ПРЕДИКТОРЫ ИСХОДОВ ОСТРОГО ИШЕМИЧЕСКОГО ИНСУЛЬТА У ПАЦИЕНТОВ, ПЕРЕНЕСШИХ ЭНДОВАСКУЛЯРНУЮ ТРОМБЭКТОМИЮ

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OUTCOME PREDICTION IN PATIENTS TREATED WITH ENDOVASCULAR THROMBECTOMY FOR ACUTE STROKE

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РЕЗЮМЕ

ВВЕДЕНИЕ И ЦЕЛЬ ИССЛЕДОВАНИЯ: Прогнозирование исходов для пациентов, перенесших эндоваскулярную тромбэктомию, является трудной задачей в клинической практике на протяжении последнего десятилетия. Методы оценки прогнозирования исходов состояния пациентов после нейроинтервенции при остром ишемическом инсульте применяются ограниченно. Целью данного исследования является разработка и проверка алгоритма прогнозирования исходов у пациентов через 90 дней после тромбэктомии по поводу острого ишемического инсульта в каротидном бассейне.

МАТЕРИАЛЫ И МЕТОДЫ: Было проведено ретроспективное изучение 75 случаев тромбэктомии в остром периоде ишемического инсульта на фоне острой окклюзии артерий каротидного бассейна кровообращения. Проанализированы 5 независимых параметра: возраст, баллы по шкале Национального института здравоохранения инсульта (NIHSS) и по шкале тромболизиса при церебральном инфаркте (TICI) до и после тромбэктомии с использованием бинарной модели логистической регрессии с определением исходов согласно модифицированной шкалы Рэнкина. Данные были проверены с использованием программ JROCFIT и JLABROC4.

РЕЗУЛЬТАТЫ: Однофакторный логистический регрессионный анализ продемонстрировал, что возраст, NIHSS после тромбэктомии и комбинированные хорошие показатели TICI (т.е. TICI 2b и 3) были значительно связаны с исходом у пациента, тогда как исходный балл по NIHSS — нет, и были признаны наиболее значимыми независимыми предикторами через 90 дней после интервенции при остром ишемическом инсульте. Данные были подтверждены с помощью кривых ROC и площади под кривой (AUC).

ВЫВОДЫ: Бинарная модель логистической регрессии в нашем исследовании точно предсказывает 90-дневные результаты в статусе пациента после механической тромбэктомии для острого ишемического инсульта. Посттромбэктомический показатель шкалы NIHSS и возраст являются единственными обязательными данными, необходимыми для точного прогноза у этих пациентов.

КЛЮЧЕВЫЕ СЛОВА: инсульт, эндоваскулярная тромбэктомия, исходы.

ABSTRACT

BACKGROUND AND PURPOSE: Prognosticating patients following mechanical thrombectomy has proven challenging for clinicians within the last decade. Several scoring paradigms have subsequently been developed with the aim of aiding providers in predicting outcomes in patients status post neuro-intervention for acute ischemic stroke. The purpose of this study is to develop and validate a condensed algorithm to predict outcomes in patients 90 days post thrombectomy for acute ischemic stroke of the proximal anterior circulation.

METHODS: A retrospective chart review of 75 patients who presented to our institution with emergent large vessel occlusion of the anterior proximal circulation was performed. Five independent variables, Age, Initial NIHSS & TICI, Post-Thrombectomy NIHSS & TICI, delta NIHSS, were identified and regressed logistically upon binary outcomes defined by functional status according to the modified Rankin scale. The data was validated using JROCFIT and JLABROC4 programs for fitting receiver operating characteristic curves using the maximum likelihood fit.

RESULTS: A statistically significant relationship was identified in two of the five independent variables analyzed in the study. Post-thrombectomy NIHSS and Age were found to be the strongest independent predictors of functional status at 90 days post-neurointervention for acute ischemic stroke. The data was validated with ROC curves and area under the curve (AUC).

CONCLUSIONS: The binary logistic regression model in our study accurately predicts 90 day outcomes in patients status post mechanical thrombectomy for acute ischemic stroke. Post-thrombectomy NIHSS and age are the only mandatory covariates required to make an accurate prognosis in these patients.

KEY WORDS: neurosurgery, stroke, thrombectomy, outcomes.

ABBREVIATIONS KEY: NIHSS — National Institute of Health Stroke Scale; TICI — Thrombolysis in Cerebral Infarction; mRs — Modified Rankin Scale; ROC — receiver operating characteristics; ICA — internal carotid artery.

