The iScore Predicts Poor Functional Outcomes Early After Hospitalization for an Acute Ischemic Stroke

Gustavo Saposnik, MD, MSc, FAHA; Stavroula Raptis, MSc; Moira K. Kapral, MD, FRCP; Ying Liu, MSc; Jack V. Tu, MD, FRCP; Muhammad Mamdani, PharmD, MPH, MA*; Peter C. Austin, PhD*; on behalf of the Investigators of the Registry of the Canadian Stroke Network and the Stroke Outcome Research Canada (SORCan—www.sorcan.ca) Working Group

Background and Purpose—The iScore is a prediction tool originally developed to estimate the risk of death after hospitalization for an acute ischemic stroke. Our objective was to determine whether the iScore could also predict poor functional outcomes.

Methods—We applied the iScore to patients presenting with an acute ischemic stroke at multiple hospitals in Ontario, Canada, between 2003 and 2008, who had been identified from the Registry of the Canadian Stroke Network regional stroke center database (n=3818) and from an external data set, the Registry of the Canadian Stroke Network Ontario Stroke Audit (n=4635). Patients were excluded if they were included in the sample used to develop and validate the initial iScore. Poor functional outcomes were defined as: (1) death at 30 days or disability at discharge, in which disability was defined as having a modified Rankin Scale 3 to 5; and (2) death at 30 days or institutionalization at discharge.

Results—The prevalence of poor functional outcomes in the Registry of the Canadian Stroke Network and the Ontario Stroke Audit, respectively, were 55.7% and 44.1% for death at 30 days or disability at discharge and 16.9% and 16.2%, respectively, for death at 30 days or institutionalization at discharge. The iScore stratified the risk of poor outcomes in low- and high-risk individuals. Observed versus predicted outcomes showed high correlations: 0.988 and 0.940 for mortality or disability and 0.985 and 0.993 for mortality or institutionalization in the Registry of the Canadian Stroke Network and Ontario Stroke Audit cohorts.

Conclusions—The iScore can be used to estimate the risk of death or a poor functional outcome after an acute ischemic stroke. (Stroke. 2011;42:00-00.)

Key Words: ischemic stroke severity ■ model ■ mortality ■ outcome ■ risk score ■ stroke

Stroke is a devastating disease for patients and their families and a leading cause of adult disability. Up to 85% of patients with stroke experience hemiparesis immediately after stroke, and between 55% and 75% of survivors continue to experience motor deficits, which are associated with diminished quality of life.1,2 The risk of a disabling stroke increases steeply with age, and as the population progressively ages, an increased prevalence of functional impairment among stroke survivors is expected.3,4 Clinicians usually attempt to estimate prognosis after stroke in part to relay this information to the patient and his or her family and in part to assist in treatment decisions. Although a variety of risk prediction tools exist, few have focused on the prediction of disability or other functional

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outcomes after stroke. For some patients and their families, surviving with a major disability or living in a long-term care facility may be as grave an outcome as dying after stroke. As such, the prediction of combined mortality with poor functional outcomes (disability at discharge or discharge to a long-term care facility) early after hospitalization may be useful for patients, their families, and clinicians in guiding supportive care plans, discharge planning, facilitating counseling, or discussions related to end-of-life decisions.

The iScore is a recently developed and validated risk score that can be used to estimate the risk of short- and long-term mortality after an acute ischemic stroke. The iScore categorizes patients with ischemic stroke into 5 risk categories, from very low to very high average risk, using clinical parameters and comorbid conditions, which include age, sex, stroke severity, stroke subtype, smoking status, preadmission dependency, and the presence or absence of atrial fibrillation, heart failure, previous myocardial infarction, cancer, renal failure on dialysis, and hyperglycemia on admission. Variables associated with death may be similar to those that predict poor functional outcome (eg, disability or institutionalization at discharge) after an ischemic stroke. Our objective was to evaluate the ability of the original iScore to predict 2 clinically relevant functional outcomes in patients admitted with an acute ischemic stroke: (1) death at 30 days or disability at discharge; and (2) death at 30 days or institutionalization at discharge.

Methods

We used 2 separate cohorts, each with differing accrual methods, to assist in the validation of the iScore for the 2 new outcomes. The Registry of the Canadian Stroke Network (RCSN) collects data on all consecutive patients seen at 12 regional stroke centers in the province of Ontario, Canada, and on a random sample of patients seen at all hospitals across the province through a periodic Ontario Stroke Audit (OSA).

The RCSN regional center database collects data by chart abstraction performed during and after admission to the hospital for the index event by trained neurology research nurses using custom software. The audit uses population-based, random sampling to collect data from patients with stroke seen in emergency departments or admitted to the hospital with a diagnosis of stroke in 154 teaching and community-based hospitals across Ontario. Data for the OSA are also collected through patient chart abstraction. Further details on the OSA can be obtained from the RCSN Report at the 2008-2009 OSA at www.rcsn.org.

