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ORIGINAL ARTICLE

Predictors of decompressive hemicraniectomy in malignant middle cerebral artery stroke

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Abstract

Identification of factors in malignant middle cerebral artery (MMCA) stroke patients that may be useful in selecting patients for DHC. This study was a retrospective multicenter study of patients referred for DHC based on the criteria of the randomized control trials of DHC in MMCA stroke. Demographic, clinical, and radiology data were analyzed. Patients who underwent DHC were compared to those who survived without surgery. Two hundred three patients with MMCA strokes were identified: 137 underwent DHC, 47 survived without DHC, and 19 refused surgery and died. Multivariate analysis identified the following factors determining DHC in MMCA stroke: age < 55 years (OR 8.5, 95% CI 3.3–22.1, $P < 0.001$), MCA with involvement of additional vascular territories (anterior cerebral artery, posterior cerebral artery (OR 4.8, 95% CI 1.5–14.9, $P = 0.007$), septum pellucidum displacement ≥ 7.5 mm (OR 4.8, 95% CI 1.9–11.7, $P = 0.001$), diabetes (OR 3.7, 95% CI 1.3–10.6, $P = 0.012$), infarct growth rate (IGR) ml/h (OR 1.11, 95% CI 1.02–1.2, $P = 0.015$), and temporal lobe involvement (OR 2.5, 95% CI 1.01–6.1, $P = 0.048$). The internal validation of the multivariate logistic regression model using bootstrapping analysis showed marginal bias. Among patients with MMCA infarctions, an increased possibility of DHC is associated with younger age, MCA with additional infarction, septum pellucidum deviation of > 7.5 mm, diabetes, IGR, and temporal lobe involvement. The presence of these risk factors identifies those MMCA stroke patients who may require DHC. Bootstrapping analysis indicated the model is good enough to predict the outcome in general population.

Keywords Middle cerebral artery · Decompressive hemicraniectomy · Infarct volume

Introduction

The distinct syndrome of space occupying middle cerebral artery (MCA) infarction initially described as "malignant MCA infarction" (MMCA) results in high rates of disability and death [1, 2]. Although there is a consensus regarding the life-saving role of decompressive hemicraniectomy (DHC) in MMCA strokes, there is considerable variation in patient selection [3–7]. Clinical decision for DHC is commonly made on the basis of radiological data showing brain swelling with herniation and concomitant neurological deterioration, similar to the European trials. A plethora of clinical, laboratory, and radiological predictors of deterioration after large MCA infarction have been reported [8–21]. However, none of these studies have addressed the question of identifying those patients who satisfy DHC selection criteria of European trials, will survive without surgery. The survival rates in the "control arm" of the randomized trials of DHC (47% in DESTINY, 22% in DECIMAL, 40% HAMLET, 29% in the pooled analysis, and 60% in HeADDFIRST) show that not all patients with MMCA strokes need DHC to survive, and not all MMCA infarctions survive even with decompression [13, 22, 23]. Thus, clinicians are faced with a dilemma of deciding to perform DHC or observe further and treat medically. While DHC can substantially reduce mortality and is becoming standard practice following publication of the randomized-controlled trials, early recognition of patients who will need surgery is critical. The main goal of this study was to identify clinical and radiographic factors that will help determine if patient with MMCA stroke will need DHC or survive without surgery.

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Patients and methods

A retrospective DHC database from tertiary referral centers in three countries (Hamad General Hospital, Qatar; Rashid Hospital, Dubai, UAE; and Shifa International Hospital, Pakistan) collected between 2007 and 2014 were analyzed. The DHC database included all patients referred for DHC.

