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Prediction Of Adverse Outcomes After Rt-Pa Treatment In Ischemic Stroke Patients

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Prediction of Adverse Outcomes after rt-PA Treatment in Ischemic Stroke Patients

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Abstract

IV thrombolysis (rt-PA) for ischemic stroke treatment carries a substantial risk for symptomatic intracerebral hemorrhage (sICH) and adverse outcome. Our purpose was to develop a computationally simple and accurate clinical predictor of adverse outcome after rt-PA therapy.

Our derivation dataset consisted of 210 ischemic stroke patients receiving IV rt-PA from January 2009 until July 2013 at Yale New Haven Hospital. Our validation 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). Patient outcomes included sICH, brain swelling, 90-day severe outcome and 90-day mortality. Severe outcome was defined as 90-day modified Rankin Scale (mRS) scores ≥ 5, 90-day Barthel Index (BI) scores < 60 and 90-day Glasgow Outcome Scale (GOS) scores > 2.

Out of seventeen clinical parameters tested, three were independent predictors of sICH: prestroke mRS score (OR 1.54, P = 0.02), baseline National Institutes of Health Stroke Scale (NIHSS) score (OR 1.13, P = 0.002), and platelet count (OR 0.99, P = 0.04). We combined these three parameters to form the TURNP (Thrombolysis risk Using mRS, NIHSS and Platelets) score. For added simplicity, prestroke mRS score and baseline NIHSS score were also combined to form the TURN (Thrombolysis risk Using mRS and NIHSS) score, which predicted sICH without a significant drop in OR or AUROC. TURN predicted sICH with AUROC 0.74 (0.58 – 0.90) in the derivation dataset, and AUROC 0.65 (0.54 – 0.77) in the validation dataset. In the validation dataset, TURN predicted 24-hour brain swelling with AUROC 0.69 (0.63 - 0.75), 90-day mRS ≥ 5 with AUROC 0.83 (0.77, 0.89),

90-day BI < 60 with AUROC 0.81 (0.76 – 0.86), 90-day GOS > 2 with AUROC 0.81 (0.76 – 0.86) and 90-day mortality with AUROC 0.82 (0.76 – 0.88).

To improve the clinical utility of TURN, we developed and tested a mobile application Risk rtPA based on TURN for predicting 90-day outcome after rt-PA treatment. Risk rtPA returned predictions of severe outcome for a range of hypothetical patients with varying clinical characteristics, demonstrating broad applicability. This mobile application brings computationally simple prediction of post-thrombolysis risk to the bedside for real-time stroke prognostication.

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Introduction

Stroke is the number 4 cause of death and a leading cause of long-term disability in the United States [1]. Roughly 6.8 million Americans 20 years and older have had a stroke, and an additional 4 million individuals are projected to have a stroke by the year 2030 [1]. About 780,000 strokes are estimated to occur annually in the United States [2]. Risk factors for stroke are well established and include family history, high blood pressure, diabetes mellitus, atrial fibrillation, high cholesterol, smoking, physical inactivity and chronic kidney disease [1].

87% of all strokes are ischemic (e.g., due to large artery thrombosis or cardiogenic embolism). As a result, much attention has been focused on developing treatment strategies for this stroke subtype. However, hemorrhagic strokes (intracerebral or subarachnoid) which comprise the other 13% of strokes are more frequently associated with impaired consciousness and thus carry increased risk of mortality within the first 3 weeks after stroke [3]. Furthermore, intracerebral hemorrhage may lead to ischemic lesions and worse clinical outcomes in up to 25% of cases [4,5]. Therefore, hemorrhagic strokes warrant careful characterization and development of optimal treatment strategies.

Hemorrhagic strokes may occur spontaneously, or may be associated with trauma or with aneurysm rupture. Additionally, hemorrhage may occur secondarily to an ischemic stroke, so-called hemorrhagic transformation (HT), leading to symptomatic intracerebral hemorrhage (sICH). sICH is of particular clinical importance because whereas thrombolytic therapy (rt-PA) for ischemic stroke decreases stroke mortality, it carries a substantial risk for sICH [6]. The National Institute of Neurological Diseases and Stroke (NINDS) rt-PA trial found that ischemic stroke patients receiving rt-PA therapy within three hours of symptom onset were at least 30% more likely to recover with little or no disability after three months,

however up to 6.5% of these patients developed sICH [7]. The European Cooperative Acute Stroke Study (ECASS) trials extended the rt-PA time window to 4.5 hours, but confirmed a risk for sICH after thrombolysis (8.8% sICH in ECASS II and 2.4% in ECASS III) [8-10].

As a result of these studies, anticoagulant and thrombolytic treatment is contraindicated in patients with hemorrhage, and risk of sICH must be considered when treating any ischemic stroke patient [3]. However some subsets of ischemic stroke patients such as those defined by stringent ECASS exclusion criteria or those with intracranial aneurysms may not suffer additional adverse effects from rt-PA therapy [11,12]. Yet, the risk of sICH has partly hindered broad adoption of rt-PA therapy. A 2005 survey reported that 40% of emergency physicians were not likely to use rt-PA, with the risk of sICH cited as the main reason in 65% of cases [13]. Emergency physicians also reported a mean upper limit of tolerable sICH rate of 3.4%, reflecting an increasing demand for wider safety margins for rt-PA therapy. Further studies are needed to establish safe criteria for thrombolytic therapy.

The use of rt-PA is also limited by delayed presentation after ischemic stroke. A pooled analysis of patients from the ECASS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), NINDS and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) trials found a significant association between decreased symptom onset-to-treatment (OTT) duration and favorable 3-month outcome [14]. Likewise, an analysis of an 80,000-patient cohort in Europe found that early treatment was associated with favorable outcome [15]. As a result, the American Heart Association Science Advisory and Coordinating Committee guidelines emphasize rapid recognition of stroke symptoms and rapid transportation of stroke patients to the closest appropriate emergency department for administration of time-dependent therapies [16,17].

Additionally, longer OTT is included in several clinical scores as an independent predictor of adverse outcome [18,19] and symptomatic intracerebral hemorrhage (sICH) [20], and newer studies have focused on institution- and system-wide strategies to decrease OTT durations in order to improve patient outcomes [21].

In addition to decreasing OTT, a number of interventions have been proposed to limit sICH after rt-PA therapy, including agents involved in the inflammatory and oxidative stress responses, free radical trap compounds, and enzymes involved in membrane remodeling such as matrix metalloprotease-9 (MMP9) [22]. Cerebral edema is a known mechanism for development of sICH after ischemic stroke [22]. Edema progresses rapidly in the first 2-3 days after an ischemic insult, initially as ionic edema through increased permeability of endothelial ion channels and transporters, and later as vasogenic edema through paracellular pathways as the integrity of tight junctions which make up the blood-brain barrier (BBB) deteriorates [23,24]. Loss of BBB integrity precedes development of sICH [23], making BBB permeability and brain edema attractive targets for prognostication [25], and opening up novel therapeutic options via MMP9 inhibition.

The MMP9 inhibitor glyburide (glibenclamide), which inhibits sulfonylurea receptor (SUR1)-regulated $NC_{Ca\text{-}ATP}$ channel activity, has been shown to reduce cerebral edema, infarct volume and mortality by 50% in a rat model of middle cerebral artery occlusion (MCAO) [26]. In MCAO rats treated with rt-PA, glibenclamide treatment significantly reduced hemispheric swelling and lowered mortality compared to controls, even when glibenclamide was administered up to 10 hours after ischemia [27]. Additionally, since glyburide is a long-time antidiabetic agent, retrospective analysis of type 2 diabetic patients with non-lacunar acute stroke who were on sulfonylurea found no incidences of sICH in patients with

sulfonylurea in sharp contrast to diabetic patients who did not take the medication [28]. Based on these data, a multicenter phase II trial Glyburide Advantage in Malignant Edema and Stroke (GAMES) is currently underway to investigate the effect of IV glyburide on sICH in patients with severe anterior circulation ischemic stroke.

