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ORIGINAL ARTICLE

Outcomes in Severe Middle Cerebral Artery Ischemic Stroke

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Abstract
Background Severe middle cerebral artery stroke (MCA) is associated with a high rate of morbidity and mortality. We assessed the hypothesis that patient-specific variables may be associated with outcomes. We also sought to describe under-recognized patient-centered outcomes.
Methods A consecutive, multi-institution, retrospective cohort of adult patients (≤70 years) was established from 2009 to 2011. We included patients with NIHSS score ≥15 and infarct volume ≥60 mL measured within 48 h of symptom onset. Malignant edema was defined as the development of midline brain shift of ≥5 mm in the first 5 days. Exclusion criterion was enrollment in any experimental trial. A univariate and multivariate logistic regression analysis was performed to model and predict the factors related to outcomes.
Results 46 patients (29 female, 17 male; mean age 57.3 ± 1.5 years) met study criteria. The mortality rate was 28 % ($n = 13$). In a multivariate analysis, only concurrent anterior cerebral artery (ACA) involvement was associated with mortality (OR 9.78, 95 % CI 1.15, 82.8, $p = 0.04$). In the malignant edema subgroup ($n = 23$, 58 %), 4 died (17 %), 7 underwent decompressive craniectomy (30 %), 7 underwent tracheostomy (30 %), and 15 underwent gastrostomy (65 %).
Conclusions Adverse outcomes after severe stroke are common. Concurrent ACA involvement predicts mortality in severe MCA stroke. It is useful to understand the incidence of life-sustaining procedures, such as tracheostomy and gastrostomy, as well as factors that contribute to their necessity.

Keywords Brain edema · Intracranial pressure · Stroke · Tracheostomy · Gastrostomy · Decompressive craniectomy

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Introduction

Large territory middle cerebral artery strokes are devastating events that result in high rates of disability and death. In fact, nearly half of all stroke survivors never regain functional independence [1]. Additionally, stroke also carries an enormous cost. For example, during the acute hospitalization period there are many potential aspects of care that contribute to resource utilization, including the need for intensive care unit monitoring, mechanical ventilation, endovascular therapy, and even decompressive

craniectomy [2, 3]. With this burden of disease in mind, it is necessary to define and predict poor outcomes in order to focus efforts on this "severe" stroke population. A better understanding of stroke severity may also allow for a more accurate determination of the effect from standard and experimental clinical interventions.

The severity of an ischemic infarct is classically defined by various criteria that relate to either factors that predict adverse outcomes [4–6] or the need for intensive therapy and surgical procedures [7–9]. It is possible that severe stroke may be independently defined by measures other than the two most common predictors of malignant edema formation and mortality (NIHSS score [10, 11] or infarct volume [7, 8]), such as the need for life-sustaining procedures. Currently, the rate of these procedures is unknown in the stroke population. We hypothesized that patient-specific variables may be associated with outcomes in severe anterior circulation ischemic stroke. We also sought to describe under-recognized outcomes as indicators of severe stroke in this population.

Methods

Study Population

We performed a consecutive retrospective cohort analysis of patients experiencing a severe anterior circulation ischemic stroke at the Massachusetts General Hospital and the University of Maryland Medical Center from January 2009–December 2011. This study was approved by respective institutional review boards.

Inclusion Criteria

Only adult patients ($\leq$70 years and $>$18 years) with both left and right hemisphere ischemic stroke and admission NIHSS $\geq$15 were considered for inclusion. The NIHSS score cutoff was selected based on previous reports describing this population as "high-risk" for the development of malignant cerebral edema [10]. Patients were excluded beyond 70 years of age because of different management strategies for stroke in the elderly, particularly with respect to the use of decompressive craniectomy.

Exclusion Criteria

Patients were excluded if their initial infarct volume was $\leq$60 mL. We selected this value not as predictor value of malignant edema, but to identify patients in which malignant edema formation was possible. Patients were excluded if they were enrolled in any therapeutic experimental trial or if they presented with posterior circulation stroke.

