CUT OFF VALUE OF GOOD PRONOSTIC FACTOR OUTCOMES IN LARGE TERRITORY ISCHEMIC STROKE UNDERGOING EARLY DECOMPRESSIVE CRANIECTOMY

Panu Boontoterm, Siraruj Sakoolnamarka**, Pusit Feungfoo**, Chesda Udommongkol****

***Neurosurgery Unit, Department of Surgery and Division of Pulmonary and Critical Care Medicine, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand**
****Department of Surgery, Phramongkutklao Hospital, Phayathai, Bangkok, Thailand**
*****Neurology Unit, Department of Medicine, Phramongkutklao Hospital, Ratchawithi Road, Phayathai, Bangkok, Thailand**

ABSTRACT

Background: Decompressive craniectomy (DC) significantly reduces mortality in large territory ischemic strokes that develop intractable cerebral edema. However, evidence for functional benefit remains sparse and contradictory.
Objective: This study aimed to assess cut-off value for predictor outcomes of early DC.
Methods: We conducted a prospective, observational cohort study from December 2016 to June 2021. Patients were screened for ischemic stroke involving the middle cerebral, internal carotid artery or both using the National Institutes of Health Stroke Scale score. All patients underwent DC. Multivariate analysis was performed for an array of clinical variables in relation to functional outcomes according to the modified Rankin Scale (mRS) and Pearson's correlation coefficient analysis. Clinical outcome was assessed after 3- and 6-month follow-up.
Results: In total, 243 patients were included in this study. Age ≤71 years (AUC=0.955, p <0.001 accuracy 89.7%), onset to DC ≤9 hours (AUC=0.824, p <0.001 accuracy 78.8%), volume of infarction ≤155 cm^3 (AUC=0.939, p <0.001 accuracy 93.6%) and the Alberta Stroke Program Early CT Score or ASPECT score ≥6 (AUC = 1, p <0.001 accuracy 100%) were significantly associated with good clinical outcomes in early DC (mRS 0 to 3).
Conclusion: Among patients with large territory ischemic strokes undergoing early DC, age ≤71 years, onset to DC ≤9 hours, volume of infarction ≤155 cm^3 and ASPECT score ≥6 was significantly associated with good clinical outcomes. All prognostic factors in early DC correlated well with functional outcomes at 6 months which could be used to predict outcome, and consider clinical indications and informed post-
operative complications among patients with large territory ischemic stroke.

Keywords: Intractable cerebral edema, Large-territory ischemic strokes, Decompressive craniectomy, Modified Rankin Scale, Outcome predictor

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Correspondence to:
Boontoterm P, Neurosurgery Unit, Department of Surgery and Division of Pulmonary and Critical Care Medicine, Department of Medicine, Phramongkutklao Hospital, 315 Ratchawithi Road, Phayathai, Bangkok, Thailand 10400
Email: sapiens_panu@hotmail.com

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Introduction

Patients presenting large-territory ischemic strokes may develop intractable cerebral edema putting them at risk of herniation and death. Patients may have severe neurological deficits, with hemiplegia, head and gaze deviation towards the side of the infarction and deterioration of consciousness. Brain edema may subsequently be associated with transtentorial brain herniation and death. In a number of clinical trials survival rates of 67 to 84% have been reported among patients with malignant middle cerebral artery (MCA) infarction treated with decompressive craniectomy (DC) compared with 20 to 30% among conservatively treated patients. Related described series have observed fatality rates of about 80%, and most survivors were left severely disabled.[1, 2] Unfortunately, medical management for malignant MCA infarction is generally ineffective, necessitating a surgical approach for its relief.[3] A pooled analysis of individual patient data of the three randomized controlled trials showed that surgical decompression reduced the risk of death or disability, defined as modified Rankin Score (mRS) ≥3.[4] Although DC was shown to significantly reduce mortality among patients compared with medical therapy alone, concern has been expressed that life is preserved at the potentially unacceptable cost of marked functional disability.[5]

Large territory ischemic stroke refers to a cerebral infarction involving more than one half to two thirds of MCA territory.[7,8] Among large territory ischemic stroke cases, those with early clinical deterioration or involvement of complete MCA territory were frequently tagged as malignant large infarction (MLI).[9] DC for MLI was scarcely performed before 2000 mainly because it might just increase survival with overwhelming neurological impairment and handicap. However, increased interest in DC has been shown since the early 21st century as a result of mortality reduction as well as a chance of outcome improvement.[10-16] Although various prognostic factors affecting the outcome after DC have been identified, the strength of association has not been well-established. Most published data has been obtained from western populations where long-term stroke rehabilitation facilities exist and stroke units are well-established.

