Validation of the DRAGON Score in 12 Stroke Centers in Anterior and Posterior Circulation

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Background and Purpose—The DRAGON score predicts functional outcome in the hyperacute phase of intravenous thrombolysis treatment of ischemic stroke patients. We aimed to validate the score in a large multicenter cohort in anterior and posterior circulation.

Methods—Prospectively collected data of consecutive ischemic stroke patients who received intravenous thrombolysis in 12 stroke centers were merged (n=5471). We excluded patients lacking data necessary to calculate the score and patients with missing 3-month modified Rankin scale scores. The final cohort comprised 4519 eligible patients. We assessed the performance of the DRAGON score with area under the receiver operating characteristic curve in the whole cohort for both good (modified Rankin scale score, 0–2) and miserable (modified Rankin scale score, 5–6) outcomes.

Results—Area under the receiver operating characteristic curve was 0.84 (0.82–0.85) for miserable outcome and 0.82 (0.80–0.83) for good outcome. Proportions of patients with good outcome were 96%, 93%, 78%, and 0% for 0 to 1, 2, 3, and 8 to 10 score points, respectively. Proportions of patients with miserable outcome were 0%, 2%, 4%, 89%, and 97% for 0 to 1, 2, 3, 8, and 9 to 10 points, respectively. When tested separately for anterior and posterior circulation, there was no difference in performance (P=0.55); areas under the receiver operating characteristic curve were 0.84 (0.83–0.86) and 0.82 (0.78–0.87), respectively. No sex-related difference in performance was observed (P=0.25).

Conclusions—The DRAGON score showed very good performance in the large merged cohort in both anterior and posterior circulation strokes. The DRAGON score provides rapid estimation of patient prognosis and supports clinical decision-making in the hyperacute phase of stroke care (eg, when invasive add-on strategies are considered). (Stroke. 2013;44:2718-2721.)

Key Words: ischemic stroke ◼ outcome ◼ prognosis ◼ thrombolysis

Intravenous thrombolysis (IVT) with alteplase is the only approved clot-busting medical therapy in acute ischemic stroke, yet approximately half of the patients treated achieve recanalization in acute setting.1 Regarding functional benefit, a similar percentage of patients achieve good outcome (independence in activities of daily life; modified Rankin scale [mRS] score, 0–2).2,3 For patients who do not benefit from thrombolysis, alternative treatment strategies may be considered. In such cases, it is of utmost importance to predict the benefit of IVT as soon as possible after patient admission, because its efficacy decreases substantially with increasing onset-to-treatment time.2 We recently described such a
prognostic tool, the DRAGON score, that was derived in the Helsinki cohort (n=1319) and validated in the Basel cohort (n=333). It consists of parameters that are available soon after patient admission—before IVT administration (Table 1). The score was developed for ultraearly estimation of patient prognosis. It reliably identifies patients who will very likely benefit from IVT but also those with high likelihood of miserable outcome, despite IVT. In the latter group, an invasive endovascular procedure can be an alternative treatment of choice, although currently that is not evidence-based. Such an approach is an alternative in some centers in situations in which severe symptoms persist, despite thrombolytic treatment, as a rescue strategy.

The DRAGON score showed very good performance in the original derivation and validation cohorts: area under the receiver operating characteristic curve (AUC-ROC) 0.84 (0.80–0.87) and 0.80 (0.74–0.86), respectively. Furthermore, the DRAGON score was recently adapted for patients undergoing MRI instead of CT as the first-line imaging modality, reporting performance similar to that in the original publication. Discrimination statistics (AUC-ROC) tested the performance of the score for good (mRS score, 0–2) and miserable (mRS score, 5–6) outcomes. Two prespecified subgroup analyses were performed: AUC-ROC in anterior versus posterior circulation strokes and in women versus men. Positive and negative likelihood ratios, positive and negative predictive values, and their 95% confidence intervals were calculated for different cut-off values of the score. Calibration of the model was tested with the Hosmer–Lemeshow test. Analyses were performed on IBM SPSS 18 (IBM Corp, Armonk, NY).

### Patients and Methods

**Study Setting**

The study includes data from 12 European and Australian stroke centers and was approved by the relevant authorities in each participating center, if required. This study was approved in the coordinating center (Helsinki) as a quality registry and did not require ethical board review. All patients were prospectively included in the database. Data from individual consecutive patients receiving IVT for acute ischemic stroke (without subsequent endovascular procedure) were collected with a standardized form with predefined variables. Local study investigators completed the forms systematically using prospectively ascertained in-hospital thrombolysis registries. Completed forms from all centers were compiled in the coordinating center (Helsinki), where the analyses of the pooled data (n=5471) were performed. We only considered patients with information available for all necessary baseline parameters, some of which were missing for 820 patients (footnote of Table 2), leaving 4519 eligible patients. None of the patients from the original derivation cohort was included in the current analysis. The merged validation cohort comprises patients with both anterior and posterior circulation strokes. CT scans were evaluated by the local investigators, who were blinded to the results of CT angiography (if performed). Early infarct signs refer to an observation of any of the following: hypodensity in any cerebral artery territory, loss of basal ganglion outline, loss of insular ribbon, or effacement of sulci.

