimates for survival probability of DECAP and DESTINY 2 (PAS-DH subgroup treated with hemicraniectomy) patients

Pooled Analysis of Individual Patient Data of DECAP and DESTINY 2-PAS-DH Cohorts

Several clinically relevant factors were tested in the combined data set ($n=79$) for possible association with acceptable functional outcome (mRS score < 5) at 12 months after hemicraniectomy (Table 4). No significant association was found between patient age, stroke severity, localization of infarction, time to surgery or other factors and functional outcome.

Table 4 Univariate analyses of pooled data (DECAP and DESTINY 2-PAS-DH, $n=79$) for associations with functional outcome (mRS 0–4) at 12 months after decompressive surgery

Factor	OR	95% CI	*p* value
Age	0.980	0.886–1.084	0.699
NIHSS score on admission	0.989	0.863–1.134	0.874
GCS score on admission	1.145	0.968–1.356	0.115
Dominant hemisphere affected	0.785	0.393–1.568	0.493
Additional ipsilateral infarction (ACA/PCA)	0.750	0.253–2.226	0.604
Time from symptom onset to surgery	1.018	0.997–1.039	0.101

ACA anterior cerebral artery, *CI* confidence interval, *GCS* Glasgow Coma Scale, *NIHSS* National Institutes of Health Stroke Scale, *OR* odds ratio, *PCA* posterior cerebral artery

Discussion

In our DECAP cohort of 40 elderly stroke patients with large MCA infarction treated with decompressive hemicraniectomy, we observed survival rates at 6 and 12 months comparable to rates reported for surgically treated patients of the randomized DESTINY 2 trial. Surviving DECAP patients primarily had poor functional status (mRS 5) during the first year after stroke and their chances of achieving better functional outcomes at 12 months were lower compared to the surgically treated DESTINY 2 patients.

The lower probability for survival without severe disability in the DECAP cohort proved remarkable. DECAP patients were significantly younger compared to the DESTINY 2 patients. Smaller observational studies have suggested that higher age might be associated with lower functional status after hemicraniectomy in patients up ≤ 60, although observational data for patients aged > 60 old were insufficient [11, 20, 21]. Compared to surgically treated younger patients of three randomized trials included in a meta-analysis [10], elderly DESTINY 2 patients had higher mortality and were more frequently severely disabled at 12 months (mRS score 5; 7% vs. 18% [PAS-DH]). Our pooled analysis of DECAP and DESTINY 2 patients revealed that patient age was not associated with functional outcome after 1 year.

The dominant hemisphere was more frequently affected in the DECAP cohort compared to the DESTINY 2 cohort. However, proportions of patients with affection of the dominant hemisphere were comparable in DECAP subgroups with poor (mRS 5–6) or better functional outcome at 12 months. Involvement of the dominant hemisphere was not predictive for clinical outcome in our pooled analysis of the DECAP and DESTINY 2 cohorts. Currently, there is no clear evidence from randomized trials or meta-analyses that infarction side impacts on functional outcome or quality of life [22]. It is increasingly recognized that neuro-psychological deficits after large infarction of the non-dominant hemisphere can have a comparable impact on rehabilitation and long-term functional outcome like infarction of the dominant hemisphere [23]. However, persistent, severely impaired ability to communicate might have had a negative impact on rehabilitation capabilities and recovery in our single-center cohort.

Hemicraniectomy size in patients with large MCA stroke is a relevant factor in achieving sufficient decompression [24, 25]. Nearly all DECAP patients exhibited hemicraniectomies > 12 cm, as recommended in recent randomized hemicraniectomy trials and guidelines [26]; therefore, it is unlikely this factor contributed to observed differences in functional outcome between both cohorts.

Median duration from symptom onset to decompressive surgery in the DECAP cohort did not differ with the DESTINY 2 cohort. Although longer duration to hemicraniectomy was associated with better outcomes at 12 months in the DECAP cohort, time to surgery was not predictive in our pooled analysis. "Late" hemicraniectomy (> 48 h) was associated with worse in-hospital outcome and higher odds for discharge to institutional care in a large cohort of MCA stroke patients treated with hemicraniectomy [27]. Currently, there is insufficient data from randomized trials on the effectiveness of "late" hemicraniectomy, especially in elderly patients, and early hemicraniectomy is thus recommended [26].