INTRODUCTION

The development of third generation thrombectomy devices combined with refined patient selection criteria has revolutionized the management of acute ischemic stroke in recent years [1]. While these advancements have undoubtedly limited the morbidity and mortality associated with stroke, acute ischemic stroke remains a leading cause of adult disability in the United States. In fact, a recent study in the NJEM found up to 36% of patients who received mechanical thrombectomy for acute ischemic stroke remained disabled (2 < mRs < 6) at 90 days following neurointervention [2]. Several factors influence the prognosis of patients after an acute ischemic stroke including age, time of onset, severity, infarct location, comorbid conditions, baseline functionality, interventions, complications, rehabilitation, etc. Numerous studies have attempted to better identify these major predictors of outcome & prognosticate patients following endovascular mechanical thrombectomy for acute ischemic stroke. According to Russian authors: M. Yu. Volodyukhin and etc. notes that the degree of neurological deficit was associated with the likelihood of a favorable clinical outcome. In patients with severe neurological deficit (NIHSS> 15 points), a favorable clinical outcome was observed in 25% of cases, unfavorable in 71.4% of cases (p <0.01). With a neurological deficit of less than 15 points, the frequency of a favorable clinical outcome was 75%, and of an unfavorable one — 28.6% (p <0.01) [3]. In patients who have suffered an ischemic stroke in the carotid basin, the performance of reconstructive operations on the carotid arteries in the acute period leads in most cases to a significant regression of neurological symptoms. The dynamics of neurological symptoms after reconstructive surgery in patients with symptomatic stenosis reflects a greater regression of neurological deficit compared to non-operated patients with symptomatic stenosis carotid artery. Carotid endarterectomy can be performed with a relatively low risk during the first 2 weeks after ischemic stroke [4]. Regardless of the timing of surgery in patients with neurological deficiency in the 1st day after surgery, there is a decrease in latency of the main peaks, along with this, starting from the 1st day and during the 1st week. After surgery, regardless of the timing, there was an increase in the amplitude of the potential on the side of both hemispheres. This, apparently, is a reflection of the improvement of blood supply in the ischemic area in the 1st day after surgery [5]. Scoring paradigms such as the ASTRAL score, iScore, and PLAN score have recently been validated as good predictors of poor functional status (mRS > 2) at 180 days following neurointervention however, their application in clinical practice today remains limited [6]. These models rely solely on information available to clinicians upon admission and disregard important prognosticating factors such as quality of treatment and post-operative complications. The purpose of this study is to develop an alternate paradigm to better prognosticate patients following endovascular mechanical thrombectomy for acute ischemic stroke. In addition, most of the existing prediction models utilize preoperative neurologic status [7]. Intuitively, neurologic status would unlikely predict the eventual outcome if treatment were effective. Moreover, if thrombectomy was performed, the degree of cerebral reperfusion (i.e. TICI score) has not been used in current models. We therefore investigated the correlation between patient preoperative and postoperative neurologic statuses, completeness of revascularization (i.e. TICI score), and eventual outcome in our cohort of thrombectomy treated patients. In this paper we analyzed outcomes of such an approach, as well as stroke outcome predictors in patients who underwent mechanical thrombectomy. To this end, we utilized sophisticated mathematical modeling techniques.

METHODS

In this single center retrospective study, a retrospective chart review was conducted on patients who underwent mechanical thrombectomy after presenting with acute ischemic stroke due to emergent large vessel occlusion of the anterior circulation from July 2015 to May 2017 at Sanford Medical Center in Fargo, ND (SMCF). Patients included in this study were functionally independent (mRs 0–2) at baseline and presented to SMCF within 12 hours of symptom onset. All patients received non-contrast CT followed by multiphase CTA confirming occlusion of M1/M2 segment of the middle cerebral artery or intracranial ICA with evidence of clinical-radiological mismatch and/or ASPECTS > 6 on DWI/ADC magnetic resonance imaging. Patient's with large ischemic core lesions, poor collateral perfusion, distal occlusions (> M2), posterior circulation occlusions, and disability at baseline (mRs > 2) were excluded from the study. Patients who met all inclusion criteria received mechanical thrombectomy with Solitaire Flow Restoration or Trevo device. All patients were managed in the intensive care unit following neurointervention. NIHSS was recorded 24 and 48 hours post-procedure. Patient's with increasing NIHSS received further imaging and or intervention as indicated.