Data Acquisition

Patient characteristics were recorded including age, gender, nadir, and peak serum sodium within the first 5 days of admission, and in-hospital mortality. Other characteristics recorded included a determination of Glasgow Coma Scale (GCS) score decline by two or more points within the first 5 days of admission. Details of the stroke laterality, admission GCS score, anterior cerebral artery (ACA) involvement (vessel occlusion), and cardiac ejection fraction were recorded. The administration of hyperosmolar therapy was recorded as either continuous hyperosmolar therapy (3 % hypertonic saline infusion) and/or bolus hyperosmolar treatment (23.3 % hypertonic saline or mannitol). Details of any surgical procedure performed were noted, including decompressive craniectomy, tracheostomy, or gastrostomy. Infarct volume was estimated using the ellipsoid method of ABC/2 for the diffusion-weighted imaging bright area on initial MRI [12]. Malignant edema was defined as the development of midline brain shift (displacement of the septum pellucidum) of $\geq$5 mm in the first 5 days following admission [13].

Statistical Methods

Statistical analysis was performed using the R programming environment (Vienna, Austria). Univariate and multivariate logistic regression analysis was performed to model and predict the factors related to outcomes. Significance was predefined at $p \leq 0.05$ (two-tailed).

Primary Analysis

Univariate and multivariate logistic regression analyses were used to analyze predictors of mortality in patients with severe anterior circulation stroke. The multivariate model was constructed using the least squares approach. Models were created including various predictors allowing for determination of individual regression coefficients and R-squared values. An analysis of variance was used to compare different models. Visual regression diagnostics were performed by plotting residual versus fitted values, standardized residuals versus theoretical quantiles, square root of standardized residuals versus fitted values, and standardized residuals versus leverage.

Secondary Analysis

Logistic regression analyses were then used to analyze predictors of secondary outcomes (including gastrostomy, tracheostomy, and malignant edema formation) in a similar fashion. Patients were censored from secondary analysis if therapeutic care was withdrawn within the first 48 h of admission.

Results

Primary Analysis

127 patients were first identified with NIHSS score ≥15. 81 patients were excluded due to either stroke size ($n = 79$) or participation in an experimental trial ($n = 2$). The final study population consisted of 46 patients (29 female, 17 male; mean age 57.3 ± 1.5 years). The mean time from symptom onset to decompressive craniectomy was 40.6 ± 6.8 h. Even though hyperosmolar therapy was administered in many patients, the correlation between serum sodium value and osmolality was good, with Pearson's correlation coefficients of 0.85 and 0.77 for nadir and peak values, respectively. In patients receiving any form of hyperosmolar therapy, peak osmolality averaged 319.5 ± 4.3 mOsm/kg water. In comparison, patients receiving only mannitol averaged 326.6 ± 6.4 mOsm/kg water. If both mannitol and hypertonic saline were used, the mean peak osmolality was 331.0 ± 6.0 mOsm/kg water. The overall mortality rate was 28 % ($n = 13$). Univariate predictors of mortality were identified as infarct volume, administration of bolus ICP treatment, and anterior cerebral artery involvement (Table 1). In a multivariate model, only ACA involvement was predictive of mortality (OR 9.78, 95 % CI 1.15, 82.8, $p = 0.04$) (Table 2).

Secondary Analysis

Seven patients were excluded from secondary analysis because of early withdrawal of care. Univariate predictors of secondary outcomes were explored. Decompressive craniectomy and admission GCS score were associated with tracheostomy but not for gastrostomy. Univariate predictors of malignant edema included acute infarct volume, peak sodium, hyperosmolar therapy, and bolus ICP treatment (Table 3).

While no significant predictors of gastrostomy were identified in univariate analysis, significant independent predictors of tracheostomy and clinically predicted variables (age, infarct volume, ACA involvement, hyperosmolar therapy, bolus ICP treatment, midline shift) were introduced into a multivariate logistic regression analysis model, where only admission GCS was found to be predictive of tracheostomy (OR 0.59, 95 % CI 0.37, 0.94, $p = 0.03$) (Table 4).