Inclusion and exclusion criteria

The DHC database included all patients referred for surgery based on the following criteria: National Institutes of Health Stroke Scale score (NIHSS) ≥ 15 including a score of 1 for item 1a (decreased level of consciousness from the beginning or progressive deterioration within 24–48 h), brain computed tomography (CT) evidence of ischemia involving two-third middle cerebral artery (MCA) or 50% MCA with additional anterior cerebral artery (ACA) or posterior cerebral artery (PCA) infarction and signs of local swelling (effacement of the sulci, compression of the lateral ventricle). All patients were managed in the intensive care units. Patients were not eligible if any of the following exclusion criteria were met: significant contralateral infarction or pre-existing infarction present on the initial CT, only a single imaging study was performed or if imaging was uninterruptable, with parenchymal hematoma grade II [24], hemorrhage causing clinical deterioration or hemorrhage with ventricular extension and missing surgical details.

Demographic and radiology data

The data collection was performed by experienced stroke neurologists at each site. Patient's clinical records were reviewed for demographics, risk factors (hypertension, diabetes, hyperlipidemia, coronary artery disease), time of stroke onset, time and type of imaging studies, medical treatment including intensive care stay, hyperosmolar therapy, signs of herniation, time to herniation, and time to surgery. The NIHSS was used to assess the severity of the neurological deficit at the time of admission, and GCS at deterioration. Each CT scan performed during hospitalization was reexamined and interpreted by a stroke neurologist and a radiologist at each center. Radiological data included measurement of the infarct volume (IV) using ABC/2 where A is the largest cross-sectional diameter, B is the largest diameter 90° to A on the same slice, C is the approximate number of CT slices on which the stroke is seen and divided by 2 to approximate the volume of an ellipsoid. The method is simple and validated before for ischemic stroke [25].

Maximum Infarct Volume (MIV) was calculated using last CT before DHC.

For the type of vessel occlusion, CT angiography (CTA), MR angiography (MRA), or a conventional digital angiogram was utilized.

For measurement of septum pellucidum shift, a straight line was drawn in the expected location of the septum pellucidum from the posterior most aspects to the falx on axial images. Shift of the septum pellucidum from this midline was measured at the level of frontal horns on each CT scan and compared to subsequent CT scans to determine any change.

Experienced clinical physicians/neurosurgeons based upon the individual clinical condition and brain imaging made the decision for DHC. Patients were generally taken for surgery if there was progressively deteriorating level of consciousness with or without early clinical signs of herniation.

Infarct growth rate calculation

Second infarct growth rate (IGR2) was measured on second CT (CT2) using the following formula:

$$\mathrm{IGR2} = \Delta\ \text{volume}\ (\text{infarct volume CT2}-\text{infarct volume CT1})/\Delta\ \text{time}\ (\text{time CT2}-\text{time CT1})$$

The hospitals included in the study are tertiary referral centers with well-established comprehensive stroke service including acute stroke diagnostic, vascular interventional services, stroke units, and rehabilitation services. An acute stroke team provides a rapid assessment service 24 h a day, 7 days a week. Each hospital has a neurological surgery program, actively participating in vascular neurology service.

Data analysis plan

All statistical analyses were performed using Statistical Package for Social Sciences Version 22 (SPSS). Descriptive and inferential statistics were used to characterize the study sample and test hypotheses. Descriptive results (including graphical displays) for all quantitative variables (e.g., age) are presented as mean ± standard deviation (SD) (for normally distributed data) or median with inter-quartile range (for data not normally distributed). Numbers (percentage) were reported for all qualitative variables (e.g., gender). Bivariate analysis was performed using analysis of variance (ANOVA), Kruskal-Wallis test, Pearson chi-square, or Fisher exact test whenever appropriate was used to compare all the independent variables (e.g., age, gender) among the three groups (DHC done, survived without DHC, and refused DHC and died).

Multivariate model

Multiple logistic regression models were used to identify significant independent factors associated with patients undergone DHC surgery compared to those who survived without DHC surgery after adjusting for potentially confounding factors. The Wald test was computed on each predictor to determine for its significance. Adjusted odds ratio and 95% confidence interval for the adjusted odds ratio were reported. A "*P*" value < 0.05 (two tailed) was considered statistically significant.

