Predicting Outcomes After Acute Reperfusion Therapy for Basilar Artery Occlusion

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Title: -- 80 characters (with spaces)

Running Title: POST-VB Score

Abstract: --250 words

Manuscript: --3043 words

References: 23

Figures: 5

Tables: 1

Key Words: Acute Stroke; CT; Diffusion-Weighted Imaging; MRI; Stroke Recovery; Thrombolysis; Transient Ischemic Attack

Abbreviation used in this paper: AIS (acute ischemic stroke), ASPECTS (Alberta stroke program early CT score), CT (computed tomography), emergency department (ED), LVO (large vessel occlusion), NIHSS (National Institutes of Health Stroke Scale), PCI (percutaneous coronary intervention)

Author contributions to the study and manuscript preparation include the following: Conception and design: Jadhav, Jovin, Lindsberg. Acquisition of data: all authors. Analysis and interpretation of data: Jadhav, Kenmuir, Rangaraju, Panczykowski, Desai, Strbian. Drafting the article: Jadhav, Panczykowski, Desai. Critically revising the article: all authors. Administrative/technical/material support: all authors. Study supervision: Jovin.

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ABSTRACT

Background: Basilar artery occlusion (BAO) leads to high rates of morbidity and mortality, despite successful recanalization. The discordance between flow restoration and long-term functional status clouds clinical decision making regarding further aggressive care. We sought to develop and validate a practical, prognostic tool for the prediction of 3-month favorable outcome after acute reperfusion therapy for BAO.

Methods: This retrospective, multicenter, observational study was conducted at four high-volume stroke centers in the U.S. and Europe. Multivariate regression analysis was performed to identify predictors of favorable outcome (90-day mRS scores 0–2) and derive a clinically applicable prognostic model (the *P*ittsburgh *O*utcomes after *S*troke *T*hrombectomy-*V*ertebro*B*asilar (POST-VB) score). The POST-VB score was evaluated and internally validated apropos of calibration and discriminatory ability. External validity was assessed in patient cohorts at 3 separate centers.

Results: In the derivation cohort of 59 patients, independent predictors of favorable outcome included smaller brainstem infarct volume on post-procedure MRI (p<0.01) and younger age (p=0.01). The POST-VB score was calculated as: *age + (10 × brainstem infarct volume)*. The POST-VB score demonstrated excellent discriminatory ability (AUC=0.91) and adequate calibration (p=0.88) in the derivation cohort (*center A*). POST-VB performed equally well across the 3 external validation cohorts (*center B*, AUC=0.89; *center C*, AUC=0.78; *center D*, AUC=0.80). Overall, a POST-VB score <49 was associated with an 88% likelihood of favorable outcome, as compared to 4% with a score ≥125.

Conclusions: The POST-VB score effectively predicts 3-month functional outcome following acute reperfusion therapy for BAO and may aid in guiding post-procedural care.

INTRODUCTION

Basilar artery occlusion (BAO) may result in devastating ischemia of critical anatomic structures within the brainstem and cerebellum, and if left untreated is associated with a dismal prognosis and high mortality (≥90%).(1,2) Recently concluded randomized controlled trials, the BEST and the BASICS trial, did not demonstrate a benefit of endovascular thrombectomy (EVT) over best medical management for acute basilar artery occlusion (BAO) strokes.(1) Retrospective data suggests that endovascular recanalization for the treatment of BAO maybe safe and effective, with successful reperfusion being achieved in 81-92% of patients.(3,4) Intravenous thrombolytic therapy (IVT) has led to at least as good outcomes as the endovascular approach.(5,6) Despite the high rate of recanalization with endovascular treatment, the majority of patients intervened upon still experience poor outcomes (90-day mRS ≥3 in 55 - 68%).(3,4,7,8)