Strategies to predict sICH may also improve outcomes after rt-PA administration by excluding patients who are predicted to be at high risk for sICH or poor outcomes. sICH prediction has been attempted using a number of imaging techniques [22]. Non-Contrast Head CT focal hypodensity has been proposed [29], but suffers from difficulties in defining the boundaries of the lesion. CT angiography has also been used to measure contrast opacity and to develop a clot burden score, which correlates with hypo-perfusion and parenchymal sICH [30]. sICH characterization was attempted in one study using prospective CT scans in ischemic stroke patients 4 weeks after stroke [31]. sICH occurred in 43% of cases, with most sICH cases occurring in the first two weeks after infarct. Other factors that correlated with sICH incidence were severe neurological deficit on presentation, disturbance of consciousness, cortical involvement and distinct blood/CSF barrier disturbances [31]. Additionally, DWI sequences on MRI imaging have been used successfuly to correlate sICH with infarct size and volume [32].

Quantitative methodologies have also been employed to assess edema or intracerebral hemorrhage volume and its association with clinical outcomes. Volume of spontaneous intracerebral hemorrhage has been positively correlated with 30-day mortality, and can predict mortality in combination with Glasgow Coma Scale scores with a sensitivity of 96% and specificity of 98% [33]. A recent small study likewise demonstrated sensitive prediction of malignant edema and sICH after ischemic stroke using perfusion CT as a marker for early

BBB permeability [34]. Another = study described a CT-based technique for accurately measuring edema volume using semi-automated volume reconstruction [35]. Using similar advanced imaging techniques, it has been demonstrated that cerebral edema independently predicts poor outcome after nonlacunar ischemic stroke [36]. Volumes of edema and intracerebral hemorrhage may therefore be applied as objective measurement tools to predict sICH and poor outcome after rt-PA therapy.

Clinical scores predicting risk of sICH may also enhance therapeutic safety after rt-PA treatment by identifying select ischemic stroke patients who may receive rt-PA without additional risk of sICH. At least 8 clinical risk scores have been developed to predict either adverse outcome or sICH after rt-PA therapy. They include the Stroke-Thrombolytic Predictive Instrument (Stroke-TPI)[37]; iSCORE[38]; Dense cerebral artery or early infarct signs on CT, mRS, Age, Glucose level on admission, Onset to treatment time and NIHSS (DRAGON) [18]; Stroke Prognostication using Age and NIH Stroke Scale-100 (SPAN-100) [39]; Acute Stroke Registry and Analysis of Lausanne (ASTRAL) [19]; Post-thrombolysis Risk Score (PRS) [40]; Hemorrhage After Thrombolysis (HAT) [41]; baseline blood Sugar, Early infarct signs, Dense cerebral artery sign, Age and NIHSS (SEDAN) [42]; and the Safe Implementation of Treatments in Stroke Symptomatic Intracerebral Hemorrhage (SITS-ICH) score [20]. Several 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 [42-44]. Future studies are needed to develop scores that are simple but yet accurately predict sICH for widespread clinical applicability.

Statement of purpose

Our aim was to objectively evaluate existing scores available for predicting sICH or adverse outcome after rt-PA, and to derive a computationally simple but accurate clinical score. Our specific aims were as follows:

1. Comparison of existing scores for predicting post-thrombolysis risk
2. Derivation and validation of a novel score
    a. Derivation of a novel score
    b. Validation of clinical score in external dataset
3. Outcome prediction using clinical score
    a. Prediction of brain swelling
    b. Prediction of adverse outcome
    c. Prediction of 90-day mortality
4. Expansion of clinical utility of score

Materials and methods

Study contributions

Study design and clinical data interpretation were done by Dr. Kevin N. Sheth. Data collection and clinical data review were done by Karin Nystrom, APRN. Radiological data was reviewed by a stroke fellow Hardik Amin, MD. Statistical analyses including data presentation and interpretation were performed by myself.

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. One patient was excluded due to incomplete data. Eligibility criteria for IV rt-PA treatment were applied following the American Heart Association guidelines [17].

Our external dataset included ischemic stroke patients who received IV rt-PA during the NINDA rt-PA Stroke Study, a multicenter, prospective, double-blind, placebo-controlled randomized trial from January 1991 to October 1994 [7]. 9 patients were excluded due to incomplete data. 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. 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 [45].

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.

Imaging data:

Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed in the derivation dataset before IV rt-PA treatment, 24 hours after treatment, and subsequent to any observed clinical deterioration. Neuroradiological assessment was performed on each patient by a board-certified neurologist (Hardik Amin, MD). CT or MRI findings in the validation dataset were reported from a consensus of three neuroradiologists blinded to treatment group and outcome as previously published [7]. 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 [7]. sICH status in the derivation dataset was determined from documented narratives in the patient's record.

Outcome measures and clinical scores:

Severe 90-day outcome was defined according to previously published studies as a 90-day modified Rankin Scale (mRS) score ≥ 5, a Barthel Index (BI) score < 60 or a Glasgow Outcome Scale (GOS) score > 2, and excellent 90-day outcome was defined as a 90-day mRS score ≤ 1, a BI score ≥ 95 or a GOS score $= 1$ [46-48].

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 [49,50]. A score of 0 indicates no symptoms, a score of 5 indicates severe

disability, and a score of 6 indicates death. The admission National Institutes of Health Stroke Scale (NIHSS) score measures stroke severity with good inter-observer reliability [51,52]. Both prestroke mRS and NIHSS scores are routinely available at most centers prior to the point of rt-PA administration. The Barthel Index measures ability to perform activities of daily living after a stroke [53]. Patients able to perform all activities of daily living such as eating, bathing, walking and using the toilet receive a score of 100. The Glasgow Outcome Scale is a global assessment of function [54], and ranges from 1 to 5 with a score of 1 indicating mild disability and a score of 5 death.

We calculated eight predictive scores for each patient: Stroke-Thrombolytic Predictive Instrument (Stroke-TPI), Dense cerebral artery or early infarct signs on CT, mRS, Age, Glucose level on admission, Onset to treatment time and NIHSS (DRAGON), Stroke Prognostication using Age and NIH Stroke Scale-100 (SPAN-100), Acute Stroke Registry and Analysis of Lausanne (ASTRAL), Post-thrombolysis Risk Score (PRS), Hemorrhage After Thrombolysis (HAT), baseline blood Sugar, Early infarct signs, Dense cerebral artery sign, Age and NIHSS (SEDAN) and Safe Implementation of Treatments in Stroke Symptomatic Intracerebral Hemorrhage (SITS-ICH). Detailed derivations of each score have been published elsewhere [19,37-42] and summarized in Table 1.

