Acute Physiology of Stroke Score

Karen C. Johnston, MD, MSc*; Guofen Yan, PhD*

Background and Purpose—The Acute Physiology, Age, Chronic Health Evaluation score for critically ill patients has provided a method of predicting outcome using major physiological variables. We hypothesized that a physiology score for stroke patients (Acute Physiology of Stroke Score [APSS]) when added to a validated clinical prediction model would improve outcome prediction.

Methods—The APSS was developed and validated using multivariable logistic regression. It was added to a previously validated clinical model to assess for increased area under the curve in predicting 3-month outcome.

Results—The bootstrap-validated bias-corrected area under the curve for just the APSS predicting alive/dead at discharge was 0.753. The clinical model area under the curve ranged from 0.77 to 0.88 and the addition of the APSS resulted in areas under the curve of 0.77 to 0.89.

Conclusions—These data suggest that the APSS is related to 3-month clinical outcome in patients with ischemic stroke. However, the APSS adds no clinically relevant additional predictive value when added to our previously validated clinical prediction model. *(Stroke. 2011;42:2336-2338.)*

Key Words: outcome ■ prediction ■ prognosis ■ stroke

The Acute Physiology, Age, Chronic Health Evaluation Prognostic System demonstrated that standard physiology measures in acutely hospitalized critical care patients could be highly predictive of patient outcome.1 A stroke prediction model including 6 standard clinical variables has been developed and validated as a predictor of 3-month functional outcome in patients with acute ischemic stroke.2 This clinical model does not include physiology data. We hypothesized that an Acute Physiology of Stroke Score (APSS) when added to the clinical model would improve the prediction of 3-month functional outcome in patients with ischemic stroke.

**Methods**

We used 1 clinical development data set (Cerner Corporation data set) and 2 clinical validation data sets (Randomized Trial of Tirilazad3 and National Institute of Neurological Disorders and Stroke Tissue Plasminogen Activator4) to test the hypothesis. Favorable outcome was defined as a modified Rankin Scale score of 0 or 1.5 Several other clinical outcomes were also considered.

Nine standard physiological variables were prespecified (Table 1). We developed and validated the APSS using univariate and multivariate techniques. We used logistic regression to examine linear relationships and nonparametric smoothing logistic regression techniques to examine nonlinear relationships.6 Bootstrap validation and external validation techniques were used.3,5

We used OR to describe the predictive value of the APSS. To evaluate the added predictive value of the APSS beyond that of the clinical model, we calculated the area under the receiver operating characteristic curve for the clinical model and then again with the addition of the APSS for each outcome. The difference in the overall performance between the 2 models was determined by the likelihood ratio test.9 For all models, we report only the bootstrap-corrected areas under the receiver operating characteristic curve.

**Results**

Areas under the curve of the apss predicting alive/dead at discharge were 0.753. The clinical model area under the curve ranged from 0.77 to 0.88 and the addition of the APSS resulted in areas under the curve of 0.77 to 0.89.

**Conclusions**

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Table 2. Univariate Analysis of Physiological Variables in Predicting Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linear Relationship*</th>
<th>OR</th>
<th>P</th>
<th>Nonlinear Relationship†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum glucose per 20 mg/dL</td>
<td>1.138</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Serum blood urea nitrogen per 5 mg/dL</td>
<td>1.164</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit per 10%</td>
<td>0.996</td>
<td>0.97</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature per 1 C</td>
<td>1.367</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Heart rate per 10 beats/min</td>
<td>1.142</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Na⁺ per 10 mEq/L</td>
<td>1.261</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine per 1 mg/dL</td>
<td>1.224</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>White blood cell count per 5000s</td>
<td>1.705</td>
<td>&lt;0.001</td>
<td>0.202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mean arterial pressure) per 10 mm Hg</td>
<td>1.017</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratio.  
*P value from univariate linear logistic regression for death.  
†P value from nonparametric smoothing logistic regression for death; P value of <0.05 indicates a statistically significant nonlinear relationship between the log odds of death and the variable.