With increasing adoption of aggressive interventions for BAO, studies have sought to elucidate the potential capabilities of pre-procedural characteristics to predict functional outcome and aid in the selection of patients most likely to benefit from recanalization.(9–11) Although the prognostic value of overall infarct volume is well established in anterior circulation stroke, initial analyses evaluating BAO did not find similar correlations with posterior circulation lesions.(12) However, recent trials incorporating pathoanatomic scoring of posterior circulation infarction have demonstrated improved correlation with functional outcome after BAO.(9,12,13) Nevertheless, even in highly selected analyses (i.e. those excluding patients with extensive brainstem ischemic changes) favorable outcomes following successful recanalization may still only be observed in 49% of BAO patients.(3) Conversely, utilizing overly selective pre-procedural criteria may increase the risk of withholding therapy from patients with a smaller yet clinically important potential for benefit.

Early and prolonged invasive supportive measures are frequently necessary in patients destined for good outcomes, thus forcing decisions regarding aggressiveness of care to be made in the immediate post-procedure period. Incongruent rates between successful recanalization and good clinical outcome necessitates accurate prognostic tools to better discriminate between those patients who will benefit from early and aggressive supportive measures and those who should be considered for de-escalation of care. No study has yet assessed and/or externally validated *post-procedural* characteristics as a means of better predicting the functional outcome of those who have undergone acute reperfusion therapy of BAO. We realize that all decisions of BAO build on rapid triage of candidates for increasingly accessible

recanalization therapy. Not too infrequently, this results in still critically ill patients with unequivocal prognosis, in whom post procedure phase requires careful weighing of optimal care, i.e. continuation of aggressive measures or rather de-escalation of advanced care. A prognostic score, with the ability to predict functional outcome at 3 months based on post procedure information, may be an important tool to support decision making for a longer-term therapy plan.

The purpose of this study was to develop, evaluate, and externally validate the utility of a post-procedural scoring system for the prediction of functional outcome after acute reperfusion therapy of BAO.

METHODS

Patient Population

This retrospective, multicenter, observational study was conducted at four high-volume stroke centers in the USA (Pittsburgh-Center A, Atlanta-Center B), Germany (Dresden-Center C), and Finland (Helsinki-Center D) with IRB (University of Pittsburgh Ethics Board) or local ethics committee approval. Informed consent was not required due retrospective analysis of the data). The data used for this study are available from the corresponding author upon reasonable request. The overall study sample was created by retrospectively identifying all consecutive patients with radiographically confirmed acute symptomatic BAO between July 2000 to July 2012. Patients were included for analysis if presenting neurologic symptomatology was referable to BAO as demonstrated on conventional catheter-based digital subtraction angiography (DSA) or MR/CT angiography, and followed by post-procedural MR imaging. BAO was defined as complete absence of anterograde flow in the basilar artery despite delayed filming. Patients were excluded from analysis if clinical or radiographic data were missing or incomplete. Baseline demographic information, clinical characteristics at presentation, and clinical course were all prospectively recorded.

Patient Selection and Treatment

In accordance with current guidelines intravenous recombinant tissue plasminogen activator (IV tPA) was administered to eligible patients. Patients were deemed to be candidates for endovascular therapy per local institutional protocols, broadly following criteria: 1) clinical symptoms referable to posterior circulation ischemia, and 2) pre-treatment imaging *without* evidence of intracranial hemorrhage and/or extensive infarction that precluded a meaningful recovery in the opinion of the treating stroke neurologist (i.e. entirety of the pons or bilateral thalami). The decision to proceed with endovascular treatment was made between the stroke neurologist and neuro-interventionalist. The endovascular reperfusion techniques utilized included intra-arterial pharmacologic thrombolysis and/or mechanical thrombectomy. The technical approach was left to the discretion of the treating neuro-interventionalist. The details of these endovascular techniques have been extensively described elsewhere.(14,15)

