Predicting outcome of IV thrombolysis–treated ischemic stroke patients

The DRAGON score

ABSTRACT

Objective: To develop a functional outcome prediction score, based on immediate pretreatment parameters, in ischemic stroke patients receiving IV alteplase.

Methods: The derivation cohort consists of 1,319 ischemic stroke patients treated with IV alteplase at the Helsinki University Central Hospital, Helsinki, Finland. We evaluated the predictive value of parameters associated with the 3-month outcome and developed the score according to the magnitude of logistic regression coefficients. We assessed accuracy of the model with bootstrapping. External validation was performed in a cohort of 330 patients treated at the University Hospital Basel, Basel, Switzerland. We assessed the score performance with area under the receiver operating characteristic curve (AUC-ROC).

Results: The DRAGON score (0–10 points) consists of (hyper)Dense cerebral artery sign/early infarct signs on admission CT scan (both = 2, either = 1, none = 0), prestroke modified Rankin Scale (mRS) score (1 = yes, 0 = no), Age (≥80 years = 2, 65–79 years = 1, <65 years = 0), Glucose level at baseline (>8 mmol/L [144 mg/dL] = 1), Onset-to-treatment time (>90 minutes = 1), and baseline National Institutes of Health Stroke Scale score (>15 = 3, 10–15 = 2, 5–9 = 1, 0–4 = 0). AUC-ROC was 0.84 (0.80–0.87) in the derivation cohort and 0.80 (0.74–0.86) in the validation cohort. Proportions of patients with good outcome (mRS score 0–2) were 96%, 88%, 74%, and 0% for 0–1, 2, 3, and 8–10 points, respectively. Proportions of patients with miserable outcome (mRS score 5–6) were 0%, 2%, 5%, 70%, and 100% for 0–1, 2, 3, 8, and 9–10 points, respectively. External validation showed similar results.

Conclusions: The DRAGON score is valid at our site and was reliable externally. It can support clinical decision-making, especially when invasive add-on strategies are considered. The score was not studied in patients with basilar artery occlusion. Further external validation is warranted.

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GLOSSARY

AHA = American Heart Association; AUC-ROC = area under the receiver operating characteristic curve; FDA = Food and Drug Administration; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OTT = onset-to-treatment time.

Not all acute ischemic stroke patients respond to IV alteplase,1,2 as only half of the patients achieve recanalization.3 Approximately 50% will have a good outcome (independence in activities of daily life and modified Rankin Scale [mRS] score 0–2). The efficacy of IV alteplase decreases substantially with increasing onset-to-treatment time (OTT).2 Other factors influencing final functional outcome after IV alteplase include baseline NIH Stroke Scale (NIHSS) score, patient age, blood glucose level on admission, and the presence of hyperdense cerebral artery sign and early infarct signs on admission head CT scan,4,5,6 all of which are available shortly after patient admission, hence, before alteplase administration. In some patients, events such as reocclusion, recanalization with insufficient reperfusion, recanalization causing hemor-
rhage, recanalization in a vascular territory that is already infarcted, and spontaneous recovery may also alter patient outcomes.

A reliable scoring tool for prediction of long-term outcome of acute ischemic stroke patients treated with IV alteplase would be useful for at least 2 reasons: 1) early estimation of prognosis and 2) early identification of such patients who have a very high likelihood for a miserable outcome despite IV thrombolytic treatment. This information can lead to rapid arrangements for invasive add-on treatment strategies such as endovascular treatment or hypothermia.\(^7,8\)

Our aim was to develop an outcome prediction scoring tool that is based on baseline parameters, is quick to perform, is based on objective criteria, and is not costly. We present the DRAGON score, derived from our single-center cohort of IV alteplase–treated acute ischemic stroke patients. We internally cross-validated the score and performed external validation.

