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Optimizing Prediction Scores for Poor Outcome After Intra-arterial Therapy in Anterior Circulation Acute Ischemic Stroke

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Abstract

Background and Purpose—Intra-arterial therapy (IAT) promotes recanalization of large artery occlusions (LAO) in acute ischemic stroke (AIS). Despite high recanalization rates, poor clinical outcomes are common. We attempted to optimize a score that combines clinical and imaging variables to more accurately predict poor outcome after IAT in anterior circulation occlusions.

Methods—AIS patients undergoing IAT at UT-Houston for LAO (MCA or ICA) were reviewed. Independent predictors of poor outcome (modified Rankin Scale 4-6) were studied. External validation was conducted on IAT-treated patients at Emory University.

Results—163 patients were identified at UT Houston. Independent predictors of poor outcome (p values ≤0.2) were identified as score variables using sensitivity analysis and logistic regression. Houston Intra-arterial Therapy 2 (HIAT2) score ranges 0-10: age (≤59=0, 60-79=2, ≥80 years=4), glucose (<150=0, ≥150=1), NIHSS (≤10=0), 11-20=1, ≥21=2), ASPECTS (8-10=0, ≤7=3). Patients with HIAT2 ≥5 were more likely to have poor outcomes at discharge (OR:6.43, 95%CI: 2.75-15.02, p<.001). After adjusting for reperfusion (TICI≥2b) and time from symptom onset to recanalization, HIAT2 ≥5 remained an independent predictor of poor outcome (OR:5.88, 95%CI 1.96-17.64, p=0.02). Results from Emory's cohort (198 patients) were consistent; patients with HIAT 2 score ≥5 had 6 times greater odds of poor outcome at discharge and at 90 days. HIAT2 outperformed other previously published predictive scores.

Conclusion—The HIAT2 score, which combines clinical and imaging variables, performed better than all previous scores in predicting poor outcome after IAT for anterior circulation LAO.

Keywords

Acute ischemic stroke; thrombolysis; Intra-arterial Therapy; HIAT2; Prediction scores

Introduction

In acute ischemic stroke (AIS), persistent large artery occlusion (LAO) often causes severe neurologic deficits or death. Current therapeutic strategies focus on recanalization as the most important factor to reduce damaged tissue and minimize neurologic deficits. Intravenous (IV) t-PA is the only FDA approved therapy to improve outcome for AIS.[1-2] However; stroke patients with proximal LAO have low recanalization rates with IV t-PA alone, leading to poor functional outcome despite treatment.[3-4]

Intra-arterial therapy (IAT) has been an approach to recanalize LAO for 3 decades now.[5-6] Intravenous therapy followed immediately by IAT in selected cases may be safe,[7-8] but only one controlled randomized trial of intra-arterial fibrinolysis has been conducted, showing significant improvement in clinical outcome[9] and recent trials have not shown IAT to confer an increased benefit compared with IV t-PA or as an adjunctive approach to IV t-PA.[10-11-12] IAT is resource intensive,[13] requires specialized infrastructure and personnel.

Decisions to pursue IAT are clinician-dependent and rest upon a number of different factors. In 2009 and in collaboration with UCLA, our group developed the Houston Intra-arterial therapy (HIAT) score which estimates the chances of poor outcome after IAT.[14] This score was developed on the Houston database and validated on the UCLA database. The score is entirely based on clinical variables (age, admission glucose and admission NIHSS). There are, however, a number of imaging factors that may correlate with outcome after fibrinolysis.

The Alberta Stroke Program Early CT Score (ASPECTS) has demonstrated utility in selecting candidates for recanalization strategies using a simple noncontrast head CT (NCCT).[15] Patients with an ASPECTS ≤7 are unlikely to have a good outcome despite treatment. While numerous studies suggest the utility of magnetic resonance imaging (MRI),[16-18] CT angiography (CTA)[19-21] and CT perfusion[22] findings in identifying patients who have poor outcome after thrombolysis, CT is more readily available, more efficient, requires the least technology, and remains easier to interpret as well as the only validated screening tool for patients undergoing IAT.