Predictive Characteristics

Baseline demographics, clinical stroke severity, procedural characteristics, angiographic reperfusion status, and final infarct burden on post-procedural MR imaging were all assessed as potential prognostic

variables. Clinical stroke severity was measured by NIHSS score. Reperfusion status was assessed on final angiographic runs according to the modified Thrombolysis in Cerebral Infarction (mTICI) scale; successful recanalization was defined as mTICI grade 2b or 3.(16) Final infarct burden was determined by post-procedural MRI that was performed within 24-hours of the procedure. MRI was performed on 1.5 or 3 Tesla scanners according to institutional protocols. At a minimum, all centers performed these sequences: 1) T2-weighted gradient-echo, 2) diffusion-weighted imaging with apparent diffusion coefficient map reconstruction; and 3) fluid-attenuated inversion recovery. Sectorial volumetric analysis of post-procedure infarct burden assessed the following anatomic regions irrigated by the posterior circulation: each thalamus, each occipital lobe, brainstem (midbrain, pons and medulla), and cerebellum [*Figure 1*]. At Center A, C and D, the infarct volume for each anatomic sector was calculated by outlining the DWI lesion perimeter with a graphing tool available on the Siemens workstation to determine infarct area on each axial slice. At center B, area measurement for each slice was performed manually (previously proven to have high correlation with Siemens graphing tool).(17) The product of the slice thickness and the summation of infarct areas gave the infarct volume for each anatomic sector.

Outcomes

The primary outcome was the degree of functional recovery at 3-month follow-up visit as determined by a trained, unblinded stroke neurologist according to the modified Rankin Scale (mRS), and was recorded prospectively. Favorable functional recovery was defined as a mRS of 0 to 2.

Statistical Analysis

Acceptable Type I error was set *a priori* at α=0.05 for all statistical tests. All analyses were defined *a priori*. Patients with missing and/or incomplete clinical, radiographic, or outcome data were excluded from analyses. Continuous demographic characteristics were assessed for normality using the Kolmogorov-Smirnov test; normally distributed data were analyzed by t-test while the remainders were compared using the Wilcoxon Rank-Sum test. Categorical data were analyzed by Pearson's chi-squared or Fisher's exact test.

Initial univariable and multivariate analysis and predictive model derivation was performed utilizing the UPMC (*center A*) cohort. Univariable regression analysis was performed to assess the association between predictive variables and 3-month favorable functional outcome. Multivariable regression analysis was performed with stepwise backwards elimination to fit a predictive model; following

adjustment, variables that did not reach significance at the α=0.10 level were excluded. A scoring system for the prediction of functional outcome (the *P*ittsburgh *O*utcomes after *S*troke *T*hrombectomy *V*ertebro*B*asilar (POST-VB)) was developed based on β-coefficients of each specific predictive variable from the fitted multivariate logistic regression model.

We assessed the performance of the POST-VB apropos of accuracy, discrimination, and calibration. Accuracy was assessed through calculation of the average prediction error, or Brier score; ideally scores should be < 0.25 (better than flip of a coin). Discrimination was assessed using the area under the receiver operating characteristic curve (AUC). Using current statistical consensus, AUC of 0.8 to 0.9 are considered very good, 0.7 to 0.8 as adequate, and below 0.7 as poor.[18] Calibration is the measurement of agreement between predicted and observed risk over the full range of predicted probabilities, and was tested with the Hosmer-Lemeshow goodness-of-fit test. To perform this test patients were grouped by POST-VB score into 5 levels and significant deviation was set *a priori* at α $\leq$0.05. The evaluation of predictive performance using patients from the original derivation sample may result in an overly optimistic estimate of predictive performance, therefore a 10-fold cross validation for the AUC was applied.[19] Clinical utility was evaluated by decision curve analysis.[20,21]

External validity of the POST-VB scoring system was assessed in separate cohorts of patients suffering BAO undergoing acute reperfusion therapy at 3 high-volume stroke centers (Atlanta, Dresden, and Helsinki); these retrospective analyses were performed on the prospectively collected data from each site. Predictive performance of the POST-VB score applied to all external cohorts was similarly assessed apropos of discrimination and calibration as described above.

Means are reported as *mean ± standard deviation*; significant associations between outcomes and predictors are reported as odds ratios (OR) with 95% confidence intervals (CI). Data were analyzed using Stata 14 (College Station, TX).