**METHODS** Derivation cohort. The baseline cohort included a total of 1,529 consecutive acute ischemic stroke patients treated with IV alteplase (0.9 mg/kg body weight) according to the written institutional guidelines at the Helsinki University Central Hospital, Helsinki, Finland, between 1995 and September 2010.\(^5\) In the present study, we excluded 152 patients with basilar artery occlusion because their natural history and treatment protocol differ markedly, i.e., always including concomitant full-dose IV heparin and allowing for OTT of up to 48 hours in patients with progressing symptoms.\(^9\)

Pretreatment NIHSS score and 3-month mRS score were assessed by certified stroke neurologists. Good 3-month outcome was defined as mRS score 0–2 (independence in daily living). Miserable outcome was defined as mRS score 5 (bedridden, incontinent, and requiring constant nursing care and attention) and mRS score 6 (dead). Poor outcome was defined as mRS score 3–6. No follow-up data were available for 27 patients,\(^1\), and necessary baseline parameters were not available for 31 patients, all of whom were excluded from the analyses, leaving 1,319 eligible patients treated with IV alteplase within 4.5 hours from symptom onset. None of these patients underwent an endovascular procedure after IV alteplase. Early infarct signs refer to an observation of any of the following: hypodensity of basal ganglion outline, loss of insular ribbon, or effacement of sulci.

Internal cross-validation with bootstrap. Internal cross-validation of the regression model between parameters of the DRAGON score and 3-month miserable outcome (mRS score 5–6) was based on 1,000 bootstrap replicates (R-project 2.10.1, package DAAG version 1.03). We reported estimated mean accuracy and 95% confidence intervals.

External validation cohort. After the score was established, we validated it externally in a cohort of acute ischemic stroke patients treated with the same dose of IV alteplase within 4.5 hours at the Department of Neurology, University Hospital Basel, Basel, Switzerland (between 2005 and January 2011, n = 414). Essential baseline parameters were missing in 81 patients, leaving 333 eligible patients. None of these patients underwent an endovascular procedure after IV alteplase.

**Statistical analyses.** Univariate comparison of groups in both cohorts was performed with the Mann-Whitney rank sum test for continuous variables (after testing for normal distribution) and with the Pearson \(\chi^2\) test for discrete variables. The predictive value of parameters associated with poor 3-month mRS score in the derivation cohort was evaluated with multivariable logistic regression, and the score was developed according to the magnitude of regression coefficients. The description of the multivariable model is as follows:

1. Selection of independent variables. We limited the likelihood of chance associations by only studying factors that had been shown to be significantly independently associated with outcome of ischemic stroke patients in previous studies.\(^2,4–6,10\)

Hence, the DRAGON score: (hypodense) middle cerebral artery sign or early infarct signs on admission CT head scan, prestroke modified Rankin Scale score \(>1\), age, glucose level on admission, OTT, and NIHSS score. We previously tested 15 additional parameters; however, they were not included in the score model because none of them was associated with outcome.\(^7\) In the derivation cohort, we tested the predictive value of multiple combinations of the baseline parameters included in the DRAGON score, and, for continuous variables, categorizations with various cutoff values.

2. Fitting procedure. All variables included in the DRAGON score were forced into the model.

3. Cross-validation. Internal cross-validation was performed using the bootstrap method, and an external validation was performed.

4. Statistical significance. Statistical significance was set at 95%, and two-sided \(p\) values together with 95% confidence intervals are reported for each variable and the entire model.

5. Statistics. Discrimination statistics (area under the receiver operating characteristic curve [AUC-ROC]) described how well the entire model matched the observed values. We considered AUC-ROC >0.75 as an acceptable value. Statistical packages SPSS 17.0 (SPSS Inc., Chicago, IL) and Confidence Interval Analysis 2.1.2 (University of Southampton) were used.

**RESULTS** The demographics and baseline characteristics of patients included in the derivation (\(n = 1,319\)) and the validation cohort (\(n = 333\)) are presented in table 1. The DRAGON score consists of variables that are available upon or shortly after ad-
mission, before administration of alteplase, with a scale ranging from 0 to 10 points (table 2). Regression coefficients used for the score derivation are shown in table e-1 on the Neurology® Web site at www.neurology.org. In general, patients in the validation cohort were older, received the treatment later, had more severe symptoms and signs on admission, more frequently had a hyperdense cerebral artery sign on admission head CT scan, more frequently had a history of atrial fibrillation and hypertension, and less frequently had hyperlipidemia (table 1). There were more patients with miserable outcome in the validation cohort.