Demographic information including age, sex, BMI, smoking history, history of diabetes, history of hypertension, history of hyperlipidemia, history of atrial fibrillation, history of prior stroke was recorded. Additional data including time to reperfusion, +/– administration of tPA, initial NIHSS on presentation, post-thrombectomy NIHSS evaluated at 24–48 hours, percent change of NIHSS at 48 hours (delta NIHSS), thrombolysis in cerebral infarction (TICI) score (0–3), as well as 90 day functional status was recorded. Patient's with missing baseline characteristics or follow-up information were excluded. The primary study outcome measure was disability or functional status at 90 days assessed by the modified Rankin scale. Scores 0–2 were classified as functionally independent and represented a favorable result defined as outcome = 1. Scores > 2 were classified as functionally dependent and represented an unfavorable result defined as outcome = 0. Binary logistic regression was used to model the data

where $p = \frac{1}{1+e^{-logit(p)}}$

and $logit\ (p) = \beta_0 X_0 + \beta_1 X_1 + .. + \beta_k X_k$

Statistical analysis was performed using logistic regression modeling with Microsoft Excel and XL Stats add on software. The independent variables of the function were age, TICI score, initial NIHSS, post thrombectomy NIHSS, delta NIHSS = *(initialNIHSS-postThrombectomyNIHSS)/(initialNIHSS).* Receiver operating characteristic curve was created and analyzed. The application used JROCFIT and JLABROC4 programs for fitting ROC curves using the maximum likelihood fit of a binary model. Approvals from the Institutional Review Board of Sanford Medical Center and the University of North Dakota were obtained prior to commencing the study.

RESULTS

A total of 117 patients underwent mechanical thrombectomy for acute ischemic stroke since the beginning of our neurointerventional program in July 2015 to May 2017. Using the previously stated inclusion and exclusion criteria, we retained 75 patients for further analyses. Average age of the remaining 75 patients was 74.3 years (range 25–96). Average initial NIHSS was 15.6 (range 1–27). Average 24 to 48 hours post-thrombectomy NIHSS was 9.2 (range 0–28). TICI 3 was achieved in 52 cases (70%), TICI 2b in 15 (20%) and TICI 2a in 8 (10%). Of the 75 patients analyzed, 30 (40%) had an unfavorable outcome, defined as mRs > 2, while 45 patients (60%) demonstrated functional independence with mRs ≤ 2 (Table 1).

Table 1.

Patient Data Summary

Predictor	Mean	Range	Result (total n=75)
Age	74.3	25–96	
Initial NIHSS	15.6	1–27	
Post-thrombectomy NIHSS	9.2	0 to 28	
TICI 3			52 (70%)
TICI 2b			15 (20%)
TICI 2a			8 (10%)

A series of univariate logistic regression analyses demonstrated that patient age, postthrombectomy NIHSS and TICI scores were individually, significantly related to the patient outcomes (Table 2), whereas initial NIHSS did not (Wald Z=1.1, p=0.23).

Table 2.

Predictor of individual significance.

Predictor	Regression Coefficient	Wald P-value
Age	0.04	< 0.05
Initial NIHSS	0.4	0.27
Post-thrombectomy NIHSS	0.22	< 0.05
TICI 3+2b	–1.8	< 0.05
TICI 2a	–1.2	0.2

A prediction model was built using logistic regression model that included all the individually significant predictors (i.e. patient age, post-thrombectomy NIHSS and TICI score) and their interactions. For predictor selection the Hierarchical Forward Selection method was utilized until the addition of more independent variables would not appreciable increase the coefficient of determination R^2 (i.e. variability of the depended variable explained by the model) or the number of correctly predicted cases. The resulting prediction model included patient age, postthrombectomy NIHSS, TICI score and interaction of TICI score. It correctly predicted 81.3% of cases at the best probability threshold (0.5) used to classify cases into favorable or unfavorable groups with an estimated R^2 of 0.39.

The leave-one-out prediction model misclassified 19 out of total 75 cases (25%) at the best probability cutoff (0.4). ROC analysis, based on the leave-one-out predictions, showed AUC0.74 (p < 0.05) (Figure 1).

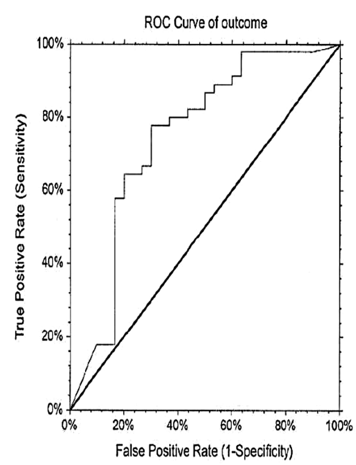

Figure 1.

Receiver operating characteristics (ROC) analysis, based on the leave-one-out predictions, showed AUC0.74 (p<0.05).

DISCUSSION

A mathematical model comprised of postoperative NIHSS, patient age, TICI score as well as an interaction between TICI score and postoperative NIHSS was the most sensitive and specific in predicting outcome in patients treated with mechanical thrombectomy. As expected, preoperative neurological status was not significantly related to patient outcome. Naturally, an effective treatment will reverse or decrease neurologic deficit and therefore decrease postoperative NIHSS. Unfortunately, this does not happen in all patients as some of the brain damage will be irreversible by the time of cerebral blood flow restoration. Also, reperfusion hemorrhage may also worsen this score. Some patients may have multiple vascular territories involved that may not allow for all to be re-perfused. Previous neurological deficit will also compound NIHSS. It has also been shown that TICI reperfusion score is significantly related to patients' outcome [8]. Our data also supports this thesis. Patient age is another significant, universally known predictor of clinical outcomes, and our results are in agreement with this thesis as well. The logistic regression model has been chosen, as it is robust and can handle both continuous and categorical variables to model binary outcomes. A leave-one-out procedure was chosen for simple validation of our predictive model [9]. In this procedure, every case was predicted based on an n-1 model (i.e. training set). Each case was predicted without using its own data to train its prediction model. Thus, this procedure renders almost an unbiased true error rate. Overall, our model could explain 39% of variability in the patient outcome. Naturally, the outcome is also dependent on multiple factors unaccounted for in the model. This may include general medical status, preexisting neurological deficit, patient family wishes, and other factors. Based on our data, postoperative NIHSS or the entire model may be used in further interventional studies as a surrogate outcome measure (i.e. predicted mRs) to decrease variability, thereby decreasing the number of patients in the study. It may also be useful for auditing and for patient family counseling.

Good functional outcomes (i.e. mRs ≤ 2) were observed in 60% of our patients, compared to 53% in ESCAPE, 32.6% in MR CLEAN, 49% in DAWN and 45% in DEFUSE3 trials [2,10]. This may be related to a more individualized approach to patient selection using DWI-clinical mismatch, not simply using NIHSS and DWI volume thresholds, but rather correlating DWI findings with specific clinical deficits and individual patient vascular anatomy. We recognize that this approach may be more subjective and not as readily standardized for clinical trial application. It is also possible that we intuitively used even stricter DWI-based selection criteria than used in the mentioned trials thereby selecting better candidates. Also, we achieved higher percentage of good TICI scores (i.e. TICI 2b and 3 in 90%) and this might have also improved overall outcome.

In our cohort average initial NIHSS was 15.6 (range 1–27) because 4 patients were treated despite low NIHSS at the time of thrombectomy due to recurrent symptoms and presence of large vessel occlusion. We anticipated imminent collateral flow failure in these 4 patients. We achieved good TICI scores (i.e. 2b and 3) more frequently than what was reported in the benchmark trials such as MR CLEAN, ESCAPE, DEFUSE3 and DAWN (90% versus 58.7%, 72.4%, 76%, and 83%) [2,10]. This may be related to the fact that stentrivers combined with suction catheters were used in all of our patients.

Thus far, a number of stroke outcome models have been developed. For example, Raphaël Le Bouc et al, developed a scoring system utilizing NIHSS and age [11]. This system outperformed the previously known prediction system SPAN-100 index [7]. Although statistically associated with worse outcomes in thrombectomy patients, these scoring systems, to our knowledge, were not tested and validated for accuracy of predictions in patients who underwent thrombectomy [12].

Venema et al developed a clinical decision tool to improve the selection of patients with acute ischemic stroke for thrombectomy based on multiple clinical and radiologic predictors using data from MR CLEAN and IMS III trials [13]. However, precision and accuracy of the model predictions were low. This may be in part related to lower rates of successful reperfusions and lack of inclusion of TICI scores in the model. Interestingly, using MRI for selection rather than CT seemed to improve precision of the model predictions [13].

Our study demonstrated a "real life" relationship between postoperative patient clinical characteristics and outcomes in the condition of a rural stroke center. Frequent delays in patient transfers to a stroke center are inevitable in a rural stroke practice. We therefore intuitively adopted biological "brain clock" instead of actual time from last known well, thus often extending therapeutic windows. Similar approaches have subsequently been proven beneficial in the recent studies such as DAWN and DEFUSE3 [14,15]. The main purpose of this paper is to demonstrate in principle that patient outcomes after mechanical thrombectomy may be modeled and predicted using postoperative NIHSS, TICI score and patient age. Further studies should revalidate and refine this approach. As more data is accumulated, more accurate prediction models may be developed.

CONCLUSION

We demonstrated that a model including post-thrombectomy NIHSS combined with patient age and TICI reperfusion score was able to predict functional status at 90 days in patients who underwent mechanical thrombectomy for acute ischemic stroke in the proximal anterior circulation with reasonable sensitivity and specificity.

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