The RCSN has the designation of a “prescribed registry,” thereby allowing the collection of patient-level information without consent for the purpose of facilitating the provision of stroke care in Ontario.

Information on poststroke all-cause mortality (including death after hospital discharge) was available through linkages to the Ontario Registered Persons Database (RPDB), which was available through the Institute for Clinical Evaluative Sciences. The RPDB is a population-based administrative database including basic demographic data and date of death, which provides complete follow-up for all residents in the province.

To assess and grade the level of stroke disability at discharge, the modified Rankin Scale was used; moderate to severe disability was defined as modified Rankin Scale ≥3. For all registry participants, the modified Rankin Scale was abstracted from patient charts according to the neurological assessment at discharge. Stroke severity on presentation was captured from the neurological assessment at admission using the Canadian Neurological Scale (CNS), which is a simple and validated scale including the following components: comprehension, level of consciousness, speech, and motor function (face, arm, and leg). Lower scores indicate greater stroke severity.

Stroke severity was categorized a priori as mild (CNS ≥8), moderate (score of 5–7), or severe (score of 1–4) based on previous studies. All ischemic stroke subtypes were included in the present study. Ischemic stroke subtype was classified as lacunar, nonlacunar, and undetermined according to the Trial of Org 10172 in Acute Stroke Treatment criteria by the study coordinator based on documentation by the treating physician and the investigations recorded in the chart.

Details of the selection of variables for the iScore, data sources, and the creation and conceptualization of the iScore have been published elsewhere. The risk scoring system is represented in Table 1.

Table 1. Risk Scoring System Derived From the 30-Day Mortality in the iScore

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>+Age (y)</td>
</tr>
<tr>
<td>Sex</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>+10</td>
</tr>
<tr>
<td>Stroke Severity (using Canadian Neurological Scale)</td>
<td></td>
</tr>
<tr>
<td>0*</td>
<td>+105</td>
</tr>
<tr>
<td>≤4</td>
<td>+65</td>
</tr>
<tr>
<td>5–7</td>
<td>+40</td>
</tr>
<tr>
<td>≥8</td>
<td>0</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>0</td>
</tr>
<tr>
<td>Nonlacunar</td>
<td>+30</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>+35</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>+10</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>+10</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>+35</td>
</tr>
<tr>
<td>Preadmission disability</td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>0</td>
</tr>
<tr>
<td>Dependent</td>
<td>+15</td>
</tr>
<tr>
<td>Glucose on admission</td>
<td></td>
</tr>
<tr>
<td>&lt;7.5 mmol/L (&lt;135 mg/dL)</td>
<td>0</td>
</tr>
<tr>
<td>≥7.5 mmol/L (≥135 mg/dL)</td>
<td>+15</td>
</tr>
</tbody>
</table>

*Patients in a coma should be assigned a score of 0.

Eligibility Criteria

We used 2 separate cohorts to evaluate the ability of the iScore to predict each of the composite outcomes. One of our study cohorts included patients aged ≥18 years of age with a primary diagnosis of acute ischemic stroke who were seen in the emergency department or admitted to any of the 12 regional stroke centers in Ontario between July 1, 2003, and June 30, 2008. During the initial derivation of the iScore, the RCSN data set was randomly split into derivation and validation components. To avoid an overestimation of the predictive ability of the iScore on the proposed functional outcomes, patients included in the sample used for the derivation of the iScore were not eligible for the present study. Our second study validation cohort was derived from patients seen at any hospital in the province and captured in the OSA. We included patients aged ≥18 years with a...
primary diagnosis for acute ischemic stroke and with data collected by the OSA in the fiscal years 2002–2003, 2004–2005, and 2008–2009. We thus used 2 study samples: first, patients with stroke in the RCSN registry who were not included in the derivation of the original iScore; second, patients with stroke in the OSA cohort.

Patients with missing baseline characteristics (eg, CNS score, glucose on admission; n = 910), those with transient ischemic attack or hemorrhagic stroke, and those with a significant disability coming from long-term care facilities were excluded (n = 221 [5.5%] in the RCSN cohort and n = 346 [6.9%] in the OSA).

Outcome Measures
Disability at discharge was defined as a score on the modified Rankin Scale of ≥3. Institutionalization was defined as having discharge disposition to long-term care or a complex continuing care facility.

The main outcomes of interest were 2 composite outcomes defined as: (1) death that occurred within 30 days after the stroke admission or severe disability at discharge (modified Rankin Scale = 3–5); and (2) death that occurred within 30 days after the stroke admission or discharge to a long-term care facility or complex continuing care facility (including palliative care).