Another crucial factor for DC in MLI is timing of surgery, performed within 24 to 48 hours that presents a benefit associated with early DC. Early DC markedly reduced mortality and the volume of infarcted brain tissue. This study aimed to assess cut off value of good prognostic factor outcomes in large territory ischemic strokes undergoing early DC.

Methods

A prospective, observational cohort study was conducted between December 2016 and June 2021 at the Department of Neurology and Neurosurgery, Phramongkutklao Hospital. The study was approved by the Institutional Review Board, Royal Thai Army Medical Department (approval no. R102h/59). Research followed Council for International Organization of Medical Science Guidelines 2012 and Good Clinical Practice of International Conference on Harmonization statement no. IRBRTA 1731/2559.

The sample size estimation revealed at least 243 patients were required for this study. Written informed consent was obtained from all patients. Patients with life-threatening malignant MCA infarction indicated to undergo DC on the basis of clinical assessment using National Institute of Health Stroke Scale (NIHSS), Glasgow coma scale (GCS) and neuroimaging using computed tomography (CT) were prospectively enrolled. Patients who died within 24 hours of presentation, those with dilated and fixed pupils at presentation, GCS <6, mRS ≥3 before the current stroke and known metabolic cause for altered sensorium were excluded to reduce the risk of bias.

The diagnosis of stroke was clinically established and confirmed by neuroimaging [noncontrast CT head]. Details of demographics including age, sex, address, contact number, body mass index (BMI, kg/m^2), detailed history of event, presenting symptoms and signs, risk factors for stroke, blood pressure, GCS and NIHSS score, laboratory parameters, imaging findings (type of stroke, arterial territory involved, the Alberta Stroke Program Early CT Score (ASPECT score), volume of infarction (cm^3) and midline shift), onset to DC (hour), intracranial pressure (ICP) at operative field and postoperative events such as surgical site infection and hydrocephalus were noted. The Western Aphasia Battery was used to record the severity of aphasia. Aphasia quotient was calculated by kerrtesz formula; a score ≤93.8 was taken as cut-off for defining aphasia.[6] DC in our patients consisted of creating a large fronto-parieto-temporal free bone flap (at least 12 cm) and duraplasty. No intervention on brain tissue was performed. Details of DC including time of onset of symptoms to DC, duration of surgery, blood loss, postoperative complications and intensive care unit (ICU) stay were recorded. Course of hospital stay including stroke recurrence, death and status at discharge was noted. Clinical status at the time of discharge was measured using GCS, Glasgow Coma Outcome Scale (GCOS), NIHSS, modified Barthel Index and mRS score. Outcome on follow-up was assessed using mRS during Out-patient Department visits in the stroke clinic at 3 and 6 months. Aphasia, using the Western Aphasia Battery, was tested on follow-up visits at the Stroke Clinic. The mRS of ≤3 was taken as a good outcome. We also analyzed the results using mRS of ≤3 as a good outcome.

Participants

A total of 243 patients admitted in the Medical Stroke Unit and Surgical ICU, Phramongkutklao Hospital, Bangkok, Thailand from December 2016 to June 2021 was monitored for invasive arterial blood pressure, peripheral O_2 saturation, and electrocardiogram. All patients were measured for oxygenation, arterial blood pressure and glucose. The inclusion criteria were age >18 years, diagnosis of large territory ischemic stroke involving ≥two thirds of the MCA territory on cranial CT or magnetic resonance imaging (MRI) within 48 hours after symptoms onset (the score of NIHSS item 1a reflecting consciousness needed to be ≥1), DC was operated within 48 hours of onset. The exclusion criteria were large volume hemorrhagic transformation, malignant herniation, severe coagulopathy, severe infection, patient refusal of treatment, patients who died within 24 hours of presentation, dilated and fixed pupils at presentation, GCS <6, mRS ≥3 before the current stroke and known metabolic cause for altered sensorium.