Results

A total of 1353 patients with complete data were included from the development data set. In the univariate logistic development model for death, 6 physiological predictors were found to be significantly linearly associated with death, and 8 physiological predictors were found to be significantly non-linearly associated with death (Table 2). The APSS was derived from maximizing the relationships of all 9 variables linearly associated with death (Table 2). The APSS was associated with outcome in both validation data sets as well (OR, 1.10 to 1.42 for poor outcome and 0.79 to 0.88 for favorable outcome). The APSS did not however add clinically relevant predictive power when added to the previously validated clinical model (Table 3).

Discussion

These data suggest that an APSS using 9 standard physiology measures is predictive of outcome in patients with ischemic stroke but it does not add sufficient predictive information over standard clinical prediction models to make it useful.

Because the model was developed in a critically ill acute stroke population to predict death, it may be intuitive that the model equations were more successful in predicting poor outcome than favorable outcome. The model weights would likely have required adjustment to predict a favorable outcome. However, because the APSS did not add clinically relevant predictive capability to our previously validated simple clinical models in the prediction of poor outcome, further development of favorable outcome models did not seem necessary.

Our analysis is limited by the lack of National Institutes of Health Stroke Scale score in the development data set because this stroke severity measure is known to provide substantial prediction value for 3-month outcome in patients with stroke. Although Glasgow Coma Scale score was used as a surrogate for stroke severity in the development data set, these 2 scales capture very different information. Additionally, the development data set population was substantially sicker than the validation data set populations, thus contributing to the worse performance of the models in the validation data sets (data not shown). Again, further refinement did not seem warranted.

This exploratory analysis of whether a simple, easy-to-capture APSS could be developed, validated, and used to help predict outcome in patients with acute ischemic stroke suggests that our standard vital signs and laboratory information are unlikely to add substantially to our current validated

Table 3. Results of External Validation in the 2 Independent Data Sets

<table>
<thead>
<tr>
<th></th>
<th>RANTTAS</th>
<th>tPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Model Alone</td>
<td>Clinical Model + APSS</td>
</tr>
<tr>
<td>Poor outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>0.876</td>
<td>0.887</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.851</td>
<td>0.869</td>
</tr>
<tr>
<td>GOS</td>
<td>0.876</td>
<td>0.887</td>
</tr>
<tr>
<td>BI</td>
<td>0.880</td>
<td>0.889</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>0.862</td>
<td>0.868</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.856</td>
<td>0.864</td>
</tr>
<tr>
<td>GOS</td>
<td>0.862</td>
<td>0.868</td>
</tr>
<tr>
<td>BI</td>
<td>0.870</td>
<td>0.875</td>
</tr>
</tbody>
</table>

RANTTAS indicates Randomized Trial of Tirilazad; AUC, area under the receiver operating characteristic curve; APSS, Acute Physiology of Stroke Score; tPA, tissue-type plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GOS, Glasgow Outcome Scale; BI, Barthel Index.  
*P value not calculated in absence of improvement with addition of APSS.
clinical prediction model. Further model development to consider other variables that may improve the prediction may be warranted.

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Disclosures
None.

References
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Clinical data sets:

Cerner Corporation (development data set): The Cerner data set used for this analysis included 2318 prospectively collected ICU patients from all over the United States from 2002 to 2003 that had a primary APACHE diagnosis of ischemic stroke. The Cerner Corporation owns and operated the APACHE clinical information and includes patients from over 70 ICUs to systematically collect APACHE III variables and other standard data on their patients. A total of 1353 patients had complete data available and were used for this analysis as a development dataset.

RANTTAS (validation data set): The Randomized Trial of Tirilazad Mesylate in patient with Acute Stroke (RANTTAS) trial was a prospective multicenter randomized masked controlled trial of 556 fully eligible acute stroke patients from 27 North American sites. A total of 408 patients had complete data and were used for this analysis as first validation dataset.

