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Validation of TURN, a simple predictor of symptomatic intracerebral hemorrhage after IV thrombolysis

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ABSTRACT

Objective: We recently described TURN (Thrombolysis risk Using mRS and NIHSS), a computationally simple tool for predicting symptomatic intracerebral hemorrhage (sICH) after IV thrombolysis (rt-PA). Our objective was to compare TURN to existing scores for predicting sICH.
Methods: Our internal dataset consisted of 210 ischemic stroke patients receiving IV rt-PA from January 2009 until July 2013 at Yale New Haven Hospital. Our external dataset included 303 patients who received IV rt-PA during the NINDS rt-PA trial. Predictive ability and goodness of fit were quantified by odds ratios (OR) and areas under the receiver operating characteristic curve (AUROC), and compared using unequal variance two-sample *t*-tests.
Results: TURN predicted sICH with a higher OR than ASTRAL in the internal dataset (2.72 versus 1.10, P = 0.05). We found no other significant differences in OR or AUROC between TURN and other scores in both datasets.
Conclusion: Despite its computational simplicity, TURN predicts sICH with accuracy comparable to existing scores.

1. Introduction

Intravenous thrombolysis (rt-PA) remains the only medical treatment for acute ischemic stroke approved by the Food and Drug Administration (FDA), but carries a substantial risk for symptomatic intracerebral hemorrhage (sICH) [1]. Predictive scores for sICH may help improve the safety profile for rt-PA treatment.

We recently described the TURN score (Thrombolysis risk Using mRS and NIHSS), a simple predictor of sICH after IV rt-PA treatment using prestroke modified Rankin Scale (mRS) scores and baseline National Institutes of Health Stroke Scale (NIHSS) scores [2]. Clinically useful sICH predictors should be computationally simple without compromising predictive accuracy [3].

Several scores exist for estimating post-thrombolysis risk, including the Stroke-Thrombolytic Predictive Instrument (Stroke-TPI) [4], iSCORE [5], DRAGON [6], Stroke Prognostication using Age and NIH Stroke Scale-100 (SPAN-100) [7], Acute Stroke Registry and Analysis of Lausanne (ASTRAL) [8], Post-thrombolysis Risk Score (PRS) [9], Hemorrhage After Thrombolysis (HAT) [10], SEDAN [11], and Safe Implementation of Treatments in Stroke Symptomatic Intracerebral Hemorrhage (SITS-ICH) [12].

Most of these scores are computationally complex. An exception is SPAN-100 which requires only two clinical variables; however it has been reported as a poor predictor of sICH in several studies [3,11,13]. The TURN score is computationally simple, however its predictive accuracy compared to existing scores is unknown. In this study we compared the strength of association and overall prediction accuracy of TURN to eight existing scores for predicting sICH after rt-PA therapy.

2. Materials and methods

2.1. Patient data

Our internal dataset included all consecutive ischemic stroke patients (n = 210) from our dual-center prospective stroke registry who received IV rt-PA therapy from January 2009 until July 2013 at Yale New Haven Hospital and Yale-New Haven Shoreline Medical Center as previously described [3]. One patient was excluded due

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Table 1
Comparison of TURN to 8 other clinical scores using the derivation dataset. P values from comparison to TURN using unequal variance two-sample *t*-tests with Welch's approximation for degrees of freedom.

Score	Odds Ratio (95% CI)	Standard error	P |T| > |t|	AUROC (95% CI)	Standard error	P |T| > |t|
TURN	2.72 (1.51, 4.89)	0.81	1.00	0.74 (0.58, 0.90)	0.08	1.00
Stroke-TPI	1.91 (1.26, 2.90)	0.41	0.38	0.74 (0.61, 0.87)	0.07	0.97
DRAGON	1.66 (1.21, 2.30)	0.27	0.22	0.76 (0.63, 0.89)	0.07	0.85
SPAN-100	2.11 (0.60, 7.36)	1.34	0.70	0.57 (0.43, 0.71)	0.07	0.11
ASTRAL	1.10 (1.03, 1.16)	0.03	0.05*	0.72 (0.59, 0.86)	0.07	0.84
HAT	1.67 (1.06, 2.62)	0.38	0.24	0.70 (0.55, 0.85)	0.08	0.70
SEDAN	1.70 (1.02, 2.84)	0.45	0.27	0.66 (0.50, 0.81)	0.08	0.44
PRS	2.19 (1.01, 4.74)	0.86	0.66	0.66 (0.52, 0.80)	0.07	0.43
SITS-ICH	1.27 (0.94, 1.71)	0.19	0.08	0.65 (0.52, 0.78)	0.07	0.37

sICH = symptomatic intracerebral hemorrhage, rt-PA = recombinant tissue plasminogen activator, AUROC = area under the receiver operating characteristic curve. TURN = Thrombolysis risk Using mRS and NIHSS, Stroke-TPI = Stroke-thrombolytic Predictive Instrument, SPAN-100 = Stroke Prognostication using Age and NIH Stroke Scale-100, ASTRAL = Acute Stroke Registry and Analysis of Lausanne, PRS = Post-thrombolysis Risk Score, HAT = Hemorrhage After Thrombolysis, SITS-ICH = Safe Implementation of Treatments in Stroke Symptomatic Intracerebral Hemorrhage.