We hypothesized that the HIAT score could be improved to better select patients for IAT by inclusion of simple imaging variables such as ASPECTS and CBS (clot burden score). We first combined imaging and clinical variables to optimize a score that would better predict poor outcome after IAT for AIS. We then compared the performance of the new score against previous predictive scoring systems that relied either on clinical or imaging variables in patients undergoing IAT.

Methods

Study population

This retrospective cohort utilized information from an ongoing, prospectively collected stroke registry. The registry contains information on consecutive stroke patients presenting to our tertiary stroke academic center at UT-Houston. We retrospectively reviewed AIS patients from 01/03 to 05/11 who underwent IAT with a final diagnosis of a large vessel anterior circulation occlusion (MCA or ICA). All subjects included in our sample underwent clinical assessment and an acute NCCT followed by CTA of the head and neck. Exclusion criteria were pre-morbid modified Rankin Scale (mRS) score >2, documented "early recanalization" on CTA or transcranial doppler (TCD) prior to IAT (if the patient had received IV t-PA), IAT >8 hours or participation in clinical trials that involve the testing of other investigational therapies. (Fig 1) shows patient enrollment flow sheet.

Demographics, Variables and Measurements

Information on baseline demographics, vascular risk factors, admission blood glucose level and NIHSS were obtained from our prospective stroke registry. Other clinical endpoints obtained from the registry included symptomatic intracerebral hemorrhage (sICH), (defined as a parenchymal hematoma Grade 2[23] associated with worsening neurological status thought to be related to the hematoma), neurological deterioration (defined as at least 4-point increase in NIHSS) and functional outcome on discharge as measured by mRS. Type of IAT, duration of procedure, and time to recanalization were also collected from our prospective IA database.

Imaging Analysis

The ASPECTS methodology is well described by Barber et al[24] and is shown to have high interobserver agreement. CBS is a scoring system to define the extent of thrombus found in the proximal anterior circulation.[25]

NCCT head scans and CTA scans were independently reviewed by 2 staff neuroradiologists (CS and JC) and one vascular neurologist (ABD) who were blinded to the patient's clinical symptoms and outcomes except for the side of the lesion.". There was good interobserver agreement in the ASPECTS scored by our 3 readers (Kappa=0.739, 95% CI=0.604-0.835). A consensus ASPECTS and CBS score of these readers was used.

For recanalization, we used the Thrombolysis in Cerebral Infarction (TICI) score.[26] Recanalization (partial and complete) was defined as TICI 2b or higher.[27] Conventional angiograms were reviewed by a staff neuroradiologist (SL) who was blinded to the patient's clinical symptoms and outcomes as well as their ASPECTS and CBS.

External Validation Cohort

To assess validity and generalizability, we used an external cohort that met the same inclusion and exclusion criteria of our internal cohort: consecutive patients treated with IAT at the Marcus Stroke and Neuroscience Center at Grady Memorial Hospital (MSNC)

(Emory University: Atlanta, GA) between 10/01/2010 and 10/01/2012. Furthermore, we evaluated HIAT2 performance in predicting poor outcomes at 90 days.

Human Protection

This study was approved by the University of Texas–Houston Health Science Center and Emory University Institutional Review Boards.

Statistical Analysis

A logistic regression model, involving the UT Houston cohort, was used to test multiple independent clinical and radiographic variables available prior to cerebral angiography. The independent variables included age, NIHSS, glucose, HTN, DM, A.fib, ASPECTS and CBS and the dependent variable was mRS:4-6 at discharge to determine if they were significant independent predictors of poor outcome. Independent predictors of poor outcome (discharge mRS:4-6) with p values ≤0.2 entered our final score as score variables and were evaluated at different values and dichotomizations using sensitivity analysis and logistic regression to identify cutoff points. Each continuous variable was evaluated using receiver operator characteristics (ROC) curves. Spearman's correlation and ROC curves were used to evaluate the final score. The points assigned to the variables were determined through the beta coefficients from the final logistic regression model.