Significant independent predictors of malignant edema formation and clinically predicted variables (age, NIHSS score, GCS score decline) were introduced into a multivariate logistic regression analysis model, where infarct volume was predictive of malignant edema formation (OR 1.02, 95 % CI 1.00, 1.04, $p = 0.04$) (Table 5). In the malignant edema subgroup ($n = 23$, 58 %) 4 died (17 %), 7 underwent DC (30 %), 7 underwent tracheostomy (30 %), and 15 underwent gastrostomy (65 %).

Table 1 Univariate analysis of predictors of mortality in patients with severe anterior circulation stroke

	Overall (%)	In-hospital morality subgroup	Survivors only subgroup	*p* value
Total patients	46 (100)	13 (28.2)	33 (71.7)	
Age, mean ± SEM (years)	57.3 ± 1.6	60.8 ± 2.9	55.9 ± 1.8	0.17
Sex, male	17 (37.0)	3 (23.1)	14 (42.4)	0.23
NIHSS score	20.9 ± 0.5	21.3 ± 0.8	20.7 ± 0.6	0.59
Infarct volume (mL)	152.0 ± 11.6	189.7 ± 27.0	137.1 ± 11.5	0.05*
Nadir sodium (mmol/L)	136.4 ± 0.4	136.0 ± 1.0	136.6 ± 0.4	0.51
Peak sodium (mmol/L)	146.1 ± 1.0	148.6 ± 2.4	145.2 ± 1.0	0.12
Hyperosmolar therapy	25 (54.3)	10 (77.0)	15 (45.5)	0.06
Bolus ICP treatment	14 (30.4)	7 (53.8)	7 (21.2)	0.04*
Decompressive craniectomy	9 (19.5)	1 (7.7)	8 (24.2)	0.23
GCS score decline	15 (32.6)	6 (46.2)	9 (27.3)	0.22
Hemisphere, left	34 (73.9)	11 (84.6)	23 (69.7)	0.31
Admission GCS score	10.7 ± 0.4	9.5 ± 0.7	11.2 ± 0.5	0.07
Midline shift (mm)	4.6 ± 0.6	5.1 ± 1.3	4.4 ± 0.7	0.61
ACA involvement	8 (17.4)	5 (38.5)	3 (9.1)	0.03*
Ejection fraction	58.9 ± 2.1	60.5 ± 3.8	58.3 ± 2.5	0.62

A univariate logistic regression analysis was used to analyze independent predictors of mortality in patients with severe anterior circulation stroke. Individual predictors of mortality were identified as infarct volume, administration of bolus ICP treatment in the form of either mannitol or 23.3 % hypertonic saline, and anterior cerebral artery involvement. Values are represented either as either number of patients (percentage of total patients) or as mean ± standard error of the mean. *p* value corresponds to all patients (*column* overall)

NIHSS National Institutes of Health stroke scale, *ICP* intracranial pressure, *GCS* glasgow coma scale, *ACA* anterior cerebral artery

* Significant

Table 2 Multivariate analysis for predictors of mortality in patients with severe anterior circulation stroke

	Odds ratio	95 % confidence interval	*p* value
Age (years)	1.08	(0.99, 1.19)	0.09
NIHSS score	1.06	(0.85, 1.34)	0.59
Infarct volume (ml)	1.01	(0.98, 1.01)	0.31
Hyperosmolar therapy	3.11	(0.42, 23.3)	0.72
Bolus ICP treatment	0.66	(0.07, 6.58)	0.27
ACA involvement	9.78	(1.15, 82.8)	0.04*

A multivariate logistic regression analysis was used to determine predictors of mortality in patients with severe anterior circulation stroke. A multivariate model was constructed using the least squares approach. Models were created including various predictors allowing for determination of individual regression coefficients and R-squared values. An analysis of variance was used to compare different models. Visual regression diagnostics were performed by plotting residual versus fitted values, standardized residuals versus theoretical quantiles, square root of standardized residuals versus fitted values, and standardized residuals versus leverage. In a multivariate model, only anterior cerebral artery involvement was predictive of mortality ($p = 0.04$)