Statistical analysis:

Clinical parameters were presented as medians with interquartile ranges, as proportions, or as means with standard deviations and compared respectively using Mann-Whitney tests, two-sample tests of proportions or two-sample T-tests after checking for equal variance and using Welch's approximation for degrees of freedom [55]. Strength of association

between clinical scores and sICH was quantified using univariable logistic regression reporting odds ratios, with clinical scores as independent variables and sICH or 90-day outcome as the dependent variable. Goodness of fit or model calibration was assessed using Hesmer-Lemeshow χ^2 statistics, with $P > 0.05$ considered a statistically significant indicator of goodness-of-fit [56]. Predictive accuracy or model discrimination was calculated using areas under the receiver operating characteristic curve (AUROC). Standard errors were calculated by the DeLong method [57]. Sensitivity and specificity were assessed by AUROC analyses and by 2x2 table analyses. Agreement between sICH and discharge mRS ≥ 5 was assessed using linear weighted kappa, which measures agreement between two raters or metrics after excluding the effect of chance [58]. Clinical scores were internally validated using the nonparametric bootstrap method. This resampling technique draws with replacement, n observations from an n observation dataset whereby some of the original observations will appear once, some more than once and some not at all, and has been successfully used in previous studies predicting post-thrombolysis risk [37]. 50-200 replications are generally adequate for estimates of standard error, and thus for normal-approximation confidence intervals [59]. We used 250 replications in this study. Agreement between independent clinical scores was assessed using the concordance correlation coefficient, which is similar to the Kappa test but for continuous variables [60]. P values < 0.05 two-tailed were considered statistically significant. GraphPad Prism 6.0 software (GraphPad Software, La Jolla, California USA) and MATLAB R2014b (MathWorks, Natick, Massachusetts USA) were used for statistical figures. Statistical analyses were performed using STATA 14 I/C software package (StataCorp LP, College Station, Texas).

Results

Aim 1: Comparison of existing scores:

We first compared 8 scores for predicting sICH or poor outcome after rt-PA treatment in our internal dataset using AUROC [44]. Details of each score are summarized in Table 1, and a summary of patient characteristics in our internal and external datasets are summarized in Table 2. Despite considerable variability in complexity, we found no significant differences in AUROC for predicting sICH between any of the scores ($P > 0.05$). We therefore set out to derive a computationally simple score that retained predictive accuracy.

Aim 2: Derivation and validation of a novel score:

Aim 2A: Derivation of a novel score:

Using univariable logistic regression, we identified clinical parameters associated with sICH in our internal dataset (Table 3) [61]. Prestroke modified Rankin scale (mRS) scores, admission National Institutes of Health stroke scale (NIHSS) scores and platelet count were significant predictors of sICH. We combined these three parameters using multivariable logistic regression to form a clinical score TURNP (Thrombolysis risk Using mRS, NIHSS and Platelets). TURNP predicted sICH with odds ratio (OR) 2.7, 95% CI (1.6 - 4.6), $P < 0.001$. Model calibration testing yielded a Hosmer-Lemeshow χ^2 of 7.64 using 10 quantiles, $P = 0.47$ demonstrating good calibration. TURNP also demonstrated fair to good model discrimination with AUROC 0.78, 95% CI (0.64 - 0.92).

However in the multivariable TURNP model, platelet count yielded an OR of only 0.99 with β coefficient < 0.01. Furthermore, platelet counts require blood draws and laboratory testing that can introduce costly delays in the hyperacute stroke setting. Therefore

we considered a simpler model using only two parameters: TURN (Thrombolysis risk Using mRS and NIHSS). TURN predicted sICH with OR 2.7 (1.5 – 4.9), P < 0.001. Model calibration was still good with a Hosmer-Lemeshow χ^2 of 5.28 using 10 quantiles, P = 0.73. Likewise, model discrimination testing yielded an AUROC of 0.74, 95% CI (0.58 – 0.90), Table 4. Therefore for clinical and parsimonious reasons, we continued our analyses using the simpler score TURN.

Aim 2B: Validation of clinical score in external dataset:

We verified prediction of sICH by TURN using our external dataset [7]. TURN predicted sICH in the external dataset with OR 1.77, 95% CI (1.08 – 2.91), P < 0.001 and AUROC 0.65 (0.54 – 0.77). There was no statistically significant difference in AUROC between TURN and six other clinical scores for predicting sICH in the external dataset (Figure 1A).

TURN was developed using the classical case-control approach for identifying outcome predictors. We also assessed whether a cohort-based approach would yield clinically meaningful results. We distinguished between patients in years with sICH rates below the NINDS trial rate of 6.4% (low sICH cohort; 2010, 2011 and 2012) and patients in years with sICH rates above 6.4% (high sICH cohort; 2009 and 2013) using our internal dataset. sICH occurred in 2 out of 101 patients (2.0%) in the low sICH cohort versus 10 out of 109 patients (9.2%) in the high sICH cohort (P = 0.025). We confirmed that there were no differences in baseline demographic and clinical characteristics between patients in the low sICH cohort and patients in the high sICH cohort.

Patients in the low sICH cohort differed significantly from patients in the high sICH cohort in several markers of stroke severity, including percent of patients with visual field deficits (38.6% versus 24.8%, P = 0.03), percent with decreased levels of consciousness (62.4% versus 39.4%, P < 0.001), percent with hyperdense MCA signs (5% versus 13.8%, P = 0.03) and percent with early CT hypodensities (14.9% versus 29.4%, P = 0.01). We did not find any other statistically significant differences in stroke outcomes or stroke-associated fatalities between the two cohorts. We determined whether these significant differences between the patient cohorts could predict sICH in individual patients. We performed multivariable logistic regression using sICH as the dependent variable and visual field deficits, levels of consciousness, hyperdense MCA signs and early CT hypodensities as independent variables. This model predicted sICH with odds ratio 2.72, 95% CI (1.12 - 6.61), P = 0.03 but AUROC of 0.66, 95% confidence interval = 0.48 – 0.83. Thus, whereas the cohort-based approach shows promise for identifying predictors of sICH, this approach did not yield predictive accuracy as high as TURN.

Aim 3: Outcome prediction using clinical score:

Aim 3A: Prediction of brain swelling using TURN:

Next we assessed the ability of TURN to predict 24-hour brain swelling [62]. Cerebral edema independently predicts poor outcome after nonlacunar ischemic stroke [36], therefore predictors of cerebral edema may selectively identify ischemic stroke patients who are at risk for poor outcome and who may benefit from additional therapy using anti-edema medications.

We first confirmed the association between brain swelling and outcome. We used composite brain swelling defined as presence of at least two out of the three measures: edema, mass effect and midline shift [36]. In univariable analysis, baseline brain swelling was associated with sICH, 90-day severe outcome and 90-day mortality. However, after adjusting for covariates (baseline NIHSS, prestroke mRS, early CT hypodensity and decreased level of consciousness), none of these associations reached statistical significance. Conversely, 24-hour brain swelling and new swelling at 24 hours were significantly associated with ICH, sICH, 90-day severe outcome and 90-day mortality ($P < 0.05$) and these correlations remained statistically significant after adjusting for covariates (baseline NIHSS, admission blood glucose, HDMCA, decreased level of consciousness and visual field deficits for 24-hour swelling; and baseline NIHSS, HDMCA, decreased level of consciousness and visual field deficits for new swelling at 24 hours), thus confirming the association between brain swelling and adverse outcome.

Given this association, we investigated clinical parameters associated with adverse outcome as potential predictors of 24-hour brain swelling including age, diabetes, admission glucose, baseline NIHSS, prestroke mRS, HDMCA, early CT hypodensity, decreased level of consciousness and visual field defects. Using univariable logistic regression, admission glucose, baseline NIHSS, HDMCA, decreased level of consciousness and visual field deficits were significantly associated with 24-hour brain swelling. However, only three of these associations remained statistically significant after adjusting for covariates: HDMCA ($P = 0.05$), decreased level of consciousness ($P = 0.05$) and visual field deficits ($P < 0.001$). These three parameters are thus independent predictors of 24-hour brain swelling after IV thrombolysis.