Results

We identified 163 AIS patients with LAO (MCA or ICA) who underwent IAT at UT Houston as shown in Fig 1. Median age was 64, median NIHSS was 18, medians for ASPECTS and CBS were (7 and 6 respectively), median blood glucose at presentation was 125 mg/dl. 75% of the patients received IV t-PA prior to IAT. sICH occurred in 2.5% of the patients and recanalization rate was 78%. Three quarters of the patients had poor outcome at discharge and overall in-hospital mortality was 18.4%. The cohort from MSNC consisted of 198 patients; Table 1 compares the baseline characteristics and clinical outcomes between UT and MSNC patients.

Poor Clinical Outcome Predictors and Score Development

The results of the logistic regression analyses in UT Houston for all the variables are shown in (Table 2). Age, NIHSS, glucose level at presentation and ASPECTS were identified as independent predictors of poor outcome and entered into the final score. The HIAT2 score (Table 3) ranges 0-10: age (≤59=0, 60-79=2, ≥80 years=4), glucose (<150=0, ≥150 mg/dl=1), NIHSS (≤10=0, 11-20=1, ≥21=2) and ASPECTS (8-10=0, ≤7=3).

Applying HIAT2 Score to Explore Clinical Outcomes

More than 80% of patients with HIAT2 score ≥5 had poor outcome and virtually all patients with a score >7 had poor outcome in UT dataset. Patients with HIAT2 score ≥5 were more likely to have poor outcome at discharge (OR:6.43, 95%CI 2.75-15.02,p<0.001) than patients with HIAT2 score <5. Even after adjustment for reperfusion and time from symptom onset to recanalization, the score was a significant independent predictor of poor outcome (OR:5.88, 95%CI 1.96-17.64,p=0.02).

External Validation at discharge and 90 day clinical outcomes

In the MSNC dataset, patients with HIAT 2 score ≥5 had 6 times greater odds of poor outcome at discharge (OR:6.22,95%CI 2.95-13.11,p<0.0001) than patients with score <5. Most importantly, a HIAT2 score ≥ 5 had a higher likelihood of mRS 4-6 at 90 days (OR: 5.66,95%CI 3.06-10.47,p<0.0001) as more than 60% patients in the HIAT2 (5-7) score category had poor 90 day outcome and almost 80% with a score of 8-10 ended up with mRS:4-6 at 3 months, Figure 2 compares the proportion of patients with poor outcome in the UT (discharge) and Emory patient populations (discharge and 90 days). Moreover, HIAT2 maintained its ability to predict poor outcome at 90 days after adjustment for recanalization, time from symptom onset to reperfusion and the use of general anesthesia (OR:5.12,95%CI 2.67-9.81,p<0.0001). Furthermore, HIAT2 ≥5 predicted poor outcome after adjustment for the use of stent retrievers (OR:4.96,95%CI 2.58-9.56,p<0.0001).

Comparing HIAT2 Performance to Previous Predictive Scores

The HIAT2 score was compared to previously developed predictive scores (HIAT, THRIVE and ASPECTS; both continuous and dichotomized) in the UT cohort. Given that ASPECTS was created to predict good rather than poor outcomes, we also compared HIAT2 to the inverted ASPECTS. HIAT2 had a greater area under the curve (AUC=0.748) compared with THRIVE (0.695), HIAT (0.679), ASPECTS continuous and dichotomized (0.667 and 0.585 respectively). HIAT2 outperformed all other scores when compared on Emory's 90 days poor outcomes (Figure 3B).

Examining The Importance of Adding Imaging Findings to HIAT2

To examine further the potential clinical and statistical value of adding ASPECTS to the HIAT2 scoring system, we removed ASPECTS from HIAT2 and created a modified 0-7 scoring system. While the modified score continued to be a significant predictor of poor outcome, removing ASPECTS underestimated the patients odds of having poor clinical outcomes (2.79, 95% CI:1.34-5.82,P=0.0061) and resulted in smaller AUCs, AUC=0.6139). This result was confirmed on the Emory cohort as well, further supporting the importance of adding the ASPECTS score to optimize HIAT2. This analysis then led us to add ASPECTS to the original HIAT score and to compare with HIAT2. Therefore, we added ASPECTS (a poor ASPECTS≤7) to the original HIAT and created a 0-4 points score that we compared to HIAT. Adding ASPECTS to HIAT resulted in a score that better estimates poor outcome than the original HIAT score, with higher ORs, narrower CIs (6.17, 95% CI: 2.42-15.71,P=0.0001), and larger AUCs (0.6802), further proving the value of adding ASPECTS to the clinical scoring system. However, HIAT-2 remained superior to this modified HIAT (AUC for HIAT2 0.7032 vs. modified HIAT 0.6802).