RESULTS

Baseline demographics and clinical characteristics for the 59 patients analyzed in the derivation cohort (patients from *center A*) are displayed in *Table 1*. The mean age was 64 ± 13 years; 34% of this cohort were female. The median NIHSS on presentation was 18 (IQR 22), and 48% presented with an NIHSS ≥20.

Twelve-percent of the patients presenting to *center A* met criteria for and subsequently received IV tPA. Median time from symptom onset to initiation of endovascular treatment was 13 hours (IQR 35). Endovascular techniques utilized for recanalization (either alone or in combination) included intra-arterial pharmacologic thrombolysis (42%), mechanical thrombectomy (including MERCI retriever, stentriever, or manual aspiration), and/or angioplasty with/without stenting; proportions of individual techniques are displayed in *Table 1*. Successful reperfusion (mTICI 2b-3) was achieved in 90% of cases.

Figure 2 displays mean final infarct volumes by anatomic region, as demonstrated on post-procedural MRI. Thirty-seven percent of patients had evidence of infarction in all anatomic regions assessed. Overall, the median total infarct volume was 26 mL (IQR 46, range 0-295).

Outcomes and Predictive Model Derivation

Overall, 56% of patients survived beyond 3 months. Thirty-two percent of the entire cohort achieved functional independence (mRS 0-2). *Figure S1* depicts a breakdown of the derivation cohort by 3-month mRS. Baseline demographics, clinical characteristics, procedural factors, and post-procedural imaging findings were assessed for association with 3-month functional outcome utilizing univariable logistic regression. The factors significantly independently associated with 3-month functional independence included smaller infarct volumes within the brainstem (OR 2.02; 95% CI 1.35-3.01) and cerebellum (OR 1.04; 95%CI 1.01-1.07). Stepwise, multivariable logistic regression analysis identified younger age and smaller brainstem infarct volume as significant independent predictors of 3-month functional independence (OR 1.04; 95% 1.01-1.07 and OR 6.57; 95% CI 1.76-24.5, respectively). The equation for the scoring system for the prediction of functional outcome was derived by incorporating the β-coefficients of these independently significant variables from this multivariable logistic regression model (POST-VB score = *age* + 10 x *brainstem infarct volume*).

Predictive Model Assessment

The POST-VB score for the prediction of 3-month functional independence displayed adequate accuracy (Brier score = 0.15). The ability of the POST-VB scoring system to discriminate between patients achieving long-term functional independence versus those being severely disabled or dead, as measured by the AUC curve was 0.91 (95%CI 0.84-0.98) indicating excellent discriminatory ability. The POST-VB score displayed effective calibration for predicting functional independence (Hosmer-Lemeshow test, p=0.88). The clinical utility of POST-VB to predict who is most likely to achieve functional independence was evaluated through decision curve analysis as an extension of clinical decision-making based on history, exam, and hospital course. Use of the POST-VB score displayed superior net benefit as compared to proceeding with aggressive care in all patients beginning at threshold probability (i.e. perceived likelihood of functional recovery) of approximately 5% or higher. This correlated with a net reduction of inappropriately pursuing aggressive care in 11 patients likely to be severely disabled or dead for every 20 patients at a decision threshold of 50% (i.e. clinicians perceived likelihood of poor outcome).

The external validity of POST-VB score to predict 3-month favorable functional outcome was assessed by retrospective application to cohorts of patients undergoing endovascular treatment for BAO at 3 independent, high-volume stroke centers (*center B*, *center C*, and *center D*). Clinical characteristics used in the model were compared between derivation and validation cohorts; brainstem infarct volume (ml) was the only significantly different characteristic between cohorts (*center A* 4.6±4.7 ml, *center B* 0.52±0.57 ml, *center C* 1.3±2.0 ml, and *center D* 3.1±3.6 ml, p<0.01). Within each cohort, age and brainstem infarct volume remained significant predictors of 3-month functional outcome in both univariate and multivariable regression analyses. *Figure 3* displays the receiver operating characteristic plot for the POST-VB score applied at each center. The discriminatory ability of the POST-VB scoring system for predicting long-term functional independence ranged from good to very good, with AUCs of 0.89 for *center B*, 0.78 for *center C*, and 0.80 for *center D*. Rates of mRS 0-2 and mRS 0-3 at 90 days by POSTVB (Binned-0-49, 50-74, 75-99, 100-124, >124) scores are displayed in *Figure S2*.