Next we investigated whether TURN could predict brain swelling after IV thrombolysis. Prediction of baseline brain swelling by TURN did not reach statistical significance (OR 2.21, P = 0.07), consistent with our finding that baseline brain swelling was not significantly associated with any measures of adverse outcome. Instead, TURN predicted 24-hour brain swelling (OR 2.5, P < 0.001) and new swelling at 24 hours (OR 2.1, P < 0.001). To rule out possible contributions of ICH to measures of brain swelling such as mass effect and midline shift, we also verified that TURN directly predicted 24-hour edema (OR 2.5, P < 0.001) and new edema at 24 hours (OR 2.2, P < 0.001) with nearly identical results. In patients who did not receive IV thrombolysis, TURN similarly predicted 24-hour brain swelling (OR 3.88, P < 0.001) and new swelling at 24 hours (OR 3.49, P < 0.001) but not baseline swelling (OR 1.29, P = 0.53) adding robustness to its predictive ability. We further assessed for agreement between TURN and 24-hour brain swelling or new brain swelling at 24 hours using areas under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow statistics. TURN predicted 24-hour brain swelling with AUROC of 0.69, 95% CI (0.63, 0.75) and Hosmer-Lemeshow χ^2 of 5.14 using 10 groups, P = 0.74 demonstrating statistically significant agreement. Likewise, TURN predicted new brain swelling at 24 hours with AUROC of 0.67, 95% CI (0.61, 0.73) and Hosmer-Lemeshow χ^2 of 6.9 using 10 groups, P = 0.55, confirming modest but statistically significant agreement.

In order to compare prediction of brain swelling between TURN and existing scores, we performed univariable logistic regression and AUROC analyses using TURN and six other scores for predicting outcome after IV thrombolysis [44], including Stroke-TPI, DRAGON, SPAN-100, ASTRAL, HAT and SEDAN. There was no statistically significant difference in AUROC for prediction of baseline brain swelling between TURN and the other

six scores. AUROC for 24-hour brain swelling was also significantly higher for TURN than for SPAN-100 (AUROC 0.61, P = 0.05) and SEDAN (AUROC 0.59, P = 0.02). Likewise, TURN predicted new brain swelling at 24 hours with an OR greater than DRAGON (OR 1.32, P = 0.02), SPAN-100 (OR 1.02, P < 0.001), ASTRAL (OR 1.07, P < 0.001) and SEDAN (OR 1.21, P = 0.01), and AUROC for TURN was higher than for SEDAN for predicting new brain swelling at 24 hours (AUROC 0.56, P = 0.01). None of the other scores predicted 24-hour brain swelling or new swelling at 24 hours with odds ratio or AUROC higher than TURN (Figure 1B).

Aim 3B: Prediction of adverse outcome using TURN:

Next we assessed for correlation between sICH and 90-day severe outcome defined as mRS ≥ 5, Barthel Index < 60 and Glasgow Outcome Scale > 2 using univariable logistic regression with sICH as the independent variable. sICH predicted 90-day mRS ≥ 5 with odds ratio 10.1, 95% CI (4.0, 25.6), P < 0.001. sICH also predicted 90-day Barthel Index < 60 with odds ratio 12.2, 95% CI (4.1, 36.9), P < 0.001, and Glasgow Outcome Scale > 2 with odds ratio 14.5, 95% CI (4.2, 49.7), P < 0.001.

We verified agreement between sICH and 90-day severe outcome using linear weighted Kappa [58]. We found 80% agreement between sICH and 90-day mRS ≥ 5, Kappa 0.27, P < 0.0001, 72% agreement with 90-day Barthel Index < 60, Kappa 0.22, P < 0.0001, and 69% agreement with 90-day Glasgow Outcome Scale > 2, Kappa 0.21, P < 0.0001. Therefore we established a direct correlation between sICH and 90-day severe outcome, with the strongest correlation between sICH and 90-day mRS ≥ 5.

We next assessed the ability of TURN to predict 90-day severe outcome using univariable logistic regression. TURN predicted mRS ≥ 5 with odds ratio 5.73, 95% CI (3.60, 9.10), P < 0.001. Goodness of fit was assessed as Hosmer-Lemeshow χ^2 of 3.63 using 10 groups, P = 0.89, demonstrating good agreement. We found an AUROC of 0.83, 95% CI (0.77, 0.89), confirming good overall accuracy.

We verified the ability of TURN to predict 90-day severe outcome using the Barthel Index (BI) and the Glasgow Outcome Score (GOS). TURN predicted 90-day BI < 60 with odds ratio 5.07, 95% CI (3.35, 7.67), P < 0.001. Likewise, TURN predicted 90-day GOS > 2 with odds ratio 5.17, 95% CI (3.42, 7.80), P < 0.001. Goodness of fit analysis yielded a Hosmer-Lemeshow χ^2 of 7.93 for 90-day BI < 60 using 10 groups, P = 0.44, and Hosmer-Lemeshow χ^2 of 9.0 for 90-day GOS > 2 using 10 groups, P = 0.34, indicating good agreement. TURN also predicted 90-day BI < 60 with AUROC of 0.81, 95% CI (0.76, 0.86), and GOS > 2 with AUROC of 0.81, 95% CI (0.76, 0.86) verifying good overall accuracy.

Next we compared TURN to six existing scores for predicting 90-day outcomes. TURN predicted 90-day mRS ≥ 5 with AUROC significantly higher than SPAN-100 and SEDAN (P < 0.05) (Figure 1F). Similar results were obtained using 90-day BI < 60 and 90-day GOS > 2 (Figure 1D-E). None of the other scores yielded an AUROC significantly higher than TURN, demonstrating its strength of association and predictive accuracy compared to existing scores.

Aim 3C: Prediction of 90-day mortality using TURN:

We also investigated whether TURN predicts 90-day mortality after IV thrombolysis. Since TURN predicted 24-hour brain swelling, and 24-hour brain swelling is associated with

90-day mortality, we hypothesized that TURN would predict 90-day mortality. Using univariable logistic regression, we found a statistically significant association between TURN and 90-day mortality (OR 5.32, $P < 0.0001$). Agreement was further confirmed by AUROC analysis and by Hosmer-Lemeshow statistics. TURN yielded an AUROC of 0.82, 95% CI (0.76, 0.88), and a Hosmer-Lemeshow χ^2 of 2.94 using 10 groups, $P = 0.94$ confirming good agreement.

We further assessed for etiology of 90-day mortality after IV thrombolysis. As expected, TURN predicted 90-day cardiovascular mortality (OR 3.84, $P < 0.001$) and 90-day cerebrovascular mortality (OR 3.50, $P < 0.001$). However, TURN did not predict 90-day mortality due to infectious causes (OR 1.52, $P = 0.16$), indicating specificity in its predictive ability.

We compared the ability of TURN to predict 90-day mortality to the other six scores for predicting post-thrombolysis outcome [44]. TURN predicted 90-day mortality with an odds ratios higher than for DRAGON (OR 2.09, $P = 0.02$), SPAN-100 (OR 1.09, $P = 0.002$), ASTRAL (OR 1.17, $P = 0.002$) and SEDAN (OR 2.1, $P = 0.02$). AUROC for TURN was also significantly higher than for SEDAN (AUROC 0.7, $P = 0.02$, Figure 1C). None of the other scores predicted 90-day mortality with odds ratios or AUROC significantly higher than TURN.