Testing HIAT2 Performance in The Context of Reperfusion Status

To further evaluate the utility of HIAT2 in patient selection for IAT, we studied poor clinical outcomes in patients with and without reperfusion, stratified by HIAT2 scores. Patients with a HIAT2 score ≥5 had significantly higher odds of poor outcome even if reperfusion (TICI >2b) had been achieved (OR:5.49,CI:1.69-17.83, p=0.0046). Furthermore, patients who did not reperfuse (TICI <2b) showed an association for even worse odds for poor outcome although only approaching statistical significance (OR:8,CI:0.69-92.7-17.83, p=0.09).

Evaluating Patients Clinical Outcomes Irrespective to Their Age: "Ageless HIAT2"

Some physicians may not want to use age in their decision to pursue IAT since there is supportive literature of on the safety of IAT in patient older than 80[28]. Since age weighs heavily in the scoring of HIAT2, we removed the age component from HIAT2 and created the "ageless HIAT2." We examined the ability of "ageless HIAT2," a 6 point score (NIHSS: 0-2, ASPECTS: 0-3 and Glucose level: 0-1) to predict poor clinical outcomes in both datasets (UT Houston and Emory's discharge and 90 days). We found that a score of ≥3 had 6.85 greater odds of poor outcome (95% CI: 2.21-21.2, P=0.0008 and AUC=0.693) at discharge and 3.79 greater odds of poor outcome (95% CI: 1.14-12.6, P=0.0294 and AUC=0.648) at 90 days. Nearly all (96.9%) patients in the 3-6 category had poor outcome at discharge in the UT dataset; these results were consistent in the Emory dataset as 80.8% with score ≥ 3 had an mRS 4-6 at discharge and 68 % of patients with scores ≥ 3 had an mRS 4-6 at 90 days (figure 2C).

Discussion

Previous trials reported favorable clinical outcomes in stroke patients treated with IAT[9,29-30]. However, recent randomized trials have failed to show benefit of adjunctive endovascular therapy in patients given intravenous t-PA in comparison with IV thrombolysis alone; nor is endovascular therapy superior to IV thrombolysis when implemented within 4.5 hrs of symptom onset [10-11-12]. These studies suggest that better selection of patients may be needed to understand who might have a poor outcome after IAT. In an effort to improve the selection of patients eligible for IAT, we studied different clinical variables that are known to affect patient outcomes and incorporated radiographic variables associated with response to therapy in patients undergoing IAT at our center. Our novel scoring system may help physicians decide whether to pursue endovascular recanalization. The HIAT 2 scoring system that we derived is a combined score incorporating age, admission glucose level, admission NIHSS, and radiographic (ischemic changes on CT) variables.

All components of the HIAT2 score have been supported in the literature as factors associated with outcome in patients with AIS. While patients of advanced age benefit from IV or IA thrombolytic therapy,[31-32] they tend to have lower recovery rates, higher incidences of complications and worse outcomes in general. Poor outcomes in "older people" may be explained by multiple co-morbidities, reduced physiological recovery reserve,[33] diminished collateral circulation[34] and reduced neural plasticity.[35] Admission hyperglycemia is widely reported as a poor prognostic factor in acute brain ischemia.[36-37] Baseline NIHSS is the most powerful predictor of long term outcome in patients with AIS [14,36,38], and patients with the most severe neurologic deficits at admission are more likely to have futile recanalization with IAT.[39] Multimodal imaging methods are widely used to identify salvageable tissue in AIS patients and ASPECTS has been a useful tool in selecting patients that may benefit from both IV[40] and IA[12] thrombolytic treatment.