DISCUSSION

The POST-VB scoring system is a simple and clinically applicable method able to reliably predict 3-month functional outcome following thrombectomy for acute BAO. This scoring system demonstrated very good discriminatory ability as well as external validity when applied to patients treated at a variety of high-volume stroke centers (center B, AUC=0.89; center C, AUC=0.78; center D, AUC=0.80).

Although BAO continues to carry a high mortality rate (approximately 30-40%), up to 4 in 10 BAO stroke patients may achieve functional independence. The POST-VB score successfully discriminated between those patients who will benefit from early and aggressive supportive measures and those who may be considered for de-escalation of care. Overall, a POST-VB score <49 was associated with an 88% likelihood of favorable outcome, as compared to 4% with a score ≥125. As a practical outcome the results of the clinical utility analyses revealed that applying the POST-VB score added significant clinical value above that currently offered by routine consideration of individual clinical factors, regardless of a treating physician's certainty of an outcome. Utilization of the POST-VB score for outcome prediction demonstrated a net benefit over standard practice beginning at a perceived certainty threshold (perceived likelihood of correctly predicting outcome) from as low as 5% and extending up to 100%. Furthermore, decision analysis demonstrated that utilizing the POST-VB score would lead to reduced inappropriate utilization of aggressive care in 11 patients likely to be severely disabled or dead for every 20 patients at a decision threshold of 50% (i.e. physician certainty of outcome equal to flipping a coin).

As of yet there are no randomized controlled trial data supporting the efficacy of thrombectomy for the treatment BAO. The Basilar Artery Occlusion Chinese Endovascular Trial (BEST) was neutral and the Basilar Artery International Cooperation Study (BASICS) Trial results are eagerly awaited.(1,22) The current American Stroke Association 2019 guidelines offer a class IIb recommendation for thrombectomy in BAO patients within 6 hours of onset. Despite a lack of definitive evidence, endovascular thrombectomy has been increasingly offered as a salvage operation based on promising results from case series.(3,4,6,7) Despite advances in technique and recanalization rates as high as 90%, the majority of patients intervened upon still experience poor outcomes. Previous studies have sought to determine which baseline characteristics are determinants of poor outcomes. Characteristics associated with poor outcome have included age, higher stroke severity in clinical and imaging work-up, longer time to recanalization, and incomplete or failed recanalization.(4,5,8) The current study is the first to demonstrate that not only post-procedural infarct volume, but also *location* is an independent

predictor of outcome following BAO. Specifically, infarcts involving the brainstem portend a worse outcome.

The relationship between final infarct volume and functional outcome has been established in the case of anterior circulation stroke. Our group has previously reported that in a homogeneous group suffering middle cerebral artery occlusion (segment 1) treated with endovascular therapy, the most powerful predictors of outcome were age and final infarct volume. From this we developed and validated a similar scoring system for outcome prediction in anterior circulation stroke (Pittsburgh Outcomes After Stroke Thrombectomy (POST)), based on patient age, final infarct volume, and presence of hemorrhage.(17)

This current study supports a similar paradigm for outcome prediction in stroke secondary to BAO treated with endovascular therapy. However, unique to BAO, these current results indicate that infarct location also plays a critical role in prediction. Our findings are in keeping with previously published analyses evaluating brainstem stroke burden utilizing a semi-quantitative approach. A scoring system based solely on brainstem infarct volume was utilized to predict presence and length of coma and outcome.(12,23) In contrast, other analyses of post-procedural DWI lesion volume following BAO have failed to demonstrate a consistent correlation with outcome. Possible reasons for this discrepancy include small sample size and the use of overall infarct volume alone, without accounting for pathoanatomic infarct distribution.(8)