Standard medical therapy

All patients were admitted to a Stroke Unit or ICU, Department of Neurology and Neurosurgery. The patient's head was kept elevated at 30°. All patients were kept in a mild fluid restriction state with 1800 mL of daily fluid in the first week. Intravenous antihypertensive agents were administered when blood pressure was higher than 220/120 mmHg. Body temperature was kept below 38°C and blood glucose level was maintained <180 mg/dL. Endotracheal intubation was performed to maintain adequate tissue oxygenation among patients with clinical deterioration or signs of respiratory insufficiency. Hyperventilation was used only in an emergency with the target level of $PaCO_2$ of 30 to 35 mmHg. Osmotherapy with mannitol or glycerol launched when evidence of mass effect was observed. Mannitol was administered at the dosage of 0.25 to 0.5 g/kg body weight bolus. During osmotherapy, blood osmolarity was maintained at approximately 300 to 320 mOsm/L. Oxygenation, blood pressure and glucose level was sustained at appropriate levels. Early enteral nutrition was provided. Pneumonia and deep venous thrombosis were monitored and well treated.

Surgical treatment

Early DC was carried out within 48 hours of onset. This consisted of a craniectomy with dimensions of at least 12 cm in the anteroposterior and 10 cm in the superoinferior direction which was sufficiently large to match the infarcted area. Additional temporal bone removal was performed so that the floor of the middle cerebral fossa could be fully explored and decompressed. The dura was opened and an augmented patch was inserted to further relieve the high intracranial pressure. Those surgical survivors received a secondary operation of cranioplasty three months after DC.

Outcome assessment

Outcome was assessed with mRS at 3 and 6 months follow-up and was first dichotomized as good (mRS 0 to 3) and poor (mRS 4 to 6) to compare and contrast survivors' functional outcome in early DC.

Hemodynamic monitoring

Radial arterial and central venous catheters were linked to a bedside monitor on one side and to a specific transducer (Philips Intellivue Philips MX600, USA) for blood pressure and central venous pressure monitoring. When patients had unstable hemodynamic values of cardiac output and stroke volume were estimated using pulse contour analysis (EV1000 clinical platform, Edwards advanced hemodynamic monitoring tools for an integrated Edwards Critical Care System, USA).

Statistical analysis

Statistical analysis was performed using SPSS, Version 23.0. The primary outcome was the cut off value of good prognostic factors in large territory ischemic stroke undergoing early DC while the secondary outcome was clinical variables in relationship to functional outcomes according to mRS. Results were expressed as mean ± SD when data were normally distributed or median and interquartile range (IQR) if not. A p-value less than 0.05 was considered statistically significant. Multivariate analysis was performed using an array of the cut off values in relationship to functional outcomes according to the mRS and Pearson's correlation coefficient analysis. Clinical outcomes were assessed at 3- and 6-month follow-up. For the cut off value of good prognostic factor, the Area Under the Curve (AUC) or Receiver Operating Characteristics (ROC) curve were used representing the degree or separable measurement, then a graphic plot was drawn to illustrate the diagnostic ability of a binary classifier system as its discrimination threshold varied in these predictive factors. The higher the AUC, the better the model was at distinguishing between patients presenting good and poor outcomes. The value of AUC near 1