NINDS tPA (validation data set): The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial was a multicenter, randomized masked controlled trial of 624 acute ischemic stroke patients from 8 centers across the United States. A total of 265 of 312 placebo treated patients with complete data were used for this analysis as the second validation dataset.

Outcome variables:
Favorable outcome by the modified Rankin Scale (mRS) was the primary outcome variable but 3 additional standard stroke clinical outcomes were also prespecified for analysis. For the mRS a score of 0 (no symptoms) or 1 (symptoms without disability) were defined as favorable outcome. The three additional outcome variables included Barthel Index (BI), NIHSS score and Glasgow Outcome Scale (GOS). A BI of 95 or 100, NIHSS score of 0,1 and GOS of 1 were all defined as favorable outcome and reflected complete or near complete recovery as have been previously defined.

Each outcome was also dichotomized to reflect poor outcome for the development of models predicting poor outcome. For these models a mRS score of 4,5,6, a BI score of ≤60 or death, a NIHSS score of ≥15 or death, and a GOS score of 3,4,5 were all reflective of poor outcome and nursing home level disability or death as have been described previously.

Missing data:
Among ten pre-specified physiologic predictor variables, billirubin was excluded because it was missing in 74% of patients in the development data set. The remaining nine variables were all used. Because the development data set did not have NIHSS score, the Glasgow Coma Scale Score (GCS) was used as a surrogate for stroke severity. Of the four validated outcomes planned for the analysis (mRS, BI, NIHSS, GOS), mRS was not collected in the RANITAS data set. Therefore, mRS was imputed based on the GOS score. A GOS of 1 (good recovery) was used to define mRS favorable outcome (No symptoms or no significant disability despite symptoms) and GOS of 3 (severe
disability), 4 (persistent vegetative state), or 5 (death) for mRS poor outcome (severe disability or death).

Of 2318 patients in Cerner development data set, 1353 patients had a complete set of the nine physiologic predictors, and they were used in the development model. Of the 556 eligible patients in the RANTTAS data set, the BI and GOS outcomes were available in 483 patients, of which, 408 patients with complete data on the physiologic predictors were used in validation for BI and GOS analysis. The NIHSS score outcome was available in 458 out of 556 patients, of which, 382 with complete data on the predictors were used for NIHSS outcome validation. For the NINDS tPA data (second validation data set), 265 of 312 placebo patients with complete data on the outcomes and predictors were included for validation analysis.

Statistics

Patient characteristics were described as means and standard deviations (SDs) for continuous variables, and frequencies and percentages for non continuous variables. We used two-sample t test and Chi-square test to examine differences in patient characteristics between the groups of patients included and excluded from the analysis due to missing data.

All nine physiologic predictors evaluated in the development data set were included in the development of the APSS model. The multivariable regression coefficients were converted to point values to allow for a simple point system that resulted in the APSS
being a weighted combination of nine physiologic variables with a score range of 0-100. Age and GCS were then adjusted for in the model as both stroke severity and age are known to be highly predictive of outcome. The model was internally validated using a bootstrap resampling technique with 250 bootstrap samples to obtain the bias corrected estimate with respect to the predictive performance. Missing values of the physiologic variables were not imputed because imputation in the development data set could have biased our model performance in the validation data set. As the development data set was large, we excluded subjects with missing data and allowed the regression analysis and validation to assign coefficients (weights) based only on true values.

The APSS was then exported and combined with the previously validated clinical model to assess the APSS’s added predictive value. The models were assessed in the two independent external datasets for their ability to predict both favorable and poor 3 month outcome. The development data set equations were updated for the models used for the RANNTAS data set and were internally validated using the bootstrap techniques. These equations were then frozen and forecasted into the tPA dataset without modification. We report the measures of model predictive performance for both validation populations.

We used the odds ratio to describe the predictive value of the APSS. To evaluate the added predictive value of the APSS beyond that of the clinical model, we calculated the area under the receiver operating characteristic curve (AUC) for the clinical model and then again with the addition of the APSS for each outcome. The difference in the overall
performance between the two models was determined by the likelihood ratio test. For all models, we report only the bootstrap-corrected AUCs.