### Statistical Analyses

The derivation of the DRAGON score (Table 1) is described in the original publication. Discrimination statistics (AUC-ROC) tested the performance of the score for good (mRS score, 0–2) and miserable (mRS score, 5–6) outcomes. Two prespecified subgroup analyses were performed: AUC-ROC in anterior versus posterior circulation strokes and in women versus men. Positive and negative likelihood ratios, positive and negative predictive values, and their 95% confidence intervals were calculated for different cut-off values of the score. Calibration of the model was tested with the Hosmer–Lemeshow test. Analyses were performed on IBM SPSS 18 (IBM Corp, Armonk, NY).

### Results

The demographics and baseline characteristics of patients included in the merged cohort (n=4519) are presented in Table 2.
Table 2. Numbers of included patients per center are as follows: Barcelona (n=226), Basel (n=694), Bern (n=79), Box Hill (n=455), Erlangen (n=688), Helsinki (n=467), Lausanne (n=463), Lille (n=277), Melbourne (n=336), Perugia (n=58), St. Gallen (n=153), and Tampere (n=623). Proportions of patients per each cut-off of each parameter of the score are outlined in Table 1 in the online-only Data Supplement together with adjusted odds ratios for miserable and good outcomes per each parameter of the score.

Distributions of 3-month outcome per increasing points of the DRAGON score are outlined in Figure 1. The Hosmer–Lemeshow test showed good calibration of the model in the merged cohort ($\chi^2=1.2$; degrees of freedom=5; $P=0.94$). Predicted risk of miserable and good outcomes per categories of the DRAGON score and observed percentages are depicted in Figures I and II in the online-only Data Supplement. Performance of the DRAGON score in the entire cohort as judged with AUC-ROC was 0.84 (0.82–0.85; Figure 2) for miserable outcome and 0.82 (0.80–0.83) for good outcome, without statistical difference between them ($P=0.10$). The majority of patients had stroke in anterior circulation (n=3944; 87.3%). There was no difference in AUC-ROC ($P=0.55$) between anterior and posterior circulation strokes: 0.84 (0.83–0.86) and 0.82 (0.78–0.87), respectively. The same held true for sex-related analysis: AUC-ROC was 0.85 (0.82–0.87) in women and 0.82 (0.81–0.84) in men ($P=0.25$).

Proportions of patients with miserable outcomes (mRS score, 5–6) were 0%, 2%, 4%, 89%, and 97% for 0 to 1, 2, 3, 8, and 9 to 10 points, respectively. For mRS score 0 to 3 and DRAGON score 9 to 10, positive likelihood ratio was 45.4 (13.9–147.6), negative likelihood ratio was 1.0 (0.9–1.0), positive predictive value was 91.7% (77.5–98.2), negative predictive value was 81.1% (79.9–82.2), specificity was 99.9% (99.8–100), and sensitivity was 3.7% (2.6–5.2). In case of DRAGON score 8 to 10, the corresponding numbers were as follows: positive likelihood ratio was 24.9 (16.3–38.1), negative likelihood ratio was 0.8 (0.8–0.9), positive predictive value was 85.8% (79.6–90.7), negative predictive value was 83.1% (81.9–84.2), specificity was 99.3% (99.0–99.6), and sensitivity was 16.4 (14.1–19.1).

Proportions of patients with good outcome (mRS score, 0–2) were 96%, 93%, 78%, and 0% for 0 to 1, 2, 3, and 8 to 10 score points, respectively. For mRS score 0 to 2 and DRAGON score 0 to 2, positive likelihood ratio was 8.3 (6.6–10.5), negative likelihood ratio was 0.7 (0.7–0.7), positive predictive value was 91.5% (89.4–93.3), negative predictive value was 51.8% (50.2–53.4), specificity was 96.4 (95.4–97.1), and sensitivity was 30.3 (28.5–32.1).

**Discussion**

In a large multicenter cohort of 4519 patients, we successfully validated the DRAGON score, which accurately predicts outcome of IVT-treated ischemic stroke patients. Performance of the score was similarly good (AUC-ROC=0.85) in the original derivation cohort4 and in the multicenter-merged cohort (Figure 2). Baseline characteristics were similar between original derivation cohort and the current merged cohort (Table 2). Advantages of the DRAGON score are manifold: (1) it is simple, (2) does not require any computer calculations, (3) consists of parameters that are available immediately after patient admission, (4) is very fast to calculate, and (5) is cost-free. In this multicenter study, we improved the generalizability of the DRAGON score by validating it in patients with both anterior and posterior circulation ischemic strokes and in women and men separately.