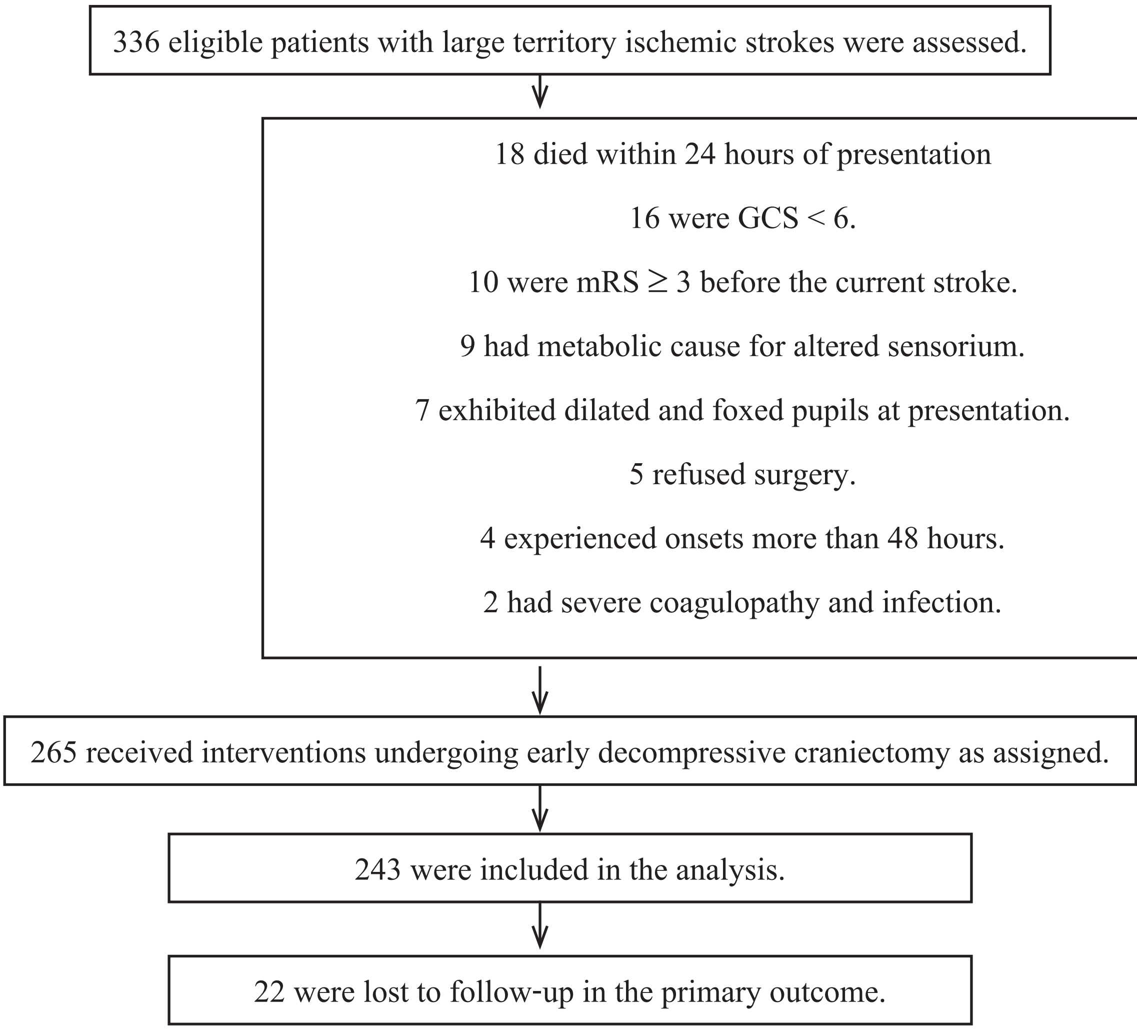

Figure 1. Flow chart of patient enrollment and analysis

showed a good separable measurement while AUC near 0 showed the worst separable measurement.

Results

Patients' characteristics

During the study period, 243 patients with large territory ischemic stroke undergoing early DC were included in data analysis. Most patients were male (80.7%) with average age of 65 years. The most frequent coexisting disease was hypertension (88%). Of these, 153 (63%) patients had left territory stroke while 90 (37%) patients had right territory stroke. Among these, mean range of NIHSS was 21 and GCS at the time of admission was 9 (9.5 ± 3). Mean onset to DC from time of onset of symptoms was 10 hours (10.41 ± 5.96). Mean ICP at the operative field was 19 mmHg (19.32 ± 8.6). Mean volume of infarction was 135 cm3 (135.19 ± 51.1), and mean ASPECT score was 5 (5.77 ± 2.41). Six patients (2.5%) had postoperative surgical site infections while 23 (9.5%) patients revealed postoperative hydrocephalus (Table 1). Outcome was assessed using GCOS, NIHSS, Modified Barthel Index at 3- and 6-month follow-up as shown in **Table 2**.