Internal validation of the model

Multivariate logistic regression was internally validated using bootstrapping re-sampling methods with 200 re-samples for the

Table 1 Demographics and risk factors

Factors	Total $n = 203$	DHC done $n = 137$ (67.49)	Survived without DHC $n = 47$ (23.15)	Refused DHC and died $n = 19$ (9.38)	*P* value
Age					
≤ 55 years	131 (64.5)	104 (75.9)	19 (40.4)	8 (42.1)	< 0.001
≥ 55 years	72 (35.5)	33 (24.1)	28 (59.6)	11 (57.9)	
Hypertension	113 (55.7)	63 (46.0)	34 (72.3)	16 (84.2)	< 0.001
Diabetes mellitus	63 (31.0)	47 (34.3)	10 (21.3)	6 (31.6)	0.249
Dyslipidemia	65 (32.0)	50 (36.5)	11 (23.4)	4 (21.1)	0.141
NHISS admission	15.55 ± 4.06	15.09 ± 4.11	16.13 ± 3.68	17.42 ± 4.11	0.034
GCS admission	12.56 ± 2.31	12.44 ± 2.37	13.00 ± 1.98	12.32 ± 2.69	0.322
Pupil abnormality	35 (17.2)	27 (19.7)	3 (6.4)	5 (26.3)	0.062
Bilateral Babinski	96 (47.3)	83 (60.6)	7 (14.9)	6 (31.6)	< 0.001
Temporal lobe involved	116 (57.1)	86 (62.8)	20 (42.6)	10 (52.6)	0.049
Uncal herniation	120 (59.1)	92 (67.2)	18 (38.3)	10 (52.6)	0.002
SP deviation ≥ 0.75 cm	106 (52.2)	81 (59.1)	11 (23.4)	14 (73.7)	< 0.001
Herniation time from onset					< 0.001
No herniation	22 (12.2)	0 (0.0)	21 (60.0)	1 (11.1)	
Within 24 h	34 (18.8)	29 (21.2)	2 (5.7)	3 (33.3)	
Within 48 h	61 (33.7)	51 (37.2)	8 (22.9)	2 (22.2)	
Within 72 h	33 (18.2)	30 (21.9)	1 (2.9)	2 (22.2)	
≥ 96 h	31 (17.1)	27 (19.7)	3 (8.6)	1 (11.1)	
Antiedema medication	138 (68.0)	115 (83.9)	19 (40.4)	4 (21.1)	< 0.001
Vessel occlusion					0.004
MCA	128 (71.9)	81 (71.1)	39 (84.8)	8 (44.4)	
MCA/ACA	14 (7.9)	12 (10.5)	1 (2.2)	1 (5.6)	
ICA/MCA/ACA	36 (20.2)	21 (18.4)	6 (13.0)	9 (50.0)	
Type of infract					< 0.001
2/3 MCA	55 (27.1)	28 (20.4)	24 (51.1)	3 (15.8)	
Complete MCA	74 (36.5)	52 (38.0)	17 (36.2)	5 (26.3)	
2/3 MCA with additional infarct	36 (17.7)	25 (18.2)	4 (8.5)	7 (36.8)	
Complete MCA with additional infarct	38 (18.7)	32 (23.4)	2 (4.3)	4 (21.1)	
Max infarct volume (MIV)	348.16 ± 117.48	367.70 ± 119.45	285.20 ± 85.32	363.02 ± 122.36	< 0.001
Time to MIV	61.63 ± 53.97	58.06 ± 55.78	64.33 ± 44.10	80.72 ± 60.88	0.214
Mean 2nd IGR ml/h	8.88 ± 7.60	9.71 ± 80	5.39 ± 4.16	11.54 ± 8.94	0.001
30-day mortality	42 (20.7)	23 (16.8)	0 (0.0)	19 (100.0)	< 0.001

Growth rate has been measured by = (Infarct volume at 2nd CT − Infarct volume at 1st CT)/(Time at 2nd CT − Time at 1st CT) model to provide more accurate estimates of model performance in new subjects [26]. Ability to discriminate the outcome between (DHC vs no DHC) of the model was assessed using area under the receiver operating characteristic (AUROC).