During ICU stay, controlled hypothermia (target temperature: 33 °C) was applied in several DECAP patients in the early phase of the study and all of these had a poor functional outcome at 12 months. Although this was not statistically significant, probably due to the sample size, we assume that application of hypothermia had a negative impact on outcome in the DECAP cohort. This might partially explain the overall difference in functional outcome at 12 months between the DECAP and the DESTINY 2 cohorts.

Furthermore, osmotherapy was frequently applied as ICP rescue therapy. In contrary to hypothermia, osmotherapy showed a positive effect on functional outcome in the DECAP cohort. Both interventions are currently routinely used at several stroke centers, although evidence for their effectiveness is lacking and they might be even harmful [8, 28, 30].

As in other prospective studies, most early deaths before day 14 in the DECAP cohort were caused by cerebral herniation. This highlights the relevance of effective, early decompressive therapy, and advanced therapeutic strategies to treat progressive infarction edema.

At 1 year, care for most survivors was provided at home by relatives and professional care-givers. In a recent prospective study, patients with severe stroke requiring tracheostomy exhibited better functional outcomes when cared for at home than those in nursing homes [29]. Surviving patients of the DECAP cohort were mainly severely disabled, often completely dependent on caregivers, rating their overall quality of life relatively low. However, a proportion of DECAP patients accepted this condition and gave retrospective consent to applied critical care, including hemicraniectomy.

Our study has several strengths. We describe the largest cohort of prospectively evaluated elderly stroke patients treated with hemicraniectomy and recruited outside randomized trials. The DECAP cohort was treated at an experienced stroke center according to a specified institutional protocol for large MCA infarction management. Patient selection bias proves unlikely, as nearly all patients screened were included in the study. For functional outcome evaluation, we used a validated assessment tool for mRS scoring [19]. Pooling the individual data of DECAP and DESTINY 2-PAS-DH cohorts enabled us to analyze one of the largest currently available, prospectively collected datasets of elderly stroke patients with hemicraniectomy. Results from the ongoing DESTINY-R registry, including patients with large MCA infarction, will provide more information on elderly, surgically treated patients [31].

An important limitation of DECAP is the single-center, observational study design. Local treatment strategies, including osmotherapy and hypothermia, and experience of critical care and neurosurgical teams, may have influenced patient management and outcome. Assessment and reporting of adverse events or treatment-related complications as performed in randomized trials was not possible, probably resulting in underestimation of these factors.

Like other prospective studies on patients with large MCA stroke, our pragmatic study collected no detailed data on inpatient rehabilitation after discharge (duration, therapeutic strategies, withdrawal of care), ambulatory medical care, or extent of care provided by relatives. All these factors may have contributed to differences in functional outcome between DECAP and DESTINY 2 patients, and they need to be addressed in more detail in further prospective studies.

Conclusions

In our DECAP cohort of elderly stroke patients with space-occupying MCA infarction and DH, we observed survival rates comparable to those of the DESTINY 2 trial cohort. Functional status of survivors in the DECAP cohort was predominantly poor, clearly worse than the cohort of surgically treated DESTINY 2 trial patients. This difference may be attributed in part to patient characteristics, applied additional therapeutic strategies (especially hypothermia), extent of post-hospital care, and outcome evaluation.

In a pooled analysis of data from DECAP and DESTINY 2 patients, none of the factors tested—including patient age, localization of infarction or time to hemicraniectomy—was significantly associated with functional outcome at 12 months.

Early DH should be considered in elderly patients as a live-saving therapeutic option. We recommend to inform patients and relatives of the relatively low chance of survival without severe, permanent functional impairment after hemicraniectomy in elderly patients observed in clinical routine. Prospectively collected, real-world data of larger cohorts are needed to further evaluate the

benefit of DH in elderly patients with space-occupying MCA infarction.

Electronic supplementary material
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Author Contributions
JR has acquired, analyzed and interpreted data. SW has acquired and interpreted data. EJ has provided data and interpreted data. LU has analyzed and interpreted data. RL has analyzed and interpreted data. JB has acquired and interpreted data. GS has interpreted data and provided administrative support. HR has interpreted data and provided administrative support. HS has designed and coordinated the study, has acquired, analyzed and interpreted data, and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Compliance with Ethical Standards

Conflict of interest
All authors declare that they have no conflict of interests.

Ethical Approval
The study was approved by the institutional review board (Ethikkommission an der TU Dresden; IRB00001473). Written informed consent was obtained from patients or their legal representatives.

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