Table 1. Demographic data of 243 patients with large territory ischemic strokes undergoing early DC

Variables	N = 243
Male, n (%)	196 (80.7%)
Age (yr)	64.82 ± 14.81
Body mass index, BMI (kg/m^2)	29.14 ± 6.2
Diabetes mellitus	186 (76.5%)
Hypertension	214 (88.1%)
Tobacco use	126 (51.9%)
Old cerebrovascular accident	87 (35.8%)
History of ipsilateral TIA	22 (9.1%)
Hypercholesteralemia	167 (68.7%)
History of angina pectoris	87 (35.8%)
Coronary artery disease	116 (47.7%)
Atrial fibrillation	116 (47.7%)
Peripheral arterial occlusive disease	48 (19.8%)
Position of large-territory infarction	
left	153 (63%)
Right	90 (37%)
bilateral	0 (0%)
Onset to DC (hr)	10.41 ± 5.96
GCS at admission	9.5 ± 3
NIHSS at admission	21.44 ± 9.64
ICP at operative field	19.32 ± 8.6
Volume of infarction(cm$^{3)}$	135.19 ± 51.1
ASPECT score	5.77 ± 2.41
Post-operative surgical site infection	6 (2.5%)
Post-operative hydrocephalus	23 (9.5%)

Value presented as mean ± SD

Table 2. Outcome was assessed with GCOS, NIHSS, Modified Barthel Index at 3- and 6-month follow-up in early DC

Variables	Baseline	3 Month	6 Month
GCOS			
Death	7 (2.9%)	7 (2.9%)	7 (2.9%)
Persistent vegetative state	90 (37%)	52 (21.4%)	52 (21.4%)
Severe disability	85 (35%)	54 (22.2%)	54 (22.2%)
Moderate disability	61 (25.1%)	110 (45.3%)	13 (5.3%)
Good recovery	0	20 (8.2%)	117 (48.1%)
NIHSS	21.95 ± 8.89	19.51 ± 9.46	18.47 ± 9.58
Modified Barthel Index	20 (0, 60)	61 (20, 90)	90 (30, 95)
No symptoms	0	0	0
No significant disability	0	0	0
Slight disability	0	60 (24.7%)	113 (46.5%)
Moderate disability	4 (1.6%)	68 (28%)	16 (6.6%)
Moderate to severe disability	85 (35%)	4 (1.6%)	1 (0.4%)
Severe disability	147 (60.5%)	104 (42.8%)	94 (38.7%)
Death	7 (2.9%)	7 (2.9%)	19 (7.8%)

Values presented as frequency (%), interquartile range (IQR) and mean ± SD

Table 3. Correlation between postoperative hydrocephalus and clinical outcome (mRS 0 to 3) at 6-month follow-up in early DC

	Good outcome (n=156)	Poor outcome (n=87)	*p-value*
Hydrocephalus	12 (9.6%)	11 (9.3%)	0.941
No Hydrocephalus	113 (90.4%)	107 (90.7%)	

Values presented as frequency (%), *p-value* corresponds to Pearson's correlation or chi-square test

Clinical outcomes

Correlation between postoperative hydrocephalus and clinical outcome (mRS 0 to 3) at 6-month follow-up showed no significant differences between good and poor outcomes. Postoperative hydrocephalus did not affect clinical outcomes (**Table 3**).

Cut off value for good clinical outcomes in early DC (mRS 0 to 3) (**Figure 2**)

This study showed that age ≤71 year was significantly associated with good clinical outcome in early DC (mRS 0 to 3) (AUC = 0.955, p <0.001 accuracy 89.7%) (**Figure 2A)**. Onset to DC ≤9 hours was also significantly associated with good clinical outcome in early DC (mRS 0 to 3) (AUC = 0.824, p <0.001 accuracy 78.8% (**Figure 2B**). Volume of infarction ≤155 cm^3 was significantly associated with good clinical outcome in early DC (mRS 0 to 3) AUC = 0.939, p<0.001 accuracy 93.6%. (**Figure 2C**). Additionally, ASPECT score ≥6 was significantly associated with good clinical outcome in early DC (mRS 0 to 3) (AUC = 1, p <0.001 accuracy 100%) (**Figure 2D**).

Discussion

In this study, management of patients with large territory ischemic stroke remained a challenge. DC could relieve the mass effect resulting from infarcted brain tissue, preventing brain herniation and death. Postoperative hydrocephalus did not

Figure 2. Cut off value for good clinical outcome in early DC (mRS 0 to 3)