The score estimates which patients have a very high likelihood of miserable outcome (bedridden incontinent patient in institutional care or death; mRS score, 5 and 6, respectively), despite administration of the only approved recanalization treatment for acute ischemic stroke, IVT with alteplase. Such patients are, in some centers, offered rescue add-on therapy (eg, endovascular procedure). These procedures are, however, not currently evidence-based. In case the use of such add-on rescue strategies is in line with local institutional protocols, the clinicians must act promptly to not lose time.\(^{10}\) In such situations, rapid arrangements of the endovascular procedures can be based on the DRAGON score, which is calculated even before IVT administration.

Based on the performance of the DRAGON score in the derivation and validation cohorts, patients with scores 0 to 3 have very high likelihood for good recovery after IVT. For patients with scores 7 to 10, the chances for good recovery are very
low. In institutions where rescue endovascular procedures are not performed because of a lack of randomized trial data, these patients may be recruited into randomized controlled trials testing endovascular procedures or other add-on experimental treatments. Naturally, not all patients with high DRAGON scores would be suitable for endovascular procedures (eg, a patient >80 years with extensive early infarction, high glucose, previous disability, and late presentation). Hence, institutional inclusion criteria for endovascular approach have to be considered in individual cases after obtaining informed consent from patients or their caregivers. Finally, because thrombolyis treatment has a risk of intracranial hemorrhage that can influence patient outcome,11 the final decision can be based both on the DRAGON score (predicting functional outcome) and a score predicting risk of symptomatic intracranial hemorrhage after IVT (eg, the SEDAN score).12

There are some limitations of this study. The datasets include mostly white patients. Also, assessments of early ischemic changes on pretreatment CT (eg, posterior circulation ASPECTS score)13 and the role of hyperdense signs in the basilar artery or changes on pretreatment CT (eg, posterior circulation ASPECTS score)13 and the role of hyperdense signs in the basilar artery or posterior cerebral artery are warranted. The strength of the study is the large number of included patients. Furthermore, baseline characteristics and the outcome distribution in our dataset were similar to those of the Safe Implementation of Thrombolysis registry,14 with somewhat different baseline National Institutes of Health Stroke Scale scores (median, 10 in our database and 12 in the SITS database).

In conclusion, the DRAGON score provides an accurate and immediate estimation of functional outcome in IVT-treated ischemic stroke patients. Validation in a large multicenter cohort and in prespecified subgroups confirms its generalizability.

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**Disclosures**
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**References**
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Supplementary Table I. Analysis of selected parameters per NIHSS and OTT category

<table>
<thead>
<tr>
<th>Paramater</th>
<th>No (%)</th>
<th>Adjusted OR (95% CI) Miserable Outcome</th>
<th>Adjusted OR (95% CI) Good Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HyperDense cerebral artery sign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1075 (23.8%)</td>
<td>1.64 (1.34-2.00)</td>
<td>0.69 (0.58-0.83)</td>
</tr>
<tr>
<td>no</td>
<td>3444 (76.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early infarct signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1187 (26.3%)</td>
<td>1.30 (1.07-1.58)</td>
<td>0.64 (0.54-0.75)</td>
</tr>
<tr>
<td>no</td>
<td>3332 (73.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-stroke mRS&gt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>278 (6.2%)</td>
<td>1.94 (1.44-2.62)</td>
<td>0.14 (0.09-0.20)</td>
</tr>
<tr>
<td>no</td>
<td>4241 (93.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>1166 (25.8%)</td>
<td>1.06 (1.05-1.07)</td>
<td>0.965 (0.960-0.970)</td>
</tr>
<tr>
<td>65-79 y</td>
<td>1954 (43.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 y</td>
<td>1399 (31.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 8 mmol/L (144 mg/dL)</td>
<td>1106 (24.5%)</td>
<td>1.06 (1.03-1.08)</td>
<td>0.95 (0.93-0.98)</td>
</tr>
<tr>
<td>≤ 8 mmol/L (144mg/dL)</td>
<td>3413 (75.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset-to-treatment time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 90 min</td>
<td>3766 (83.3%)</td>
<td>1.001 (1.000-1.002)</td>
<td>0.999 (0.998-1.000)</td>
</tr>
<tr>
<td>≤ 90 min</td>
<td>753 (16.7%)</td>
<td></td>
<td></td>
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<tr>
<td>NIHSS on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 15</td>
<td>1286 (28.5%)</td>
<td>1.16 (1.14-1.17)</td>
<td>0.86 (0.85-0.87)</td>
</tr>
<tr>
<td>10-15</td>
<td>1113 (24.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>1431 (31.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>689 (15.2%)</td>
<td></td>
<td></td>
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</tbody>
</table>
Supplementary Figure I

Legend: Predicted risk of miserable outcome (mRS 5-6) per categories of the DRAGON score and observed percentages.

Supplementary Figure II

Legend: Predicted risk of good outcome (mRS 0-2) per categories of the DRAGON score and observed percentages.