Prior series evaluating reversal of BAO have demonstrated that the time window during which reperfusion continues to be beneficial is longer than in anterior circulation strokes.(13) A putative reason is that the brainstem may be more resistant to long-term ischemia than the cerebrum, including a more extensive network of collateral circulation and/or neuronal metabolism unique to the brainstem; which however remains unproven.(6) Regardless of mechanism, this suggests that a subset of well selected patients may continue to benefit from recanalization even at late time points.[8]

Our study has certain limitations. First, this is a retrospective study without a predetermined imaging inclusion/exclusion protocol. Patients included in this study were treated across 4 high-volume stroke centers in both the US and Europe, and therefore represent a broad, multinational spectrum of patients undergoing treatment for BAO. Second, numerically higher mortality rates in our derivation cohort

(44%), compared to mortality rates in the BEST (36%, p=0.19) and BASICS trials (41%, p=0.46), may be explained by longer time to treatment in our patients. Third, outcomes were only analyzed at 3 months, which may be too early of a time point to fully capture eventual neurological recovery.(14) Fourth, the POST-VB score utilizes post-procedural scans, and therefore does not specifically address patient selection, but is instead limited to post-treatment prognostication. Nevertheless, this scoring system has significant clinical utility for prognostication, as even those patients destined for good recovery may still have poor clinical exams early after treatment when important decisions guiding post-procedural care are being made. Future studies will be necessary to address whether such information can be applied prior to continuation of intensive care to determine the likelihood of benefit.

Conclusions

This study demonstrates that the POST-VB scoring system can reliably predict outcome following acute reperfusion therapy for stroke due to BAO.   This scoring system cannot replace diligent patient evaluation and comprehensive assessment. Nonetheless, the use of this grading system may help guide judicious patient selection for continued aggressive therapy following endovascular therapy and possibly decrease the risk inappropriately pursuing such care and avoid therapeutic futility. Importantly, the POST-VB demonstrated external validity across centers in both the US and Europe.

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Table 1. Baseline Characteristics of Derivation Cohort (Center A, n=59)

Age (mean, years)	64 ± 13 years
Sex (male)	34% (20)
NIHSS Score (median)	18 (IQR 22)
Last known well to arrival (mean, hours)	13 (IQR 35)
Vascular Risk Factors	
Hypertension	59% (35)
Diabetes Mellitus	22% (13)
Atrial Fibrillation	19% (11)
Hypertriglyceridemia	39% (23)
Coronary Artery Disease	22% (13)
Smoking	22% (13)
Intra-venous tPA	12% (7)
Intra-arterial thrombolytics	42% (25)
Endovascular thrombectomy	85% (50)
TICI 2B or more	90% (53)
mRS 0-2 at 90 days	32% (19)
mRS 0-3 at 90 days	39% (23)