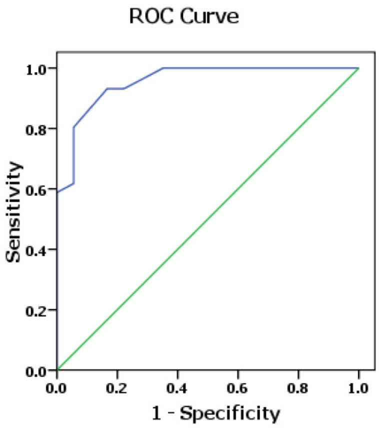

Figure 2A.
ROC Area = 0.955, p <0.001

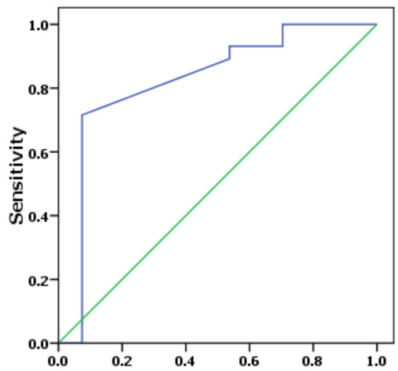

Figure 2B.
ROC Area = 0.824, p <0.001

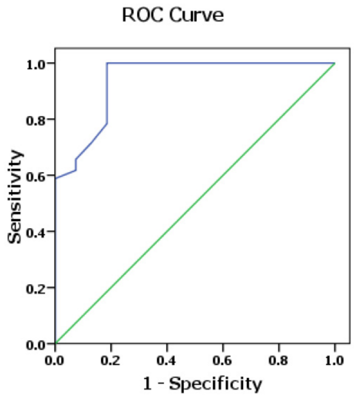

Figure 2C.
ROC Area = 0.939, p <0.001

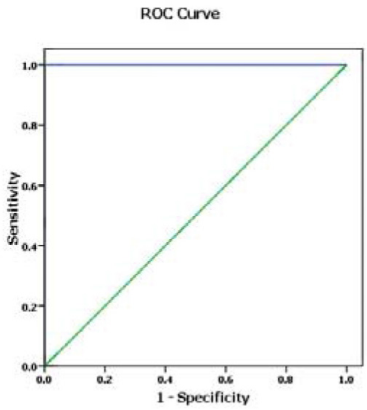

Figure 2D.
ROC Area = 1, p <0.001

Figure 2A. Age cut off value for good clinical outcome in early DC (mRS 0 to 3)
Figure 2B. Onset to DC (hr) cut off value for good clinical outcome in early DC (mRS 0 to 3) (set accuracy more than 70%)
Figure 2C. Volume of infarction (cm^3) cut off value for good clinical outcome in early DC (mRS 0 to 3)
Figure 2D. ASPECT score cut off value for good clinical outcome in early DC (mRS 0 to 3)

Table 4. Multivariate analysis cut off value in relationship to functional outcome at 6-month follow-up (mRS 0 to 6)

	Beta coefficient	Standard Error (95%CI)	*p-value*
(Constant)	1.425	0.265	<0.001*
Onset to DC (hr) ≤ 9 hrs	-0.068	0.13	0.6
ASPECT score ≥ 6	3.766	0.236	<0.001*
Volume of infarction ≤ 155 cm^3	0.718	0.198	<0.001*
Age ≤ 71 yrs	0.274	0.159	0.086

Value presented as mean ± SD or n (%), p-value corresponds to Pearson's correlation. Multivariate analyses were performed for an array of clinical variables in relation to functional outcome at 6-month follow-up. Linear regression was performed for an array of clinical variables in relation to functional outcomes.

affect clinical outcome. Age ≤71 years, onset to DC ≤9 hours, volume of infarction ≤155 cm^3 and ASPECT score ≥6 were significantly associated with good clinical outcome in early DC (mRS 0 to 3). Three randomized controlled trials; HAMLET[17] DECIMAL[14] and DESTINY[12] compared decompressive surgery plus medical treatment with medical treatment alone among patients with large territory ischemic stroke. The present study showed similar mortality benefits and better functional outcomes (mRS ≤3) at the end of one year when compared with those studies mentioned earlier. Inclusion of patients with less severe stroke to the study when compared with related studies could have resulted in better functional outcomes. A recent Cochrane review concluded that surgical decompression lowered the risk of death or severe disability (defined as mRS ≥4) in selected patients at 60 years or younger with a large territory ischemic stroke and cerebral edema. [18] This meta-analysis involving 134 patients, 60 years or younger suggested that surgical decompression reduced the risk of death at the end of follow-up (OR = 0.19, 95% CI = 0.09-0.37) and the risk of death or disability defined as mRS ≥4 at 12 months (OR = 0.26, 95% CI = 0.13-0.51). Death or disability defined as mRS >3 at the end of follow-up did not differ between the treatment arms (OR = 0.56, 95% CI = 0.27-1.15). Because all trials had to stop early, the possibility of an overestimation of the effect size was expressed. A review of 13 uncontrolled studies of 138 patients, older than 50 years constituted a strong predictor of poor functional outcome after surgical decompression. However, timing of the operation, side of the infarction and involvement of other vascular territories did not affect the outcome.[19] In one recent uncontrolled study, only 6 (8%) of 72 patients older than 60 years had a favorable outcome after surgery when compared with 77 (54%) of 143 younger patients.[20]