Aim 4: Expansion of clinical utility of clinical score:

To improve the clinical utility of TURN, we developed and tested a mobile application Risk rtPA based on TURN for predicting 90-day outcome after rt-PA treatment [63]. Risk rtPA requires only prestroke mRS scores and admission NIHSS scores for each

patient, and predicts both severe outcome (90-day mRS ≥ 5) and excellent outcome (90-day mRS ≤ 1) using the inverse logit of TURN and –TURN as follows: TURN predictor for severe outcome = $\frac{e^{TURN}}{(1+e^{TURN})}\%$ and –TURN predictor for excellent outcome = $\frac{e^{-TURN}}{(1+e^{-TURN})}\%$. TURN and –TURN were calculated as follows: TURN = -4.65 + (mRS * 0.27) + (NIHSS * 0.10), and –TURN = 4.65 – (mRS * 0.27) - (NIHSS * 0.10). The response of Risk rtPA followed an S-shaped pattern over the range of possible prestroke mRS scores and admission NIHSS scores as expected from the inverse logit function (Figure 2). Risk rtPA also returned predictions of severe outcome for a range of hypothetical patients with varying clinical characteristics (Figure 3), demonstrating broad applicability.

After AUROC analysis and using 2x2 tables, we selected a cutoff of 3.5 for severe outcome and a cutoff of 97 for excellent outcome for Risk rtPA. At these cutoffs, Risk rtPA predicted severe outcome with sensitivity of 94.4% but specificity of 52.2%, and predicted excellent outcome with specificity of 83.9% but sensitivity of 61.2%. These cutoffs were chosen to maximize sensitivity for predicting severe outcome and to maximize specificity for predicting excellent outcome to ensure that patients deemed safe for rt-PA therapy are at minimal risk for sICH and poor outcome. Thus, Risk rtPA brings accurate but computationally simple prediction of outcomes using TURN to the bedside, and enables real-time prediction of 90-day outcome in ischemic stroke patients being evaluated for anti-thrombolytic therapy.

Testing of supplemental hypotheses:

We tested whether mRS scores at patient discharge could serve as a clinically useful surrogate for long-term outcome [64]. First we assessed the correlation between discharge mRS

scores and sICH. There was 83.4% agreement between patients with sICH and discharge mRS ≥ 5 (kappa 0.22, P < 0.001). Next we performed logistic regression and AUROC analysis using discharge mRS ≥ 5 as the dependent variable and each of the eight clinical scores as independent variables. All clinical scores showed good agreement with discharge mRS ≥ 5 (ROC area > 0.7). The two scores showing the best agreement with discharge mRS ≥ 5 were Stroke-TPI with AUROC 0.86, 95% CI (0.80, 0.94) and ASTRAL with AUROC 0.85, 95% CI (0.79, 0.93), with odds ratios of 1.3, 95% CI (0.86, 1.73) and 0.17, 95% CI (0.12, 0.23) respectively. SPAN-100 showed the least agreement with discharge mRS ≥ 5 with AUROC 0.71, 95% CI (0.62, 0.79) and odds ratio 2.09, 95% CI (1.30, 2.87). Therefore, whereas most clinical scores agreed with discharge mRS, this measure does not show sufficient correlation with sICH to warrant routine use as a surrogate measure of long-term outcome.

Another question we addressed was whether the time of treatment impacted outcome of ischemic stroke patients receiving rt-PA therapy [65]. We defined on- and off-hour patient cohorts based on time of symptom onset according to published criteria [66]. Briefly, the on-hour cohort consisted of patients developing symptoms between 8am and 6pm Monday through Friday. Patients in the off-hour cohort developed symptoms Monday through Friday 6pm to 8am, weekends, Memorial Day, Labor Day, Independence Day, Thanksgiving (Wednesday 6pm through the following Monday 8am), Christmas (December 24th and 25th) and New Year's Day (December 31st and January 1st).

Patients in the on-hour cohort were older (mean age 73.3 versus 68.2, P = 0.03), had significantly more previous strokes or transient ischemic attacks (TIAs) (27.6% versus 16.3%, P = 0.05) and had higher average pre-stroke mRS scores (1.0 versus 0.6, P = 0.04)

than off-hour patients. We found no other statistically significant difference in baseline clinical characteristics between patients in the on- versus off-hour cohorts.

On-hour cohort patients did not have a significantly different median onset-to-treatment time compared to patients in the off-hour cohort (137 minutes versus 145 minutes, P = 0.53), nor were there differences in the percentage of patients treated after 3 hours or after 4.5 hours (16.1% versus 26%, P = 0.09; and 1.1% versus 4.9%, P = 0.14 respectively). We assessed stroke severity between on- and off-hour cohort patients and found no significant differences in mean NIHSS scores (12.4 versus 11.3, P = 0.27) or in percentages of patients with visual field deficits (34.5% versus 29.3%, P = 0.42), decreased levels of consciousness (57.5% versus 45.5%, P = 0.09), early CT hypodensities (26.4% versus 19.5%, P = 0.24) or the hyperdense MCA sign on imaging (26.4% versus 19.5%, P = 0.24).

We also compared clinical outcomes between patients in the on- and off-hour cohorts and found no significant differences in the percentage of patients developing ICH (17.2% versus 20.3%, P = 0.58) or sICH (4.6% versus 6.5%, P = 0.56). On-hour cohort patients did not have significantly different mean change in mRS scores (2.4 versus 2.8, P = 0.16), and did not have significantly different mean discharge mRS scores compared to off-hour patients (3.4 versus 3.4, P = 0.85). Furthermore, we found no statistically significant differences in stroke fatality between the on- and off-hour patient cohorts (9.2% versus 9.8%, P = 0.89). Therefore, despite differences in baseline clinical characteristics, there were no significant time-dependent differences in stroke severity or outcome in the internal patient dataset from our primary stroke centers.

Discussion

Development and validation of TURN:

In this project we described TURN, a new clinical predictor of sICH, poor outcome and 90-day mortality in ischemic stroke patients receiving IV thrombolysis. Despite its computational simplicity, TURN predicts outcome with comparable or better accuracy than existing scores. We further developed and tested a mobile application Risk rtPA for ready assessment of ischemic stroke patients at the bedside.

At least six of the clinical scores we evaluated in this series require the baseline NIHSS score for their calculation (Table 1). DRAGON also requires the prestroke mRS score, therefore it is equivalent to TURN plus four other parameters: age, hyperdense middle cerebral artery sign or early CT infarct, blood glucose and symptom onset-to-treatment duration [18]. The other five clinical scores do not require the prestroke mRS score but rather evaluate a number of other baseline parameters such as history of diabetes or blood glucose for HAT [41], or early stroke findings such as level of consciousness and visual field deficits for ASTRAL [19].

It is perhaps surprising that TURN predicts outcome as well as or better than some of the other scores given its simplicity. The performance of TURN is likely due to its reliance on the prestroke mRS score. The prestroke mRS score is influenced by a patient's age, prior stroke, existing comorbidities, physical or mental disabilities and coping mechanisms. Interestingly, individual contributors to the prestroke mRS score such as age, hypertension, diabetes and prior stroke were not independent predictors of sICH [61]. In our view, the prestroke mRS score can be considered similarly to frailty as a measure of physiological vulnerability or the gestalt of a patient's biopsychosocial stressors normalized to their ability

to cope with such stressors [67], and teasing out individual comorbidities does not appear to increase predictive ability.

In spite of this, we believe our model can be improved by going beyond the prestroke mRS score. The prestroke mRS score suffers from limited interobserver reliability due in part to its reliance on patient or family-member narratives which may not be reliably available at the time of stroke [68]. Other markers of overall function such as the Rockwood frailty index, Charlson comorbidity index and need for caregivers have greater interobserver reliability, and may increase the predictive ability of our score if substituted for the prestroke mRS score. However many of these markers also rely on family narratives which limits their utility in the acute stroke setting. Biomarkers such as plasma MMP-9 have been shown to correlate with cardiovascular risk factors in the general population [69]. Future studies are needed to investigate biomarkers as surrogate measures of baseline functional status.