Patients with HIAT2 ≥5 were less likely to have a good outcome despite efforts to recanalize and reperfuse their ischemic bed. While our results are in agreement with previous studies that reported the association between better clinical outcomes with higher recanalization rates,[41-42] patients with HIAT2 ≥5 still had poor outcome despite successful reperfusion.

While other studies have chosen to examine patients who may respond favorably after IAT,[43-44] we sought to devise a score that would predict poor outcome in spite of recanalization and thus improve our patient selection for IAT by excluding patients who will do poorly, even after a radiographically successful intervention. Furthermore, good clinical outcome also can depend heavily on multiple factors in the angio-suite after the decision to intervene and many of these factors are difficult to account for or predict in advance, such as whether the procedure itself was successful or not, the length of the procedure,[45-46] the status of the patients' collaterals and blood pressure during the intervention.

HIAT2 was originally designed with hospital discharge as the primary outcome. Some patients with poor outcome on discharge can have significant improvement in dependency after the acute phase of stroke. However, we validated our results on long-term outcome on an external dataset from another stroke center with the same robustness.

HIAT2 combines both clinical and radiographic independent predictors in one score that uses easily retrievable variables and provides a quick assessment of the likelihood for a poor outcome if IAT is pursued, in contrast to more time consuming approaches such as MRI diffusion-perfusion mismatch. The HIAT2 score could provide a reliable tool in selecting patients for IAT given its superior performance when compared to all currently developed clinical (HIAT and THRIVE) as well as radiographic scores (ASPECTS). Few patients with HIAT2 scores of 5-7 may benefit from IAT. HIAT2 is the only method that combines both clinical and radiographic elements in one unified system that may help physicians in their decisions to pursue IAT by potentially excluding patients from treatment (possibly with scores above 5 and even more likely above 8)

Our study has several limitations. It is retrospectively designed and warrants a prospective validation. It extends over 8 years during which notable changes and progressions were made in the field of interventional vascular neurology with the introduction of both Multi mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever[7] and the Penumbra system.[47] Moreover, with the growing data reporting the effectiveness, rapidity, higher recanalization rates and favorable outcomes of the newer devices,[48-49] it is also possible that the development of newer generation devices may improve the recanalization time and could provide benefit for more patients, and while HIAT2 maintained its predictive ability after adjustment for the usage of stent retrievers, further validation of the score in trials that use stent retrievers is warranted. Our cohort of patients at UT were routinely mechanically ventilated for IAT, which might alter their outcomes negatively[50], we however adjusted for this variable on Emory's dataset with no change in the results. Our analysis concentrated on NCCT and CTA changes as the main imaging variables; we did not study MRI perfusion-diffusion mismatch or CT-Perfusion data in our analysis. A comparison of simple versus more advanced imaging methods against HIAT2 in predicting patients' outcomes will be important in future studies. Furthermore, as ASPECTS plays a key role in HIAT2, it is important to point out that ASPECTS scoring can be challenging in "real time" in the emergency department and requires training and experience; however, the score does have good interobserver agreement [24] as well as low variation between ASPECTS performed in "real time" and "core lab/experts" scores [51].

Conclusion

In an era where IAT is becoming a more utilized treatment for AIS, and in a field that lacks solid evidence showing superiority of IAT over the only proven standard of care (IV t-PA), HIAT2 may present a useful tool in deciding whether to pursue endovascular intervention for LAO. Based on the data from this study, we are designing a prospective trial to identify variables that predict long-term outcome in patients receiving IA therapy for AIS to further investigate predictors of poor outcomes in these patients.