In this study, we used high accuracy for each cut off value of prognostic factors affecting good outcome in early DC and also calculated the sensitivity, specificity, positive predictive value, negative predictive value, accuracy. Then, the AUC or ROC was plotted representing the degree or separable measurement. Our results showed that age ≤71 years was a cut off value as a predictor of surgery outcome. The impact of age on outcome has not been well studied in malignant MCA infarction. Poor functional outcome and increased mortality were observed among older patients undergoing hemicraniectomy.[21-24] Moreover, the potential for recovery of function after stroke generally declines steeply after the age of 60 years. [25] Foerch et al. reported that age was the only factor affecting functional outcomes.[26] Walz et al. agreed that the outcome was related to age.[23] Uhl et al. evaluated 188 patients undergoing decompressive craniectomy and found that those older than 50 years had higher mortality and poorer outcomes.[27] Age was the most important pretreatment prognostic factor. Thus, age could be the most important factor in deciding which patients should undergo DC.

Timing of surgery could be another crucial factor for DC among patients with malignant MCA infarction. Animal and clinical studies have provided evidence that a benefit was associated with early DC. In a rat MCA occlusion model, early DC markedly reduced mortality and reduced the volume of infarcted brain tissue.[28] Schwab et al. found that decompression within 24 hours of ictus (early DC) was associated with a lower mortality rate (16%) and a mean Modified Barthel Index (BI) score of 68.8.[29] In their series, 26 of 31 (84%) patients had a BI ≥60. Similar results were also reported in a related study.[30] Decompression within 6 hours of ictus was associated with a 8.3% mortality rate and a mean modified BI score of 70.0, compared with a 36.7% mortality rate. Further, a mean BI score of 52.8 was reported among patients in whom decompression was carried out after 6 hours of ictus. Our study as well as others showed that onset to DC ≤9 hours was significantly associated with good clinical outcomes in early DC.

Although some studies have found that clinical signs of herniation were not associated with functional outcome among patients with malignant MCA infarction undergoing hemicraniectomy,[26, 28] anisocoria indicating herniation leads to mesencephalic ischemia and links to a worse prognosis. Better outcomes can be expected from early treatment before the clinical signs of herniation appear. In our study, poor functional outcome was associated with the presence of clinical signs of herniation before treatment. Thus, we excluded patients who had signs of herniation from the study. Our suggestion for DC was to be performed within 6 hours of ictus, and before the clinical signs of herniation appeared among patients with malignant MCA infarction. This means that time of operation rather than early operation was likely more important to obtain a better outcome. Theoretically, when strong evidence supports the very high risk of subsequent clinical deterioration, early surgery before clinical worsening would be the ideal surgical timing. Several clinical studies have shown several promising parameters in the early prediction of malignant MCA infarction, i.e., lesion volume >145 cm^3 in diffusion weighted imaging of MRI and a complete MCA territory perfusion deficit shown on MR angiography.[31, 32] In this study, we found that volume of infarction ≤155 cm^3 was significantly associated with good clinical outcomes in early DC. Involvement of more than one vascular territory (internal carotid artery infarction) and hemispheric infarction of the dominant hemisphere are often cited as prognostic indicators of poor function outcome and contraindications to decompression. In this study, ASPECT score ≥6 was significantly associated with good clinical outcome in early DC (mRS 0 to 3).

This study encountered several limitations. First, outcome assessment at 3 and 6 months might be insufficient to understand the true benefit of early DC that constituted a lifesaving surgery. At least one year follow-up is recommended to assess functional benefits. Second, the study was conducted at a single center. Finally, many patients undergoing early DC were excluded from the study.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interests:

No potential conflict of interest relevant to this article was reported.

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