Results (Tables 1 and 2)

Two hundred twelve patients were selected for DHC based on the above criteria. One hundred forty-six patients underwent DHC; 66 patients initially selected for surgery were not operated ($n = 19$ who refused surgery and died and $n = 47$ stabilized without further deterioration and treating physician/surgeon decided not to operate). Nine patients were excluded from the DHC analysis (incomplete data $n = 2$, hemorrhage with ventricular extension $n = 4$, hemorrhage deemed to have caused acute worsening [PH II] $n = 3$).

Clinical characteristics, demographics and radiology data are summarized in Table 1.

Mean age of patients who underwent DHC (47.88 ± 11.00) was younger than those who survived without DHC (55.66 ± 14.37) $P < 0.001$. There was no significant difference in diabetes, dyslipidemia, and GCS on admission. Admission NIHSS was higher in patients who survived without surgery and those who refused DHC and expired compared to DHC group ($P = 0.034$). While MIV was less in patients who survived without DHC ($P < 0.001$), the time to MIV was not statistically significant ($P = 0.214$). Mean second IGR in DHC was 9.71 ± 80 ml/h, no DHC was 5.39 ± 4.16, and patients who refused and died was 11.54 ± 8.94 ml/h ($P = 0.001$). Herniation signs were more common in DHC group and group that expired without surgery ($P < 0.001$). More patients had MCA with additional infarcts in DHC and group that expired without surgery ($P < 0.001$). Median time to DHC was 51.33 h (range 12 to 312 h), 15 (10.9%) patients in less than 24 h, 39 (28.5%) in less than 24 to < 48 h, 44 (32.1%) in less than 48 to < 72 h, and 39 (28.5%) in more than 72 h. There were 23 (16.8%) patients who expired with DHC. Outcome was better (mRS < 4 vs. mRS > 4) in non-DHC group ($P = 0.009$). However, when stratified by time, no difference was observed in the outcome between subgroups of DHC ($P = 0.747$).

Multivariate analysis (Table 2)

After multivariate adjustment, six factors showing the strongest independent association with DHC were age ≤ 55 years—more than eight times the odds of surgery, MCA with additional infarction; more than four times the odds of surgery, septum pellucidum deviation of ≥ 7.5 mm; more than four times the odds of surgery, diabetes; more than three times the odds of surgery, temporal lobe involvement; and more than two times the odds of surgery and IGR, 11% chance of DHC with each unit ml/h increase in the IGR (ml/h) on second CT.

In another multivariate model when infarct volume was used along with type of infarct (MCA with additional infarction), infarct volume becomes insignificant (OR 1.004; 95% CI 1.000–1.009; $P = 0.077$) whereas MCA with additional infarction retained its predictive value (OR 4.88; 95% CI 1.618–14.177; $P = 0.005$).

Prediction of the model (Table 3)

Bootstrapping analysis (Fig. 1) showed marginal bias in estimated parameters from the model indicating developed model is good enough to predict the outcome in general population. C-statistics: 0.87, 95% CI (0.81–0.93) discriminate 87% accurately between DHC and non-DHC cases in the study.

Discussion

The present study sought to identify risk factors that can help decide the optimal management of patients presenting with MMCA stroke. Such risk factor identification can help in the patient management and influence treatment decisions regarding DHC as well as communication between physicians and

Table 2 Significant independent predictor associated with to whom to do surgery ($n = 184$)

Factors	Adjusted odds ratio	95% CI for adjusted odds ratio	*P* value
Age < 55 years	8.52	3.28–22.11	< 0.001
MCA with additional infract	4.75	1.52–14.89	0.007
Septum pellucidum displacement ≥ 0.75 cm	4.81	1.97–11.75	0.001
Diabetes	3.76	1.34–10.56	0.012
Infarct growth rate (ml/h)	1.11	1.02–1.21	0.015
Temporal lobe involvement	2.48	1.01–6.13	0.048