* P values < 0.05 two-tailed considered statistically significant.

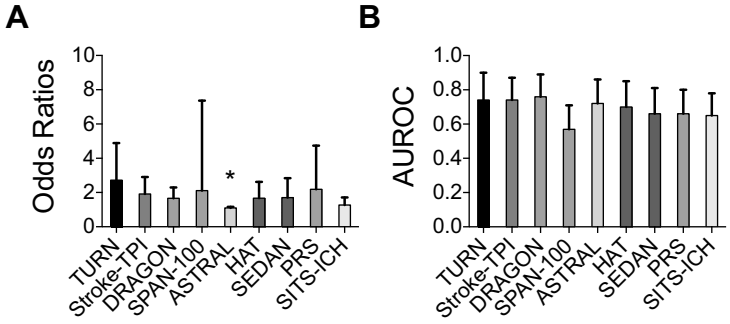

Fig. 1. Odds ratios and AUROC for TURN compared to 8 clinical scores using the derivation dataset. P values from unequal variance two-sample *t*-tests with Welch's approximation for degrees of freedom. *P value < 0.05 two-tailed considered statistically significant. AUROC = area under the receiver operating characteristic curve, sICH = symptomatic intracerebral hemorrhage, TURN = thrombolysis risk using mRS and NIHSS, Stroke-TPI = Stroke-thrombolytic Predictive Instrument, SPAN-100 = Stroke Prognostication using Age and NIH Sroke Scale-100, ASTRAL = a Cute Stroke Registry and Analysis of Lausanne, HAT = Hemorrhage After Thrombolysis, PRS = Post-thrombolysis Risk Score, SITS-ICH = Safe Implementation of Treatments in Stroke Symptomatic Intracerebral Hemorrhage.

to incomplete data. Eligibility criteria for IV rt-PA treatment were applied following the American Heart Association guidelines [14].

Our external dataset included ischemic stroke patients who received IV rt-PA during the NINDA rt-PA Stroke Study [1]. Data from the NINDS trial were purchased from the National Technical Information Service (NTIS; http://www.ntis.gov/) using internal funds from the Yale Department of Neurology as previously described [15]. Clinical data was converted to Microsoft Excel format using Statistical Analysis System software (SAS Institute Inc., Cary, NC). Individual variables were decoded using instructions included in the CD-ROM from NTIS in accordance with published guidelines [16].

This study was approved by the Yale Human Investigation Committee and the Yale Human Research Protection Program. Written informed consent was not required for reviewing retrospective de-identified patient data.

2.2. Imaging and outcome data

Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed in the derivation dataset before IV rt-PA treatment, 24 h after treatment, and subsequent to any observed clinical deterioration as previously described [3]. Neuroradiological assessment was performed on each patient by a board-certified neurologist (HA). Adverse outcome was defined as presence of symptomatic intracerebral hemorrhage (sICH) using the National Institute of Neurological Diseases and Stroke (NINDS) rt-PA trial definition [1]. sICH status was determined from documented narratives in the patient's record.

2.3. Clinical scores

We previously identified independent predictors of sICH using univariable logistic regression with sICH as the dependent variable, and combined them using multivariable logistic regression to form the TURN score [2]. In this study, we used the β coefficients from that multivariable logistic regression analysis to calculate TURN for each patient using prestroke mRS scores and admission NIHSS scores as follows: TURN = −4.65 + (mRS × 0.27) + (NIHSS × 0.10) [2]. The prestroke mRS score is an indication of patients' baseline ability to look after themselves in daily life, and measures overall independence with moderate to good inter-observer reliability [17,18]. The admission NIHSS score is a measure of stroke severity with good inter-observer reliability [19,20]. Both prestroke mRS and NIHSS scores are routinely available at most centers prior to the point of rt-PA administration. The predictors for severe outcome were calculated using the inverse logit of TURN as follows: TURN predictor = $e^{TURN}\left(1+e^{TURN}\right)$ %. We also calculated eight scores for each patient in the derivation dataset: Stroke-TPI, DRAGON, SPAN-100, ASTRAL, PRS, HAT, SEDAN and SITS-ICH. Detailed derivations of each score have been published elsewhere [4,5,7–11] and summarized in Supplemental Table S1 as previously described [3]. In the external cohort we excluded PRS and SITS-ICH due to unavailability of required data.

2.4. Statistical analysis

Predictive accuracy was calculated by areas under the receiver operating characteristic curve (AUROC), a measure of how well each predictive score discriminated between patients with and