Distribution of 3-month outcome per increasing points for the DRAGON score in the derivation cohort is shown in figure 1. The higher the DRAGON score was, the higher the likelihood of miserable outcome. Accuracy of the derivation model based on 1,000 bootstrap replicates was 86% (84%–89%). The performance of the DRAGON score in the derivation cohort (evaluated with AUC-ROC) was 0.84 (0.80–0.87).

The model was externally validated in a cohort of patients treated at the University Hospital Basel (figure 2) with AUC-ROC of 0.80 (0.74–0.86). There was no statistical difference in AUC-ROC between the derivation and validation cohorts (figure e-1). Finally, we calculated specificity, sensitivity, and likelihood ratios for each individual DRAGON score (table 3). In both extreme poles of the DRAGON score, the specificity reaches up to 100%.

**DISCUSSION** Here, we present the DRAGON score (table 2), which reliably predicts outcome of IV alteplase–treated ischemic stroke patients at our site (figure 1), with accuracy of the model of 86% (84%–89%). External validation of the DRAGON score showed very similar results (figure 2). There are several differences in baseline characteristics between the derivation and validation cohorts (table 1). Different baseline NIHSS scores well reflect the changes in IV alteplase treatment in our institution in the recent years. More patients with mild strokes (baseline NIHSS score <H110215) were treated at our site, which reflects the current institutional6 and international guidelines and licenses,11,12 and is in line with previ-

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### Table 1 Demographics, baseline characteristics, and proportions of the 3-month outcome

<table>
<thead>
<tr>
<th>Category</th>
<th>Derivation cohort (n = 1319)</th>
<th>External validation (n = 333)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>69 (60–77)</td>
<td>75 (65–81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>44.7%</td>
<td>41.5%</td>
<td>0.29</td>
</tr>
<tr>
<td>Onset to treatment time, min, median (IQR)</td>
<td>118 (88–158)</td>
<td>160 (135–195)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline NIHSS score, points, median (IQR)</td>
<td>9 (5–14)</td>
<td>12 (7–17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early infarct signs, %</td>
<td>17.7</td>
<td>28.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prestroke mRS score &gt; 1, %</td>
<td>6.2</td>
<td>4.9</td>
<td>0.35</td>
</tr>
<tr>
<td>BP and glucose level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP before, mm Hg, median (IQR)</td>
<td>156 (140–171)</td>
<td>155 (139–174)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diastolic BP before, mm Hg, median (IQR)</td>
<td>83 (74–92)</td>
<td>85 (75–95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Glucose, mmol/L, median (IQR)</td>
<td>6.6 (5.7–7.8)</td>
<td>6.5 (5.6–7.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>59.7</td>
<td>66.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14.5</td>
<td>15.9</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>12.7</td>
<td>11.3</td>
<td>0.49</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39.1</td>
<td>27.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27.7</td>
<td>33.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Proportions of 3-month outcome, mRS score, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>60.5</td>
<td>56.8</td>
<td>0.24</td>
</tr>
<tr>
<td>3–4</td>
<td>25.7</td>
<td>23.4</td>
<td>0.43</td>
</tr>
<tr>
<td>5–6</td>
<td>13.8</td>
<td>19.8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

### Table 2 DRAGON score (0–10 points) for prediction of the 3-month outcome in ischemic stroke patients undergoing intravenous alteplase