Growth rate has been measured by = (Infarct volume at 2nd CT − Infarct volume at 1st CT)/(Time at 2nd CT − Time at 1st CT). *P* value has been calculated using binary multiple logistic regression Wald test

CI confidence interval

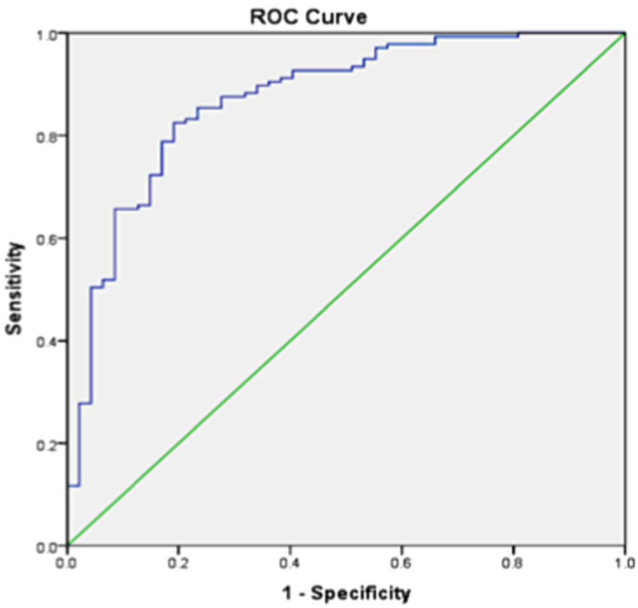

Fig. 1 Predicted probability of patients underwent DHC. OR 0.87, 95% CI (0.81–0.93). AUC area under the curve, CI confidence interval, ROC receiver operating characteristics

family members. In the current analysis, 23.15% patients with MMCA stroke referred for DHC, survived without surgery. We identified the following factors were independently associated with DHC in patients with MMCA stroke were age < 55 years, MCA with additional infarction, septum pellucidum deviation > 0.75 cm, diabetes, temporal lobe involvement, and IGR on second CT scan.

The patients were drawn from three countries and were demographically and ethnically diverse. We choose the 55 years age cut off based on the published data about stroke in patients from South Asia and the Gulf States occurring at a significantly younger age than in Caucasian patient [26, 27]. The patients who underwent DHC were younger than the non-DHC group as reported earlier [13, 28]. This might be the result of rapid rise in the intracranial pressure in younger patients due to less intracranial reserve compensating for the increase in infarct volume [2].

In the preliminary bivariate analyses, neither risk factors (except hypertension being more frequent in non-DHC group) nor stroke severity on presentation was associated with DHC. Only diabetes contributed to the final multivariable analysis. The lack of association could be due to no real predictive role of these clinical features. Because we only evaluated large strokes (NIHSS > 15), the severity of the stroke as measured by the NIHSS was not useful for distinguishing which patients will progress to DHC.

The radiographic findings in the present study do not support the predictive role of major early CT changes in the MCA territory for DHC [11]. The percentage of patients with complete MCA infarction who underwent DHC (36.2%) was similar to those who survived without DHC (38%). However, we found that the presence of concurrent additional vascular infarcts was highly indicative of DHC. Malignant evolution of an infarct is consistently related to the volume of ischemic brain. Though the infarct volume was comparatively less in non-DHC group in bivariate analysis, in multivariate model, when infarct volume was used along with type of infarct (MCA with additional infarction), infarct volume becomes insignificant whereas MCA with additional infarction retained its predictive value. This is likely due to the multicollinearity between infarct volume and MCA with additional infarction. Only DECIMAL trial included patients with an infarct volume on DWI of > 145 cm^3 and no difference was noted in the infarct volume of DHC and control group (DHC 211.5 ± 67.1, non-DHC 214.7 ± 45.2) [29].