Prediction of brain swelling:

We demonstrated the ability of TURN to predict 24-hour cerebral edema in ischemic stroke patients. Cerebral edema is associated with sICH and poor outcome after ischemic stroke. Therefore, clinical scores that predict cerebral edema may be helpful in screening for ischemic stroke patients who are at increased risk for poor outcome.

Blood-brain barrier (BBB) breakdown occurs early in ischemic stroke, and contributes to vasogenic edema. BBB breakdown is primarily due to increased matrix metalloproteinase-9 (MMP-9) and cellular fibronectin after ischemic stroke [70]. As a result, early vessel leakiness has been proposed as a prognostic marker for sICH [71-74]. Rt-PA administration may further exacerbate BBB leakiness by directly upregulating MMP-9 [75,76]

and LDL receptor-related protein [77]. Indeed, both the NINDS part 1 trial and the ECASS1 trial reported more brain edema in rt-PA treated patients compared to controls [7,9], suggesting that increased cerebral edema occurs by at least two separate mechanisms in ischemic stroke patients receiving rt-PA treatment.

Cerebral edema is associated with poor outcome after rt-PA treatment. It was noted in the NINDS rt-PA trial that cerebral edema occurred more frequently in patients with intracranial hemorrhage, however this difference was not quantified [7]. We elaborated on this finding and demonstrated that 24-hour edema including edema at 24 hours not previously seen at baseline is independently associated with ICH, sICH, 90-day severe outcome and 90-day mortality. This result is consistent with studies from our group and others showing that cerebral edema independently predicts worse outcome after ischemic stroke [36,78]. Ongoing efforts seek to address cerebral edema as a therapeutic target using Glyburide, an agent that may decrease plasma MMP-9 levels and vasogenic edema in ischemic stroke patients [79].

Given the association between cerebral edema and poor outcome, it is perhaps not surprising that clinical scores developed to predict post-thrombolysis sICH or poor outcome also predict 24-hour cerebral edema, albeit modestly. Likewise, the three factors we identified after multivariable logistic regression as independent predictors of 24-hour edema (HDMCA, decreased level of consciousness and presence of visual field deficits) have previously been identified as sICH predictors after IV thrombolysis [80].

TURN is calculated using prestroke mRS scores and admission NIHSS scores, suggesting that these two parameters are associated with development of edema within 24 hours. The prestroke mRS score indicates a patient's baseline ability to look after themselves in daily life, and shows moderate to good inter-observer agreement [49,50]. The admission

NIHSS score measures initial stroke severity and also shows moderate to excellent inter-rater reliability [51,81]. The link between these two parameters and cerebral edema is currently unclear. Plasma MMP-9 levels are independently associated with cardiovascular risk factors in the general population [69], and may thus indirectly correlate with baseline functional status. Likewise, plasma MMP-9 levels 48 hours after ischemic stroke are significantly associated with baseline NIHSS scores [82]. Given the potential role of MMP-9 in the pathogenesis of cerebral edema, it is tempting to speculate that prestroke mRS scores and baseline NIHSS scores are mechanistically linked to development of cerebral edema after ischemic stroke. However, neither parameter was independently associated with 24-hour edema in our dataset after adjusting for covariates. Further studies are needed to help clarify these findings.

One limitation of our study is its reliance on CT scans from the 1995 NINDS rt-PA trial. Advances in CT technology since the publication of the NINDS rt-PA trial may have affected the interpretation of our results. We expect newer CT scanning and reconstruction techniques to be more accurate, and markers of brain swelling more readily detected. Therefore, any limitations in the CT technology used in the NINDS rt-PA trial would tend to bias our results towards the null. Newer scans may show even stronger associations between brain swelling and adverse outcome, and TURN may better predict brain swelling as seen on newer scans.

Risk rt-PA, a mobile application based on TURN:

We extended the clinical utility of TURN using a mobile application readily available at the bedside. To our knowledge, iSCORE remains the only risk calculator available on the iOS platform. We were unable to directly compare iSCORE to TURN in previous studies due

to unavailability of required data. Nevertheless, iSCORE has been estimated in the NINDS dataset [83], and was found to predict sICH with higher overall accuracy compared to TURN as measured by AUROC (0.75 versus 0.65 for TURN), but lower accuracy for detecting 90-day adverse outcome (mRS ≥ 4; AUROC 0.67 versus 0.77 for TURN). iSCORE benefits from validation in several large patient datasets [38,84,85]. However iSCORE relies on 8 clinical parameters including presence of lacunar infarcts and history of renal dialysis, which may not be routinely accessible in the acute stroke setting, whereas TURN requires only two readily available clinical parameters. Risk rtPA therefore provides a comparatively accurate but computationally simpler alternative for estimating risk of severe outcome at the bedside.

One limitation of Risk rtPA is its non-linear response at extreme values for mRS and NIHSS. This is largely due to a limitation of the inverse logit function. The logit function forms the basis of model fitting using univariable and multivariable logistic regression. The inverse logit function or logistic function describes the probability of an event given weighted exposures. It has the same general form as the log odds function from linear regression but has a sigmoidal or S-shaped profile ranging from 0 to 1 [86]. It is therefore not surprising that the output of our mobile application becomes increasingly nonlinear as we approach the limits of input values. Nevertheless we demonstrated its functionality over a wide range of clinically relevant values.

We based our cutoffs for outcome probabilities on maximal sensitivity for predicting severe outcome in order to minimize the number of false negatives, i.e. patients who are deemed safe for treatment but experience severe outcome. Likewise, for predicting excellent outcome, we preferentially maximized specificity and therefore minimized number of false positives, which in this case also means patients who are deemed safe but experience severe

outcome. Therefore, although our objective was to rule-in all eligible patients who may receive rt-PA therapy safely, we chose conservative cutoff values in order to maintain a sufficient margin of safety.

Study limitations:

Our study suffers from a number of limitations. It is a retrospective study with relatively small sample sizes, which may have limited our ability to detect statistically significant differences between the clinical scores we tested. Future studies are needed to verify our results using large prospective datasets. Another limitation of our study is our singular use of the NINDS trial definition of sICH [7], which may have placed scores derived using other sICH definitions at a relative disadvantage [44]. However, 3 scores used in our study were derived using the NINDS definition [39-41], and this definition captures a greater percentage of hemorrhages compared to the European-Australasian Cooperative Acute Stroke Study (ECASS) II and SITS-Monitoring Study (SITS-MOST) definitions [87], which require more extensive neurological worsening from baseline (i.e. NIHSS $\geq$ 4 points). A recent comparison of sICH definitions found no clear consensus on the best sICH definition in terms of predictive value and interrater agreement [87], and other studies comparing clinical scores using multiple sICH definitions have found no meaningful differences between their results across sICH definitions [43,88].

Conclusions and future directions

We developed and tested TURN a simple clinical score to predict sICH and poor outcome after rt-PA treatment in ischemic stroke patients. A mobile application Risk rtPA is available for prognostication at the bedside. A large multicenter prospective study is being planned to verify our findings in an independent patient cohort. The study design will be a pragmatic randomized clinical trial comparing risk assessment by a clinician alone versus a clinician plus the Risk rtPA mobile application in a real-world clinical setting. These results may bring Risk rtPA closer to incorporation into routine clinical practice for assessment of ischemic stroke patients being evaluated for rt-PA therapy.