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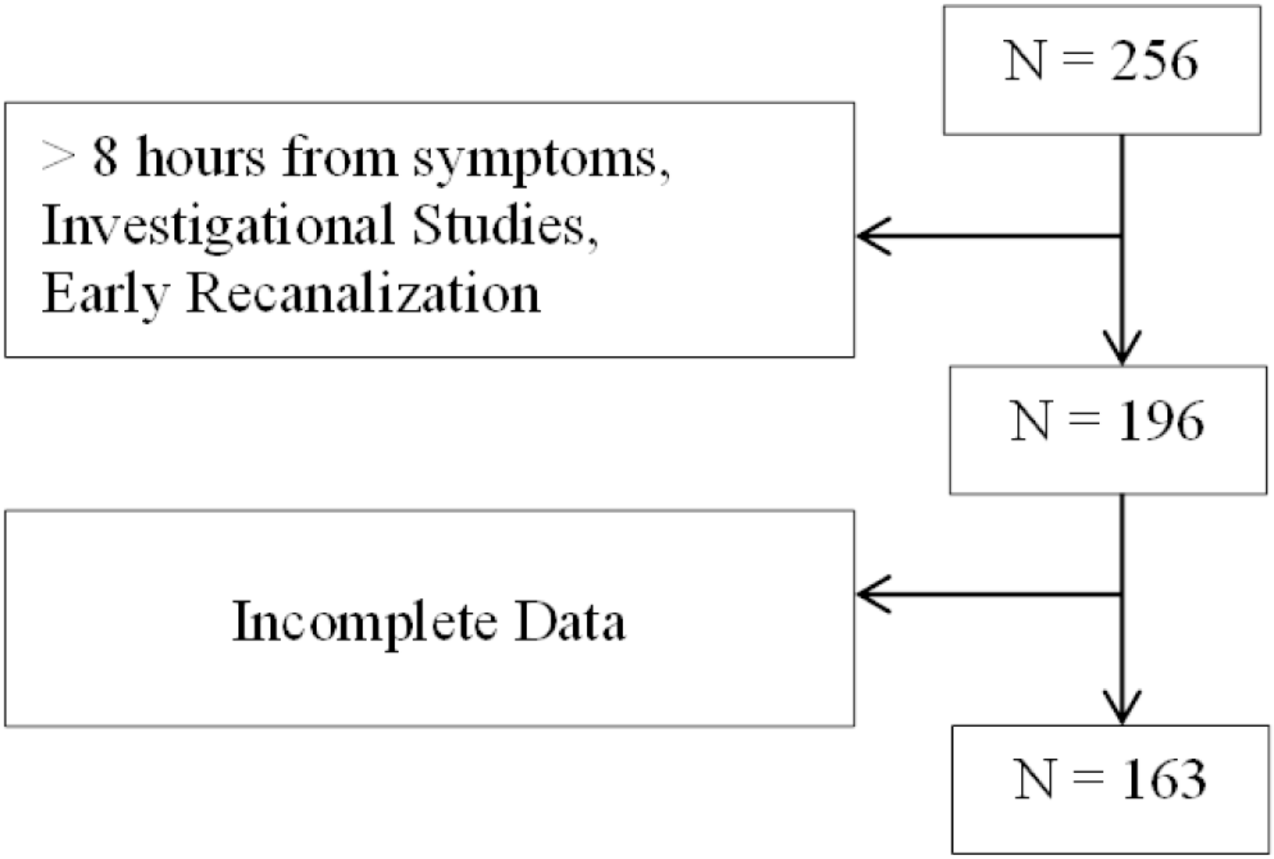

Figure 1. Patient enrollment flow sheet and exclusion criteria

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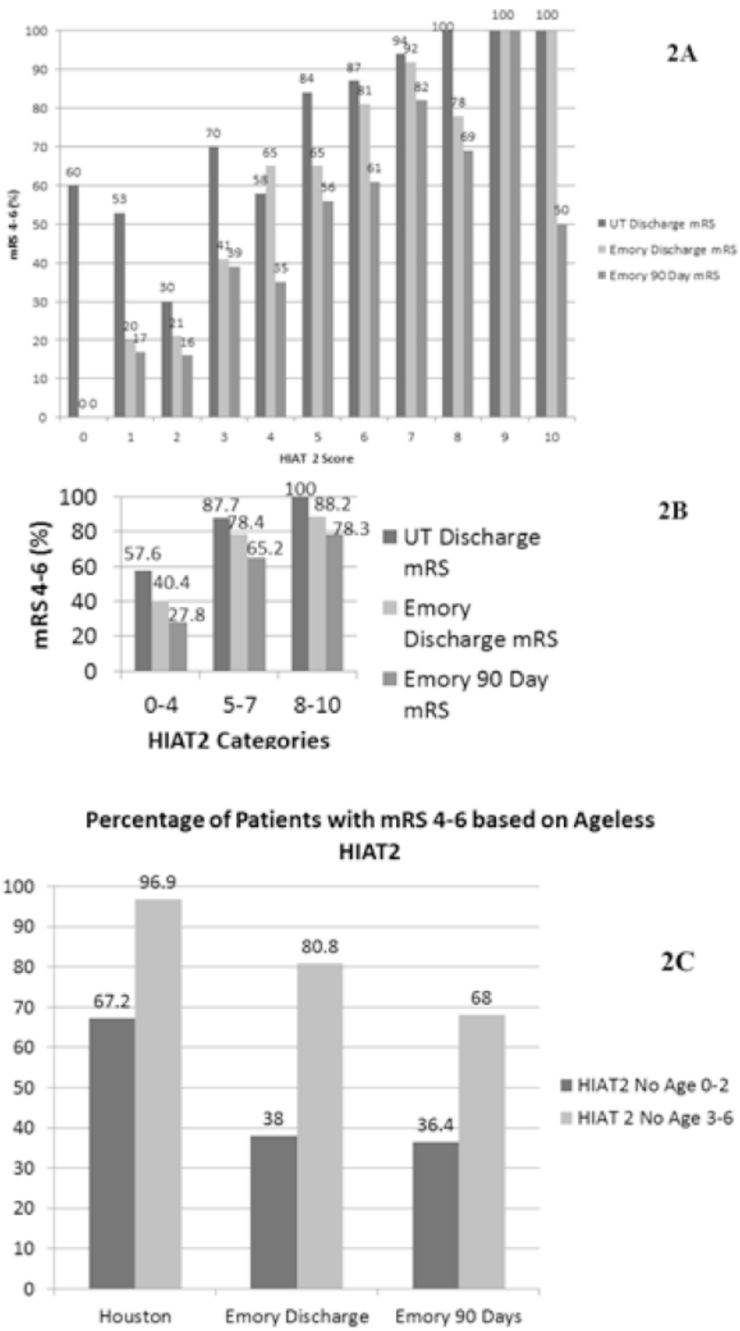
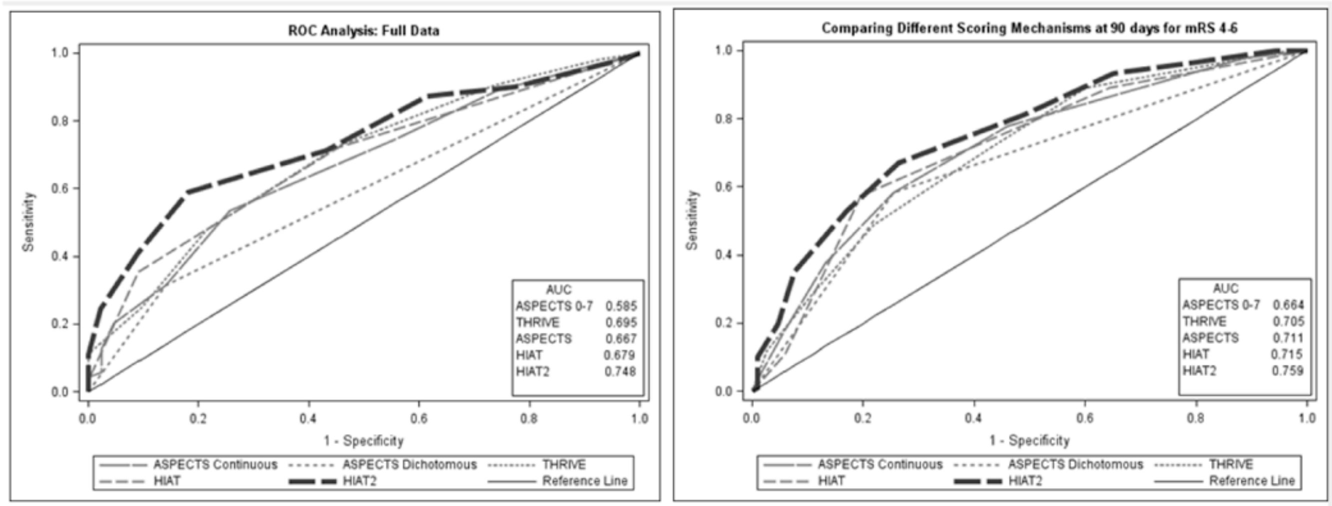


Figure 2.

2(A,B and C): Comparison of the proportion of patients with poor outcome in UT (discharge) and Emory (discharge and 90 days).



3A: UT Houston dataset **3B: Emory dataset**

Figure 3.

3(A,B): Receiver Operating Characteristics curves comparing the performance of HIAT2 score against other predicting scores in the UT and Emory's datasets, ASPECTS:Alberta Stroke Program Early CT Score;THRIVE:Totaled Health Risks in Vascular Events score;HIAT:Houston Intra-Arterial Therapy score;ROC: Receiver Operating Characteristics;AUC:Area Under the Curve.

Table 1

Baseline Characteristics and Clinical Outcomes in UT and Emory data sets.

	Emory(N=198)	UT (N=163)	P value
Age, median (range)	65 (32-94)	66 (15-91)	0.9
Gender, % male	52	55	0.2
Smoker %	17	19	0.5
Hypertension %	72	68	0.9
Diabetes Mellitus %	28	26	0.3
Hyperlipidemia %	23	22	0.5
Atrial fibrillation %	30	28	0.9
NIHSS admission, median	19	18	0.1
ASPECTS	8 (4-10)	8 (0-10)	0.2
Glucose, median (range)	127 (68-472)	125 (75-381)	0.7
IV t-PA %	56	77	0.02
D/C mRS, median (range)	4 (1-6)	4 (0-6)	0.02
mRS 4-6, %	59	72	0.001
Death %	22	18	0.9

* P – values for comparison of build and test groups, NIHSS: National Institute Health Stroke Scale, IV: Intravenous, t-PA: Tissue Plasminogen Activator, ASPECTS: Alberta Stroke Program Early CT Score, CBS: Clot Burden Score, D/C mRS: Discharge Modified Rankin Scale

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Table 2

Results of the analyses performed in the score-building process derived from the UT Houston dataset for all tested variables

Variable	Univariate analysis p-value	Multivariate analysis p-value	Beta from the Multivariable Model	Score given
Age *	0.200			
≤59		Reference	reference	0
60-79		0.4962	0.3192	2
≥80		0.0230	1.0620	4
Glucose*	0.146			
<150		Reference	reference	0
≥150		0.1576	0.8577	1
NIHSS*	0.059			
≤10		Reference	reference	0
11-20		0.1797	0.8237	1
≥21		0.0340	1.6825	2
ASPECTS*	0.053			
8-10		Reference	reference	0
≤7		0.2798	0.6270	3
CBS**	0.387			
DM**	0.499			
HTN**	0.525			
A fib**	0.988			

*Variables that met the ≤0.2 cut point for the p-value in the Univariate analysis and entered the final score

**Variables that did not meet met the ≤0.2 cut point for the p-value in the Univariate analysis

ASPECTS: Alberta Stroke Program Early CT Score, NIHSS: National Institute Health Stroke Scale, CBS: Clot Burden Score, DM: Diabetes Mellitus, HTN: Hypertension, A fib: Atrial fibrillation

Table 3
The Houston Intra-Arterial Therapy 2 "HIAT2" score

Variable	Categories	Score
Age (years)		
	≤ 59	0
	60 - 79	2
	≥ 80	4
NIHSS score		
	≤ 10	0
	11 - 20	1
	≥ 21	2
Glucose (mg/dl)		
	< 150	0
	≥ 150	1
ASPECTS		
	8 – 10	0
	≤ 7	3
Total Possible Points		10