NIHSS National Institutes of Health stroke scale, *ICP* intracranial pressure, *ACA* anterior cerebral artery

* Significant

Table 3 Univariate analysis of predictors of secondary outcomes in patients with severe anterior circulation stroke

$n = 39$ (total)	Gastrostomy ($n = 19$) *p* value	Tracheostomy ($n = 8$) *p* value	Malignant edema ($n = 23$) *p* value
Age (years)	0.53	0.93	0.24
Sex, male	0.91	0.92	0.86
NIHSS score	0.18	0.49	0.63
Infarct volume (ml)	0.85	0.34	0.01*
Nadir sodium (mmol/L)	0.45	0.56	0.82
Peak sodium (mmol/L)	0.96	0.45	0.03*
Hyperosmolar therapy	0.63	0.39	0.003*
Bolus ICP treatment	0.41	0.09	0.04*
Decompressive craniectomy	0.11	0.004*	–
GCS score decline	0.91	0.92	0.61
Hemisphere, left	0.34	0.29	0.73
Admission GCS score	0.17	0.03*	0.91
Midline shift (mm)	0.14	0.14	–
ACA involvement	0.42	0.80	0.68

A univariate logistic regression analysis was used to analyze independent predictors of secondary outcomes (including gastrostomy, tracheostomy, and malignant edema formation) in patients with severe anterior circulation stroke. Significant individual predictors of secondary outcomes included decompressive craniectomy and admission GCS (for tracheostomy), as well as infarct volume, peak sodium, hyperosmolar therapy, and bolus ICP treatment (for malignant edema). Decompressive craniectomy was not analyzed for malignant edema, as it was felt to be a treatment for the condition rather than a predictive event. Midline shift was also not analyzed for malignant edema, as it was sine qua non for the condition itself

NIHSS National Institutes of Health stroke scale, *ICP* intracranial pressure, *GCS* glasgow coma scale, *ACA* anterior cerebral artery

* Significant

Additional rates of tracheostomy were 5/8 (63 %) in patients undergoing DC, 3/31 (9 %) in treated patients not undergoing DC, 0/13 (0 %) in patients suffering in-hospital mortality, and 8/33 (24 %) in all survivors.

Discussion

Severe middle cerebral artery (MCA) stroke can be generally defined based on the initial degree of neurological deficit,

Table 4 Multivariate analysis for predictors of secondary outcome (tracheostomy) in patients with severe anterior circulation stroke

	Odds ratio	95 % confidence interval	*p* value
Age (years)	1.04	(0.95, 1.13)	0.42
Infarct volume (ml)	1.01	(1.00, 1.02)	0.24
Admission GCS	0.59	(0.37, 0.94)	0.03*
ACA involvement	0.29	(0.02, 4.01)	0.36

While no significant predictors of gastrostomy were identified in univariate analysis, significant predictors of tracheostomy and clinically predicted variables (age, infarct volume, ACA involvement, hyperosmolar therapy, bolus ICP treatment, midline shift) were introduced into various multivariate logistic regression analysis models, fitted using the method of least squares. An analysis of variance was used to compare different models. In a multivariate model, only admission GCS was predictive of tracheostomy ($p = 0.03$)

ICP intracranial pressure, *GCS* glasgow coma scale, *ACA* anterior cerebral artery

* Significant

Table 5 Multivariate analysis for predictors of secondary malignant edema formation in patients with severe anterior circulation stroke

	Odds ratio	95 % confidence interval	*p* value
Age (years)	0.95	(0.88, 1.03)	0.24
Infarct volume (ml)	1.02	(1.00, 1.04)	0.04*
Peak sodium (mmol/L)	1.01	(0.80, 1.27)	0.94
Hyperosmolar therapy	6.26	(0.62, 6.33)	0.12
Bolus ICP treatment	1.01	(0.05, 19.4)	0.99

Significant predictors of malignant edema formation and clinically predicted variables (age, NIHSS score, GCS score decline) were introduced into various multivariate logistic regression analysis models, fitted using the method of least squares. An analysis of variance was used to compare different models. In a multivariate model, only infarct volume was predictive of malignant edema formation ($p = 0.04$)