<table>
<thead>
<tr>
<th>Category</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hyper)Dense cerebral artery sign or early infarct signs on admission CT head scan</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Either of them</td>
<td>1</td>
</tr>
<tr>
<td>Both</td>
<td>2</td>
</tr>
<tr>
<td>mRS score &gt;1, prestroke</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>0</td>
</tr>
<tr>
<td>65–79 y</td>
<td>1</td>
</tr>
<tr>
<td>≥80 y</td>
<td>2</td>
</tr>
<tr>
<td>Glucose level on admission</td>
<td></td>
</tr>
<tr>
<td>≤8 mmol/L (144 mg/dL)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;8 mmol/L (144 mg/dL)</td>
<td>1</td>
</tr>
<tr>
<td>Onset to treatment time</td>
<td></td>
</tr>
<tr>
<td>≤90 min</td>
<td>0</td>
</tr>
<tr>
<td>&gt;90 min</td>
<td>1</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>0</td>
</tr>
<tr>
<td>5–9</td>
<td>1</td>
</tr>
<tr>
<td>10–15</td>
<td>2</td>
</tr>
<tr>
<td>&gt;15</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
ous reports on outcome of patients with mild or improving symptoms. Observed heterogeneity (table 1) between the 2 cohorts supports generalizability of the score. Moreover, performance of the score model (AUC-ROC) in both cohorts was very good with no significant difference between the 2 cohorts (figure e-1). Specificity of the prediction at both extreme poles of the score reaches up to 100%, and the likelihood ratios are correspondingly high (table 3). Maximum possible specificity minimizes the possibility of incorrect prediction of dismal prognosis, which gains more importance when invasive add-on rescue strategies, which are not risk-free, are being considered. These have risks of severe complications and are costly and labor-intensive, requiring a highly trained expert labor force urgently, and their efficacy has not yet been tested in randomized trials.

There have been 2 past attempts to predict 3-month outcome in ischemic stroke patients. It is not our intention to show superiority of the DRAGON score over the earlier scores; however, we want to point out the major differences between them. The first comes from the analysis of the National Institute of Neurological Disorders and Stroke trial, but rather than predicting the outcome of alteplase-treated ischemic stroke patients, it was developed to predict the outcome of untreated patients. That score was derived to predict outcome using baseline, 2-hour, 24-hour, and 7- to 10-day data and included the total baseline NIHSS score and its components and a history of atrial fibrillation. Another score, the HAT score, although also tested in the original report for the predictability of long-term outcome, was developed as a tool to predict the risk of symptomatic intracerebral hemorrhage after IV alteplase. This score consists of 3 parameters, which are included in the DRAGON score: baseline glucose level (or history of diabetes), baseline NIHSS score, and early infarct signs on the admission head CT scan. However, the categorization of the HAT score is different from that of the DRAGON score. The worst possible points a patient can receive in the HAT score for baseline NIHSS score is bordering on the contraindication for IV alteplase in our institution and European product license and was given a warning by the Food and Drug Administration (FDA) and American Heart Association (AHA) guidelines. For early infarct signs, the worst category in the HAT score (hypodensity comprising more than one-third of middle cerebral artery territory) is already a contraindication for IV alteplase treatment in our institution and in the European product license and the AHA guidelines and warned about by the FDA. Furthermore, in addition to the predictors included in the HAT score, more predictors of long-term outcome have been identified previously and are included in the DRAGON score. Finally, AUC-ROC of the HAT
score for predicting 3-month mRS score 5–6 was 0.75 (0.69–0.80), whereas it was 0.84 (0.80–0.87) for the DRAGON score.

Although it is not a predicting score per se, the 3-month outcome can be reliably derived from early functional activity level as observed 7 to 10 days after an index ischemic stroke as recently reported by Ovbiagele and Saver. Our aim was to develop a score based solely on parameters available at or shortly after admission and before administration of IV alteplase to help in evaluation of the acute situation so the physician can deliver accurate information and the patient and relatives can make choices for application of the most relevant treatment with the greatest speed.

Our study has some limitations. Although we controlled for known stroke outcome predictors, we cannot rule out the possibility that additional baseline variables (unmeasured confounds) may have some impact. The score does not apply to patients with basilar artery occlusion who were excluded from the study because of the marked difference in their natural history and treatment protocol. Another limitation is the small size of the external validation cohort, and the score has to be further evaluated in other centers. The interrater reliability of the DRAGON score was not assessed, but assessment is warranted in future studies. However, we believe that there is little variability in our center because of the standardized training process in the stroke research unit.

The DRAGON score is simple and fast to obtain, it is cost-free, and it is valid at our site for prediction of outcome of acute ischemic stroke patients treated with IV alteplase (excluding patients with basilar artery occlusion). It was evaluated externally, where it showed similar performance. It consists solely of parameters known at admission. Median door-to-needle time in our institution is 22 minutes, and our first experiences with using the DRAGON score in clinical practice showed that it takes less than 1 minute to obtain the score (data not shown). The DRAGON score not only provides an immediate estimation of the outcome but also can support the decision-making process in individual patients regarding possible rescue add-on therapies when IV alteplase alone does not offer high likelihood of good outcome. Once considered, arrangements for rescue therapies should be made quickly because “time is brain.” Patients with scores of 0–2 or 3 can be informed that the likelihood for a good recovery after IV alteplase is extremely high or high, respectively; with specificity being almost 100% or 90%. For patients with scores of 7–10, the chances for good recovery are extremely low. In fact, patients with scores of 8 and 9–10 never achieved good outcome, whereas the proportion of miserable outcome was 70% and 100%, respectively, and specificity for this prognosis is 99%–100%. Therefore, these patients may be suitable candidates for 1) add-on rescue approaches, e.g., endovascular procedures in patients with persistent major cerebral artery occlusion, 2) enrollment in future randomized controlled trials testing rescue strategies (not only endovascular), or 3) enrollment in trials testing new experimental treat-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Sensitivity, specificity, and likelihood ratio for good and miserable 3-month outcome per each individual DRAGON score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRAGON score</td>
<td>Good outcome (mRS score 0–2)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity, %</td>
</tr>
<tr>
<td>0–1</td>
<td>14 (12–16)</td>
</tr>
<tr>
<td>2</td>
<td>21 (19–24)</td>
</tr>
<tr>
<td>3</td>
<td>25 (22–27)</td>
</tr>
<tr>
<td>4</td>
<td>18 (16–21)</td>
</tr>
<tr>
<td>5</td>
<td>15 (12–17)</td>
</tr>
<tr>
<td>6</td>
<td>6 (5–8)</td>
</tr>
<tr>
<td>7</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>8–10</td>
<td>0 (0–1)</td>
</tr>
</tbody>
</table>

Abbreviations: LR = likelihood ratio; mRS = modified Rankin Scale.

*Note that sensitivity, specificity, and likelihood ratios were not obtained from the corresponding receiver operating characteristic curves (hence the increasing values of the score do not represent various cutoff points of the DRAGON score) but were calculated for each individual value of the score using a 2 x 2 table. For example, for the DRAGON score of 7 and the miserable outcome the table would look like this:

<table>
<thead>
<tr>
<th>Miserable outcome</th>
<th>Nonmiserable outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRAGON score 7</td>
<td>a</td>
</tr>
</tbody>
</table>

Sensitivity and specificity based on the cutoff points of the receiver operating characteristic curve are outlined in figure e-1.
ment modalities. Further external validation of the DRAGON score is warranted.

AUTHOR CONTRIBUTIONS
Dr. Strbian: design and conceptualization of the study, data collection, analysis and interpretation of the data, statistical analysis, drafting of the manuscript. Dr. Meretoja: data collection, analysis and interpretation of the data, revising the manuscript. Dr. Ahlhelm: data collection, interpretation of the data, revising the manuscript. Dr. Pirkkanemi: analysis of the data, statistical analysis, revising the manuscript.

Drs. Lyner, Kaste, and Engelert: conceptualization of the study, data collection, interpretation of the data, revising the manuscript. Dr. Tatlisumak: design and conceptualization of the study, data collection, interpretation of the data, revising the manuscript.

DISCLOSURE
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