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Tables and figures

Score	Components
Stroke-TPI	Age, NIHSS, Glucose
DRAGON	Age, prestroke mRS, HDMCA or early CT infarct, glucose, OTT, admission NIHSS
SPAN-100	Age, admission NIHSS
ASTRAL	Age, admission NIHSS, OTT, decreased level of consciousness, visual field defects, glucose
MSS	Age, admission NIHSS, glucose, platelets
HAT	DM or glucose, admission NIHSS, early CT hypodensity
SEDAN	Age, NIHSS, glucose, HDMCA sign, early CT infarct
SITS-ICH	Age, weight, hypertension, Aspirin/Clopidogrel, admission NIHSS, systolic BP, glucose, OTT

Table 1. Patient characteristics used to derive clinical scores. NIHSS = National Institute of Health Stroke Scale score, mRS = modified Rankin Scale, HDMCA = Hyperdense Middle Cerebral Artery sign, OTT = Onset To Treatment interval, DM = Diabetes Mellitus, CT = Computed Tomography, BP = Blood Pressure. 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. HAT = Hemorrhage After Thrombolysis.

	YNHH (n = 210)	NINDS (n = 303)	P value
Patient characteristics			
Mean age	70.3	67.5	0.033*
% Males	48.6	57.1	0.057
Mean weight (lbs)	181.1	167.9	0.006*
Mean systolic BP (mmHg)	156.5	159.8	0.183
% Hypertension	73.8	66.6	0.078
% on Aspirin	38.6	40.7	0.625
Mean admission glucose (mg/dL)	133.3	148.9	0.006*
% Diabetic	23.3	21.9	0.708
% Previous stroke/TIA	21.9	27.6	0.087
Median prestroke mRS score	0	0	<0.001*
Median OTT (mins)	140	90	<0.001*
Stroke severity			
Median NIHSS score	10	14	<0.001*
% Visual field deficits	31.4	54.5	<0.001*
% Decreased LOC	50.5	32.7	<0.001*
% Hyperdense MCA sign	9.5	88.3	<0.001*
% Early CT Hypodensities	22.4	8.5	<0.001*
Stroke outcomes			
% ICH	19.0	15.4	<0.001*
% sICH	5.7	8.0	0.320

% Fatalities	9.5	2.9	0.001*

Table 2. Demographic and clinical characteristics, stroke severity and outcomes in the derivation dataset (YNHH) compared to the external validation dataset (NINDS). P values from Mann-Whitney tests, two-sample tests of proportions and two-sample t tests after checking for equal variance. * P values < 0.05 two-tailed considered statistically significant. TIA = transient ischemic attack, mRS = modified Rankin Scale, OTT = onset-to-treatment duration, NIHSS = National Institute of Health Stroke Scale, LOC = level of consciousness, MCA = middle cerebral artery, CT = computed tomography, ICH = intracerebral hemorrhage, sICH = symptomatic intracerebral hemorrhage.

	Odds ratio	95% Confidence Interval		z	P > |z|
Patient characteristics					
Age	1.04	0.99	1.09	1.71	0.09
Gender	0.33	0.09	1.27	-1.61	0.11
Hypertension	4.13	0.52	32.72	1.34	0.18
Aspirin	1.64	0.51	5.27	0.83	0.41
Diabetes	1.10	0.29	4.24	0.14	0.89
Previous stroke/TIA	1.72	0.55	5.39	0.92	0.36
Labs on admission					
Weight (lbs)	1.00	0.98	1.01	-0.67	0.50
Systolic BP (mmHg)	1.00	0.98	1.02	-0.05	0.96
Admission glucose (mg/dL)	1.00	0.99	1.01	0.02	0.98
Platelets (1000/mcL)	0.99	0.98	1.00	-2.05	0.04*
Prestroke mRS score	1.54	1.09	2.18	2.44	0.02*
OTT (mins)	0.99	0.98	1.01	-0.96	0.34
Stroke severity					
NIHSS score	1.13	1.05	1.22	3.08	0.002*
Visual field deficits	1.10	0.32	3.78	0.15	0.88
Decreased LOC	2.04	0.60	7.00	1.13	0.26
Hyperdense MCA sign	3.55	0.88	14.36	1.78	0.08
Early CT Hypodensities	1.80	0.52	6.27	0.93	0.35

Table 3. Results of univariate logistic regression identifying predictors of sICH in the derivation dataset. *P values < 0.05 two-tailed considered statistically significant. sICH = symptomatic intracerebral hemorrhage, TIA = transient ischemic attack, BP = blood pressure, mRS = modified Rankin scale, OTT = onset-to-treatment time, NIHSS = National Institute of Health stroke scale, LOC = level of consciousness, MCA = middle cerebral artery, CT = computed tomography.

TURNP	
Clinical parameters	**β coefficients**
Constant term	-2.346
Baseline NIHSS score	0.102
Prestroke mRS score	0.298
Platelet count	-0.0096
Prediction of sICH	
Odds ratio	2.7 (1.6, 4.6)
AUROC	0.78 (0.64, 0.92)

TURN	
Clinical parameters	**β coefficients**
Constant term	-4.648
Baseline NIHSS score	0.104
Prestroke mRS score	0.270
Prediction of sICH	
Odds ratio	2.7 (1.5, 4.9)
AUROC	0.74 (0.58, 0.90)

Table 4. Comparison of TURNP and TURN in the derivation dataset: results of multivariate logistic regression reporting log-odds ratios (β coefficients). Dependent variable sICH, independent variables NIHSS score, prestroke mRS score and platelet count. sICH = symptomatic intracerebral hemorrhage, NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin Scale, TURNP = Thrombolysis risk Using mRS, NIHSS and Platelets, TURN = Thrombolysis risk Using mRS and NIHSS. AUROC = area under the receiver operating characteristic curve.

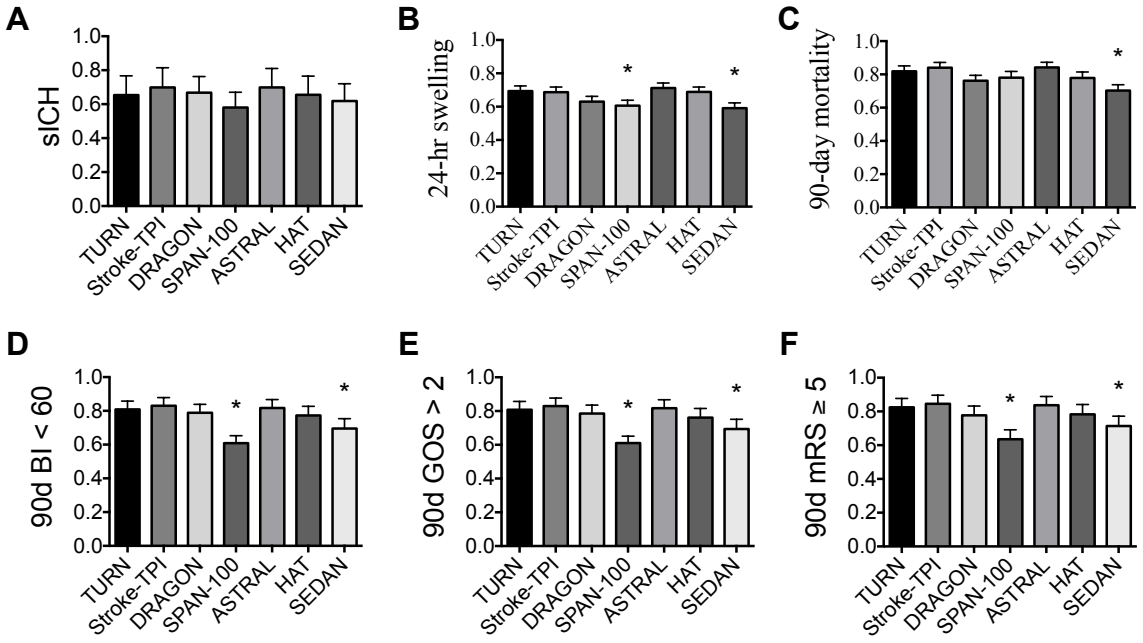

Figure 1. AUROC values for prediction of outcome in the external validation dataset. TURN compared to other clinical scores using unequal variance 2-sample T-tests with Welch's approximation for degrees of freedom. * P values < 0.05 two-tailed considered statistically significant. AUROC = area under the receiver operating characteristic curve. sICH = symptomatic intracerebral hemorrhage. BI = Barthel index. GOS = Glasgow outcome score. mRS = modified Rankin scale. 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. HAT = Hemorrhage After Thrombolysis.