Figure 1. Example of Volume Measurement by Infarct Location

Figure 2. Median Infarct Volume by Location

Figure 3. Receiver Operator Characteristic Curve for POST-VB Score at Different Sites
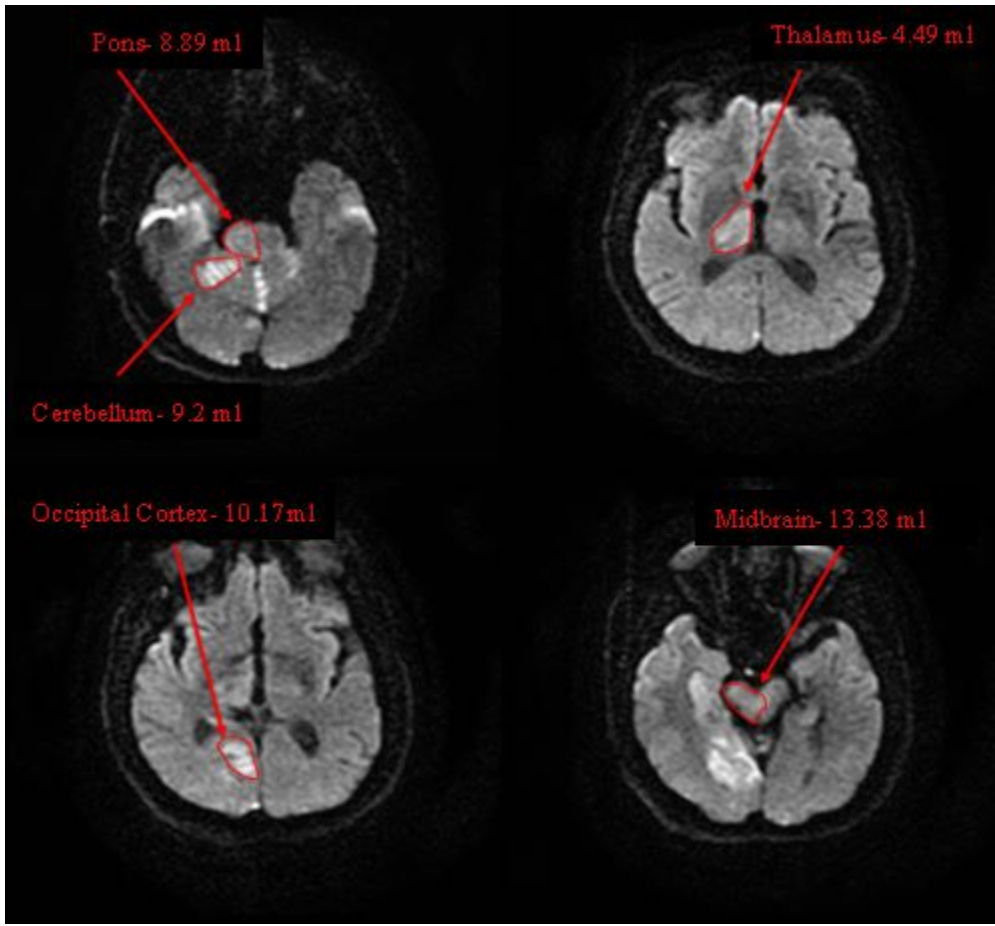
ROC- Receiver Operator Characteristic

Supplemental Material

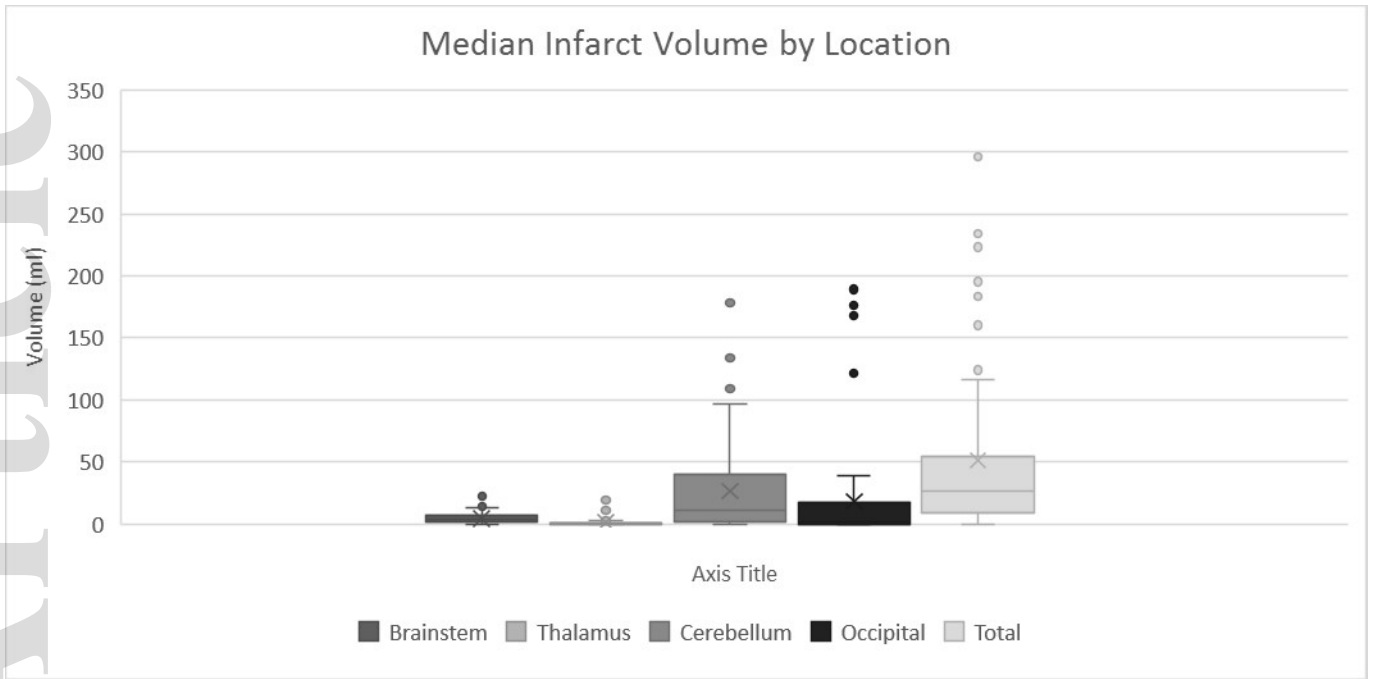**Figure S1**. **Modified Rankin Scale Score at 3 months**

Figure S2. Modified Rankin Scale Score at 90 days by binned POSTVB Score
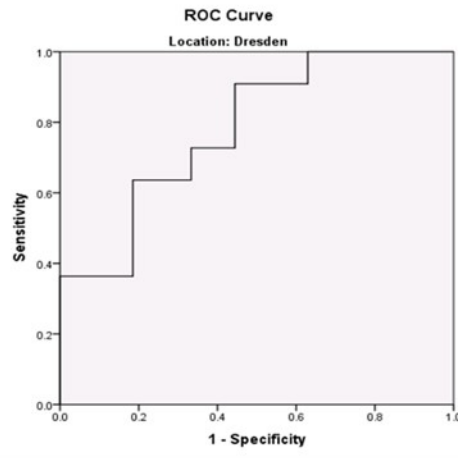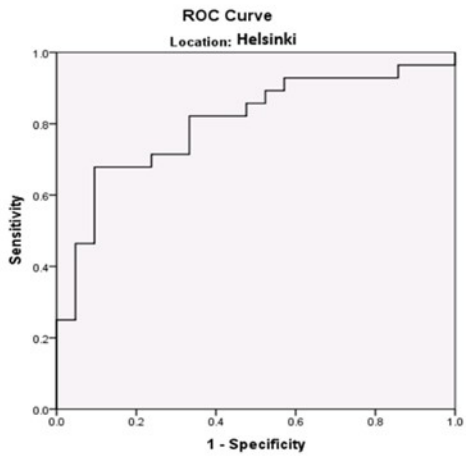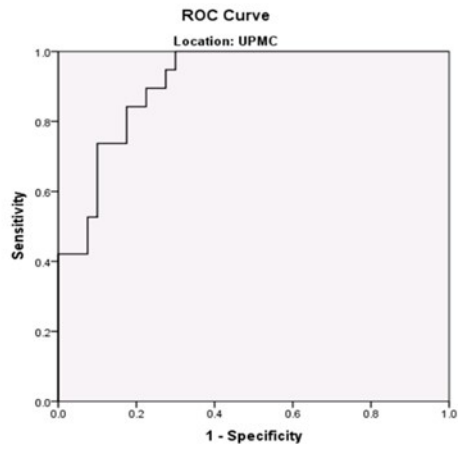
mRS-modified Rankin Scale Score

ene_14406_f1.jpg

Median Infarct Volume by Location

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ene_14406_f3.jpg