ICP intracranial pressure

* Significant

size of the stroke, or the propensity to require further interventions. With an emphasis on the latter, we utilized a large cohort of stringently selected patients to assess the hypothesis that patient-specific variables may be associated with outcomes. We also sought to describe under-recognized outcomes. The major finding of the analysis was that concurrent ACA involvement was associated with increased rates of mortality. Additionally, in certain subgroups, such as those undergoing decompressive craniectomy, a high percentage of patients underwent life-sustaining procedures such as tracheostomy (63 %). As the armamentarium in stroke care is growing with the expansion of image-guided decision making [14–16], novel pharmacologic therapies [17, 18], endovascular therapy [19–24], neurosurgery [25–28], and telemedicine [29, 30], it is important to establish benchmarks to evaluate outcomes related to these changes.

In our cohort, only ACA involvement was predictive of mortality. The ACA is well known to provide important collateral blood flow to the conventionally defined MCA territory [31], and therefore ACA ischemia is likely to be detrimental to the perfusion of various MCA territories as well. This is consistent with the finding that poor collateral circulation correlates with worse outcome [32–34]. The underlying mechanism, although not well defined, could be related to the development of cerebral edema. It has been shown that impaired collateral circulation is associated with this phenomenon [35, 36], one of the key determinants of outcome in severe stroke [9, 10, 37]. Therefore, it is possible that ACA involvement contributes to mortality as a mediator of collateral circulation and cerebral edema formation. It is also possible that ACA involvement co-varied with stroke volume, explaining why infarct volume was not a significant predictor in the multivariate analysis of mortality.

Our study is relevant in the context of an overall trend in severe stroke care towards being more interventional than observational. The increasing rate of endovascular treatment is likely to be magnified with the recent results of several stentreiver trials [19, 20]. Furthermore, surgical procedures that were once controversial, such as decompressive craniectomy, are becoming standard practice following recent randomized controlled trials demonstrating efficacy in selected populations [25–28]. With any of these treatment interventions, it is important to both define and predict outcomes. Severe strokes are more likely to require intensive care, have longer length of stays, require more neuroimaging, have a need for ventilator support, and suffer complications related to their hospitalization [38–42]. Importantly, our study quantifies that they may also require both life-saving and life-sustaining procedures, such as decompressive craniectomy, tracheostomy, and gastrostomy. This data may be useful for patient counseling, particularly when prognosticating an individual patient's hospital course and the need for further intervention.

The vast majority of strokes can be described as "non-severe" [43, 44], therefore our study is strengthened by the

utilization of two high-volume centers to maximize enrollment with this relatively small subset of patients. Our stringent selection criteria of both initial neurological deficit and stroke size allowed for a more homogenous selection of an inherently heterogeneous population. The use of any one single variable to screen for patients with "severe" stroke has the potential to miscategorize patients. For example, it is possible to have patients with NIHSS $\geq$15 without significant propensity for cerebral edema or neurological deterioration because of small volume, punctate lesions in eloquent cortex. Furthermore, we were also able to obtain detailed information from the medical record, such as neurological decline and neuroimaging volumetrics, variables that are not necessarily available in larger databases [45].

Limitations of the study are mainly attributable to its retrospective nature [46]. We attempted to overcome selection bias by utilizing a consecutive cohort from a comprehensive registry. There also exists practice variability between institutions and even between individual patients that is difficult to account for [47–49]. Additionally, while several factors were identified as significant, no single factor can predict outcome or neurological deterioration in severe stroke. One of the key applicable pieces of data useful for everyday practice is the quantitative assessment of life-sustaining procedures. These are outcome measures that can be used as benchmarks for future study and to guide prognostication for individual patients.

Conclusions

Adverse outcomes after severe stroke are common. Concurrent ACA involvement predicts mortality in severe MCA stroke. Knowledge of the incidence of life-sustaining procedures, such as tracheostomy and gastrostomy, is meaningful in clinical practice and should continue to be assessed in future study.

Disclosure None.

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