An interesting finding was the speed of infarct growth. IGR was nearly double in patients who underwent DHC compared to those who survived without surgery. Our IGR calculation supports the earlier reports of fast and slow MCA deteriorates [7, 30]. The low mortality observed in the conservatively treated patients randomized after 48 h, 36% in HAMLET, and 40% in HeADDFIRST compared with patients randomized less than 48 h of 78% in HAMLET, 53% DESTINY, and 78% DECIMAL points to a possibility of two different MMCA stroke groups, i.e., those that deteriorate more rapidly, hence operated early and those with slower deterioration operated late group [31, 32]. In our cohort, patients operated < 48 h had a

Table 3 Bootstrapping multivariate logistic regression analysis for bias corrected and accelerated (BCa) with 95% CI

Factors	Regression coefficients	Bias	Std. error	95% confidence interval		*P* value
				Lower	Upper	
Age < 55 years	2.142	0.131	0.527	1.228	3.855	0.005
Diabetes	1.325	0.115	0.564	0.359	3.041	0.010
Temporal lobe involvement	0.910	0.083	0.489	− 0.265	2.268	0.040
Septum pellucidum displacement ≥ 0.75 cm	1.571	0.075	0.548	0.568	3.041	0.005
Infarct growth rate (ml/h)	0.105	0.015	0.046	0.014	0.259	0.005
MCA with additional infract	1.559	0.090	0.691	0.397	3.282	0.015

higher IGR (13.64 ± 8.76 ml/h) compared to those operated after 48 h (7.15 ± 6.23 ml/h). The use of IGR is supported by the MRI-based infarct volume of more than 82 ml within 6 h or more than 145 ml within 14 h of stroke onset (corresponding IGR 13.66 and 10.35 ml/h respectively) as predictors of malignant transformation [17, 18].We choose IGR on second CT since early CT signs of ischemia may be quite subtle, and the detection of these signs has wide interobserver and intraobserver variability. Our data shows that patient with septum pellucidum deviation of ≥ 7.5 mm were four times more likely to have DHC. However, nearly one fourth of those who survived also had more than ≥ 7.5-mm septum pellucidum deviation. In the control arm of HeADDFIRST, 4/6 survivors had septum pellucidum deviation of > 7.5 mm [32].

Though clinical and radiological herniation was significantly associated with DHC group in the bivariate analysis, in multivariate stepwise regression analysis in the presence of temporal lobe and septum pellucidum deviation ≥ 7.5 mm, clinical signs lost their significance. Temporal lobe involvement retained its significance compared to uncal herniation when adjusted for other confounder variables. In addition, herniation signs have been shown to reverse with appropriate medical management [33] and do not impact outcome in DHC [3].

Limitations

Our study has several limitations including the retrospective nature of the study with the lack of a randomized comparison between groups. Another limitation relates to the assessment of the IGR on CT scans. Although DW-MR would be more sensitive, logistical and financial reasons preclude repeated MR imaging. Moreover, MRI imaging-based data may not be generalizable to many centers that may not have access to MR imaging. Non-contrast CT of the brain remains the mainstay of imaging in acute stroke as it is fast, inexpensive, and readily available. Our data was collected from multiple hospitals in three countries and reflects actual clinical practice rather than clinical trials. There were differences in the demographic, clinical, and radiological characteristics. The multivariate analyses performed may not have adequately addressed this issue due to sample size limitations. To address this, we performed internal validation of the multivariate logistic regression model.

Conclusion

In conclusion, the current study identified several features that may be useful in determining which patients with MMCA strokes will need DHC or survive without DHC. The factors identified in this study may be more generalizable than those in prior studies because we used a broad-based population in real clinical practice. Our study is relevant in the context of an overall increasing trend of DHC in MMCA stroke. These predictors should be validated in a prospective study.

Compliance with ethical standards

The study adhered to the tenets of the declaration of Helsinki and was approved by the Institutional Review Board of Hamad Medical Corporation, Qatar (15246/15).

Conflict of interest The authors declare that they have no conflict of interest.

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