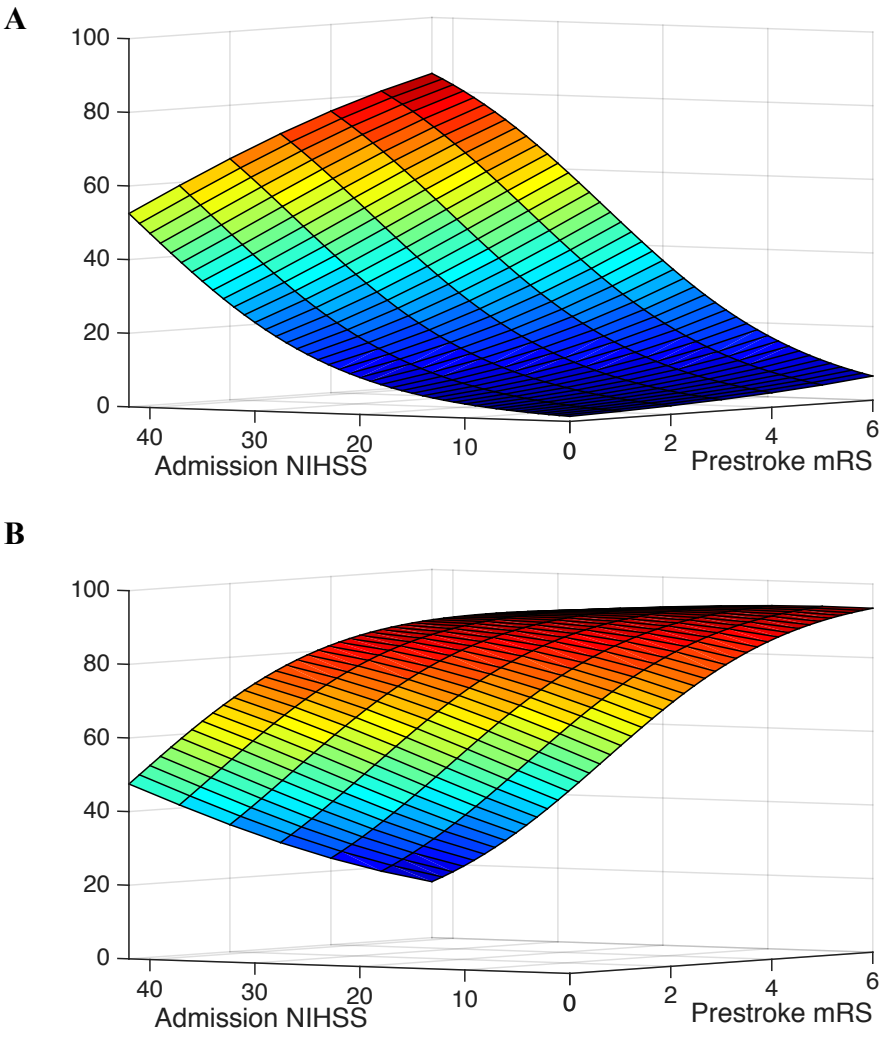

Figure 2. Expected response curves using Risk rtPA mobile application to predict severe and excellent outcome. Severe and excellent outcome defined as 90-day mRS scores ≥ 5 and 90-day mRS ≤ 1 scores respectively. X-axis prestroke mRS score; Y-axis admission NIHSS score; Z-axis TURN or –TURN predictors predicting 90-day outcome. **A**. Prediction of severe outcome for range of prestroke mRS scores and admission NIHSS scores. **B**. Prediction of excellent outcome for range of prestroke mRS scores and admission NIHSS scores. mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale.

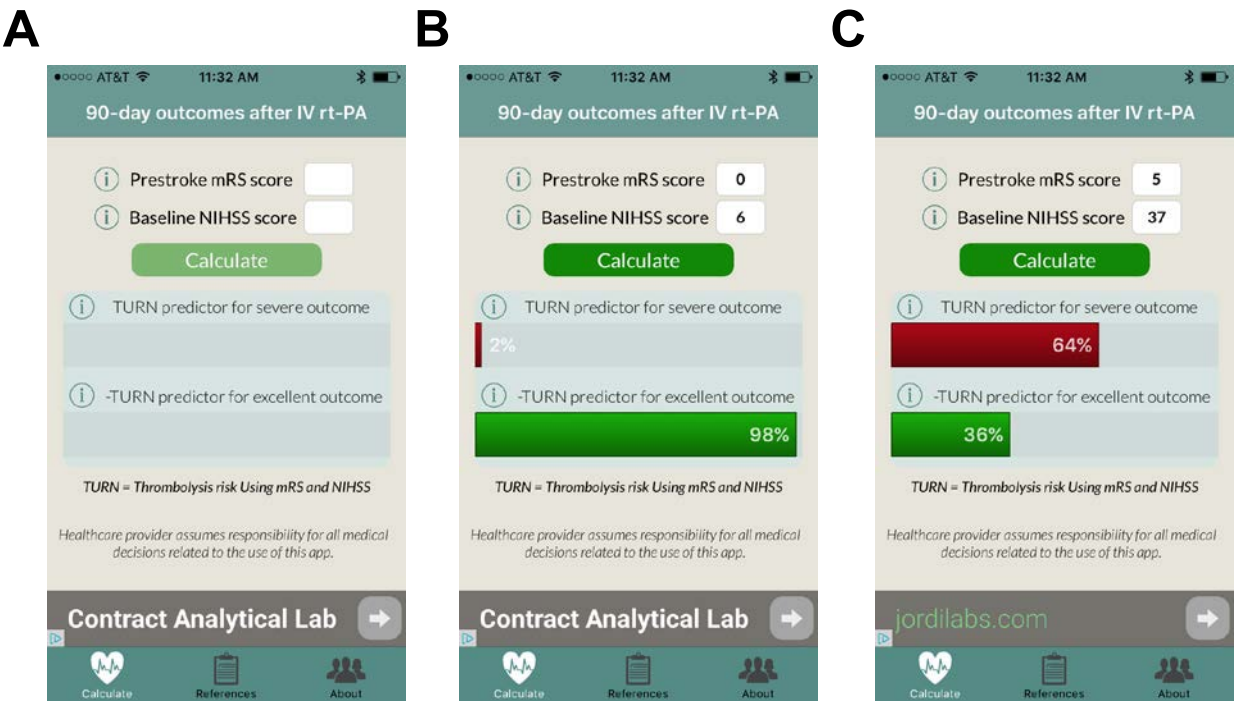

Figure 3. Risk rtPA mobile application for predicting 90-day outcome after IV rt-PA therapy. **A**. Inputs are prestroke mRS score and baseline NIHSS score. Outputs are TURN predictor for severe outcome and –TURN predictor for excellent outcome. Severe 90-day outcome defined as 90-day mRS scores ≥ 5. Excellent outcome defined as 90-day mRS scores ≤ 1. **B**. Hypothetical patient #1 with a prestroke mRS score of 0 and baseline NIHSS score of 6 received a TURN predictor of 2 a –TURN predictor of 98. **C**. Hypothetical patient #2 with a prestroke mRS score of 5 and baseline NIHSS score of 37 received a TURN predictor of 64 and a –TURN predictor of 36. mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale.