Research Article

Validation of the DRAGON Score in a North American Cohort

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Abstract

Objective: To provide external validation of the DRAGON Score for predicting outcome after intravenous thrombolysis

Methods: A retrospective chart analysis was performed in stroke patients receiving IV-tPA within the 4.5 hour time window from January 2009 to September 2013. A total of 149 patients were included in the analysis. DRAGON scores were calculated for each patient and compared to modified Rankin scores (mRS) at 90-day follow up. Comparison of baseline patient characteristics to the original derivation cohort was made using Chi Square derived p-values for analysis where appropriate. Validity of the model was determined using area under the receiver operating characteristic (ROC) curve analysis for good and bad outcomes.

Results: Proportions of patients with good outcomes (mRS of 0-2) were 100%, 89%, 75%, 5%, 0% and 0% for DRAGON Scores 0-1, 2, 3, 7, 8 and 9-10 respectively. Proportions of patients with miserable outcome (mRS of 5-6) were 0%, 5%, 4%, 82%, 100%, 80% for DRAGON Scores 0-1, 2, 3, 7, 8 and 9-10 respectively. AUC-ROC was 0.93 for our model. When using the score to evaluate only good or bad outcomes the AUC-ROC was 0.88 and 0.89, respectively.

Interpretation: The DRAGON Score is a relatively easy to apply tool that is based information readily available at a patient's initial presentation. The score predicts the functional outcome of stroke patients treated with IV-tPA. Despite statistically significant differences in baseline characteristics in this North American cohort compared to the derivation cohort, the DRAGON score model remains a reliable stratification tool with good predictive value.

INTRODUCTION

Intravenous tissue plasminogen activator (IV-tPA) remains the most effective treatment of acute ischemic stroke after its initial introduction in 1995 supported by the National Institute of Neurologic Disease and Stroke (NINDS) [1]. However, it carries a 2-8% risk of symptomatic intracranial hemorrhage [1,2,3] requiring a thorough risk benefit analysis of its utilization. Therefore, risk assessment tools that can reliably predict clinical outcome can be helpful in guiding treatment decisions when considering the potential need for experimental interventions such as intra-arterial thrombolysis or mechanical thrombectomy.

The DRAGON score (Figure 1) is a tool that can be used to predict the likelihood of a good or miserable outcome when delivering IV-tPA in the treatment of acute ischemic stroke [4]. Other models to predict outcomes from ischemic stroke include the HAT score [5], THRIVE score [6], iScore [7] and SPAN-100 [8]. The HAT score aims to predict incidence of symptomatic hemorrhage after thrombolysis [5], THRIVE intends to predict outcomes related to endovascular intervention [6], iScore predicts

mortality independent of treatment [7] and SPAN-100 aims to predict both functional outcome and symptomatic intracerebral hemorrhage risk in the setting of IV-tPA [8]. The DRAGON score is fundamentally different from these other tools in that it aims to predict functional outcome, as measured by modified Rankin score (mRS) at 90 days, when the patient is treated with IV-tPA.

In the original publication for DRAGON by Strbian et al [4], the DRAGON score was calculated for a derivation cohort of 1,319 patients at Helsinki University Hospital in Finland receiving IV-tPA within 4.5 hours for a diagnosis of acute ischemic stroke and then subsequently compared to their mRS at 90 days. The data indicated that lower DRAGON scores were associated with good outcomes (mRS 0-2), while higher DRAGON scores were associated with miserable outcomes (mRS 5-6). Included in the original article was a validation cohort of 333 patients from University Hospital Basel in Switzerland which mirrored the derivation cohort results. Since publication of this original article, there has been a multi centered validation in 12 centers across Europe and Australia [9], as well as two other validations, one in an elderly Spanish population [10], and one from Denmark [11].

These previous external validations have confirmed the validity of the model in each of their study populations.

Here we present a validation of the DRAGON score using a North American cohort derived from patients treated at Penn State Hershey Medical Center.

MATERIALS AND METHODS

A retrospective chart analysis was performed using an institutional database to identify patients receiving IV-tPA within the 4.5 hour time window for a presumed diagnosis of acute ischemic stroke. Institutional Review Board (IRB) approval was obtained prior to collection of data. Informed consent was waived due to retrospective nature of the study. Data were collected from consecutive cases of ischemic stroke patients treated with IV tPA who presented between January 2009 and September 2013 at Penn State Hershey Medical Center. Data collected included age, sex, blood glucose on admission, NIHSS on admission, mRS on admission, CT head radiology report and images, and onset to treatment time. In compliance with meaningful use all of the aforementioned data elements except CT head report were collected through electronic abstraction of data points logged in the medical record. When data elements were missing a hand abstraction was performed by the first author and if the data point remained elusive the patient was then removed from the study population. All modified Rankin scores were calculated in person by a certified neurologist, neurology resident or advanced practice clinician.

Two hundred –thirty seven patients were eligible for study inclusion. Eighty eight were excluded from the analysis due to being lost to follow up and therefore having missing mRS at 90 days. The remaining 149 patients were included in the primary analysis. DRAGON scores were calculated for each patient and were compared to mRS at 90 day following the stroke. Good outcomes were defined as mRS of 0-2 and miserable outcomes as mRS 5-6. The DRAGON score ranges from 0 to10 with higher scores indicating increased risk for poor clinical outcome. The score is comprised of computed tomography (CT) imaging information (presence of dense middle cerebral artery (MCA) sign or early infarct sign), pre-stroke modified Rankin score, patient age, glucose on presentation, onset to treatment time with IV-tPA and National Institutes of Health Stroke Scale (NIHSS). Scoring details can be seen in (Table 2).

Chi Square analysis was used to compare baseline characteristics of our cohort to the derivation cohort in order to determine similarity of the two populations.

Validity of the model was determined using area under the receiver operating characteristic (ROC) curve analysis for good and miserable outcome. The Youden index was utilized to determine optimal DRAGON score cut off for each patient. Statistical analysis was completed using SAS software 9.3 (SAS Institute, Cary, NC, USA).

RESULTS AND DISCUSSION

Results

Baseline characteristics of our patient population are summarized in (Table 1) along with comparison to the

derivation cohort [4]. Chi square analysis was performed where appropriate and there were statistically significant differences between proportions of patients with early infarct signs and pre-stroke mRS in our cohort compared with the derivation cohort. Age, glucose, onset to treatment time and NIHSS could not be directly compared as the derivation cohort report lacked details regarding mean and standard deviations. Outcome measures were also significantly different between the two populations in regards to proportions of patients in each 90 day mRS category. Despite proportional differences in outcomes when comparing our cohort to the derivation cohort, accuracy of the model is maintained. (Figure 1) displays DRAGON Score outcomes when measured by mRS at 90 with area under the ROC curve (AUC-ROC) of 0.93, which is comparable to 0.84 for the derivation cohort model [4].

When good and miserable outcomes were stratified in separate AUC-ROC analyses the values were 0.88 and 0.89 for good and miserable respectively. The Youden indices identified 4 as the optimal DRAGON score value for determining good outcome and 5 for miserable outcome based on the AUC-ROC analysis.

As depicted in (Figure 1), proportions of patients with good outcomes were 100%, 89%, 75%, 5%, 0% and 0% for DRAGON Scores 0-1, 2, 3, 7, 8 and 9-10 respectively. Likewise, proportions of patients with miserable outcome were 0%, 5%, 4%, 82%, 100%, 80% for DRAGON Scores 0-1, 2, 3, 7, 8 and 9-10 respectively.

Discussion

The DRAGON score utilizes data that is readily available at the time of treatment decision for acute ischemic stroke. Despite statistically significant differences in our cohort compared to the derivation cohort [4] we found that the model remained valid based on AUC-ROC analysis. The initial study and all subsequent external validations [9,10,11] have been in European and Australian populations. This is the first North American cohort to which this scoring tool has been applied.
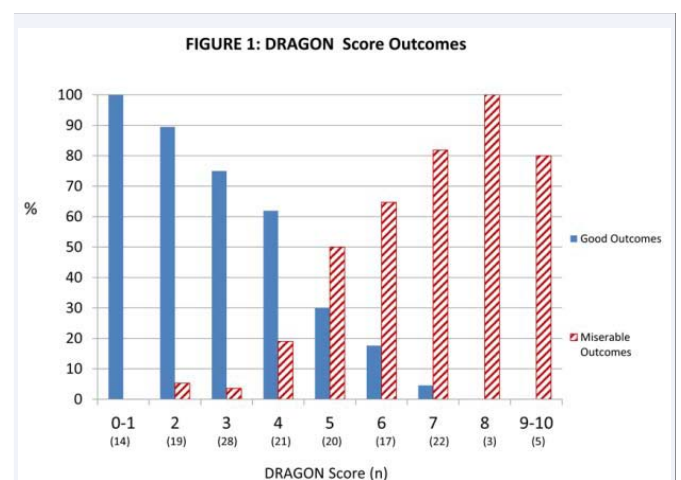

Figure 1 DRAGON score outcomes displaying DRAGON score with correlating percentage of patients with good outcomes (solid bars) and miserable outcomes (slashed bars).

The previous validation studies have all found the DRAGON model valid for predicting outcomes with AUC-ROC >0.75 in each [9,10,11]. In comparing data we chose to analyze our data in comparison the derivation cohort to determine if there were any outstanding differences amongst baseline characteristics of patients. Given the potential variability in population characteristics we sought to validate the DRAGON score in a different population than it had originally been studied. Certain baseline characteristics were identified as being significantly different from the derivation cohort as noted in (Table 1). Having such differences in baseline characteristics that comprise the DRAGON score was imperative to determining if the model is versatile. Since direct statistical analysis of some characteristics could not be performed, we cannot draw explicit conclusions regarding any potentially significant differences amongst the age, glucose, onset to treatment times and baseline NIHSS. Although, it does appear that our population may have been older than the derivation cohort, this cannot be validated with statistical comparison due to lack of details in the derivation cohort-report [4].

Within the outcome data we noted a significant difference amongst patients in each mRS category compared to the derivation cohort. We believe this difference is likely accounted for by the fact that data collection was completed using an electronic health record, and as such, we were able to identify deceased patients with greater ease than to capture those patients who had been lost to follow-up. When taking into account the 88 patient's excluded from this analysis due to missing mRS at 90 day visit, this creates some bias in the analysis as this was about one third of our entire study population. Since the electronic record is more adept at capturing those who are deceased, one can conclude that the distribution of mRS amongst those remaining 88 individuals, who were likely surviving, would have been similar to that of the complete data, which would likely resulted in different fractions of patients in each mRS category. Thus, the high proportion of

Table 2: DRAGON Score Calculation displaying individual elements and explanation of scoring.

Dense MCA sign or early infarct sign on CT	None: 0 Either: 1 Both: 2
Preadmission modified **R**ankin Score	≤1: 0 >1: 1
Age	≤65: 0 65-79: 1 ≥80: 2
Blood **G**lucose	≤144mg/dL: 0 >144mg/dL: 1
Onset to treatment time	≤90 minutes: 0 >90minutes: 1
NIHSS	0-4: 0 5-9: 1 10-15: 2 >15: 3

Abbreviations: MCA=Middle Cerebral Artery, CT=Computed Tomography, NIHSS=National Institutes of Health Stroke Scale.

miserable outcomes in our data is not adequately reflective of true outcomes, but rather reflects a bias in our sample.

Recently ROC analysis has come under question when it comes to determining validity of scoring systems related to predicting outcomes after ischemic stroke [12]. It has been suggested that additional statistical methods such as bootstrapping and external validation are necessary before clinical risk assessment scales can be broadly applied [12]. In the case of the DRAGON Score, the initial publication performed both of these techniques finding a 95% confidence interval for their AUC-ROC of 0.80-0.87 via bootstrapping and their external validation cohort showed a AUC-ROC of 0.80 with 95% confidence interval 0.74-0.86 [4]. When combined with further external validations [9-11] including ours, it appears that this score is effective and valid at predicting clinical outcome of ischemic stroke patients who receive IV-tPA.

Standard of care therapy remains use of IV-tPA when in the thromblytic window. Calculation of the DRAGON score may be helpful to clinicians when considering their patient's need for additional therapy beyond intravenous thrombolysis. Those patients with high DRAGON scores do not appear to have good outcomes with IV-tPA alone, and perhaps this tool could be used in selection of patients for investigational therapies such as intra-arterial thrombolysis or mechanical thrombectomy.

Future directions should include determination of additional factors to help dichotomize the intermediate zone of DRAGON Score 4-6 where outcomes are neither clearly good nor miserable. Also, the DRAGON score could be applied to patients receiving the additional investigational treatments of intra-arterial thrombolysis and/or mechanical thrombectomy to determine if this additional therapy results in a shift in mRS compared to the baseline published data.

CONCLUSION

The DRAGON Score is relatively easy to apply tool for prediction of clinical outcome in the setting of ischemic stroke patients treated with IV-tPA. This is the first study to use the DRAGON score to in a North American cohort. Despite statistically significant differences in baseline characteristics

Table 1: Patient Characteristics. Patient characteristics from Penn State Hershey Medical Center compared to the derivation cohort group. Chi square analysis was used to calculate p-values.

		PSHMC Cohort (n=149)	Derivation Cohort (n=1319)	p Value
Female (%)		48.3%	44.7%	0.413
Dense artery sign		22.8%	17.7%	0.122
Early infarct sign		19.5%	30.6%	0.005
Age, y, median (IQR)		75 (62-83)	69 (60-77)	n/a
Pre-stroke mRS>1 (%)		18.8%	6.2%	<0.001
Glucose, mg/dL, median (IQR)		117 (101-142)	119 (103-140)	n/a
Onset to treatment time, minutes, median (IQR)		150 (112-176)	118 (88-158)	n/a
Baseline NIHSS, points, median (IQR)		9 (4-16)	9 (5-14)	n/a
Proportions of 3-month outcome, mRS	0-2 3-4 5-6	49.7% 15.4% 34.9%	60.5% 25.7% 13.8%	<0.001 <0.001 <0.001

Abbreviations: mRS= modified Rankin Score, NIHSS= National Institutes of Health Stroke Scale, IQR= Inter Quartile Range.

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between the cohorts, the DRAGON score model remains a reliable stratification tool.

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REFERENCES

1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med. 1995; 333: 1581-1587.

2. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007; 369: 275-282.

3. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359: 1317-1329.

4. Strbian D, Meretoja A, Ahlhelm FJ, Pitkäniemi J, Lyrer P, Kaste M, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology. 2012; 78: 427-432.

5. Lou M, Safdar A, Mehdiratta M, Kumar S, Schlaug G, Caplan L, et al. The HAT Score: a simple grading scale for predicting hemorrhage after thrombolysis. Neurology. 2008; 71: 1417-1423.

6. Flint AC, Cullen SP, Faigeles BS, Rao VA. Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. AJNR Am J Neuroradiol. 2010; 31: 1192-1196.

7. Saposnik G, Kapral MK, Liu Y, Hall R, O'Donnell M, Raptis S, et al. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation. 2011; 123: 739-749.

8. Saposnik G, Guzik AK, Reeves M, Ovbiagele B, Johnston SC. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. Neurology. 2013; 80: 21-28.

9. Strbian D, Seiffge DJ, Breuer L, Numminen H, Michel P, Meretoja A, et al. Validation of the DRAGON score in 12 stroke centers in anterior and posterior circulation. Stroke. 2013; 44: 2718-2721.

10. Giralt-Steinhauer E, Rodríguez-Campello A, Cuadrado-Godia E, Ois Á, Jiménez-Conde J, Soriano-Tárraga C, et al. External validation of the DRAGON score in an elderly Spanish population: prediction of stroke prognosis after IV thrombolysis. Cerebrovasc Dis. 2013; 36:110-114.

11. Ovesen C, Christensen A, Nielsen JK, Christensen H. External validation of the ability of the DRAGON score to predict outcome after thrombolysis treatment. J Clin Neurosci. 2013; 20: 1635-1636.

12. Esteghamati A, Hafezi-Nejad N, Sheikhbahaei S, Heidari B, Zandieh A, Eslami V. Comparing the Predictive Ability of Prognostic Models in Ischemic Stroke; Derivation, Validation, and Discrimination Beyond the ROC Curve. Front Neurol. 2014; 5: 9.