Statistical Analysis
Chi-square tests were used to compare categorical variables between RCSN and OSA cohorts; analysis of variance or Kruskal-Wallis tests were used to compare mean and median differences for continuous variables in baseline characteristics. Details of the analytic approach for the creation of the iScore have been published elsewhere.6 Variables included in the iScore used to predict mortality at 30 days included age, sex, stroke severity (as determined by the CNS), stroke subtype (lacunar, nonlacunar, undetermined), predialysis independence, glucose on admission, and presence of atrial fibrillation, congestive heart failure, cancer, or renal failure (on dialysis). The scoring system was additive, and we used quintiles to divide the initial derivation cohort into 5 risk categories.6 To test the performance of the iScore for predicting death or disability, we used the same variables and redefined the outcomes as (1) disability at discharge or death at 30 days; and (2) institutionalization at discharge or death at 30 days.6

A logistic regression model with the iScore predictor variables and the iScore regression coefficients were used to predict the probability of the occurrence of each of the composite outcomes. Model discrimination was assessed by the C-statistics (equivalent to the area under the receiver operating characteristic curve).15 Calibration was assessed using the Hosmer-Lemeshow. However, because Hosmer-Lemeshow test is known to be oversensitive to small deviations from good fit in large samples, we compared predicted versus observed outcome at the risk score level.16 The observed and predicted outcomes were plotted as continuous function of the risk score. Pearson correlation coefficient was used to compare the observed and predicted outcomes at the risk score level. Analyses were conducted using SAS statistical software (Version 9.2; SAS Institute Inc, Cary, NC).

Approvals from the Institutional Review Board of St Michael’s Hospital as well as of each of the Institutional Review Boards of participating stroke centers and the RCSN Publications Committee were obtained before starting this study.

Results
Overall, there were 3818 eligible patients in the RCSN (who were not involved in the derivation of the original iScore) and 4635 eligible patients in the OSA. Patients in the RCSN were younger, had a higher prevalence of coronary artery disease and smoking, and had more severe strokes compared with patients in the OSA. There were no other significant differences in between the cohorts (Table 2).

Death at 30 days or disability at discharge occurred in 2126 (55.7%) patients in the RCSN regional center cohort and 2043 (44.1%) in the OSA cohort. There were 647 (16.9%) patients dead at 30 days or discharged to long-term care institutions in the RCSN and 751 (16.2%) in the OSA. Death at 30 days occurred in 478 patients (12.5%) in the RCSN and 502 patients (10.8%) in the OSA cohort. Overall, 5.6% (n = 212) patients in the RCSN and 6.4% (n = 298) patients in the OSA cohort were discharged to a long-term care institution.

Risk Score
The distribution of the iScore in both cohorts (RCSN validation cohort and OSA cohort) was approximately normally distributed with mean scores and SDs of 136.71 ± 39.32 for the RCSN validation cohort and 134.36 ± 33.43 for the OSA cohort. Quintiles of the original iScore were used to divide the cohorts into 5 risk categories. The magnitude of the scores had prognostic implications (Figure 1A–B). There was a graded increase risk for both outcomes and in both cohorts by quintile of risk score. The 30-day risk of mortality or disability at discharge in the RCSN cohort was 27.8% for Quintile 1; 37.3% for Quintile 2; 52.8% for Quintile 3; 80.5% for Quintile 4; and 91.9% for Quintile 5. Similarly, a graded increase in risk occurred with 30-day mortality or institutionalization at discharge. Death at 30 days or institutionalization at discharge for the RCSN cohort was 2.1% for Quintile 1; 4.6% for Quintile 2; 11.0% for Quintile 3; 24.2% for Quintile 4; and 50.9% for Quintile 5. In examining death at 30 days or disability at discharge and death at 30 days or institutionalization at discharge, the results for the OSA cohort resembled the trend of a graded increase (as observed in the RCSN) across each quintile, respectively, beginning in the second quintile. Mean predicted mortality for each quintile is provided in Supplemental Table I (http://stroke.ahajournals.org).

Because these results ignore within-quintile risk gradients, we also plotted the observed and predicted death at 30 days or disability at discharge (Figure 2A) and death at 30 days or institutionalization at discharge (Figure 2B) by narrower risk score categories, in which each risk score group was defined at 10-point intervals. Figure 2A–B shows a worsening prognosis with higher risk scores in the RCSN cohort.

In addition, we analyzed the predictive ability of the iScore by adding other comorbid conditions to those reported by other simple risk score models (Figure 3A–B).17,18 For example, for a lower risk category (70 years with a moderate stroke), the addition of male sex (10 points), presence of hyperglycemia (>135 mg/dL), and dependency on admission (+15 points each) would double the predicted 30-day mortality or disability at discharge from 34.8% to 67.2% (Figure 3A). Similarly, there is a significant increase in the estimated risk of death at 30 days or institutionalization at discharge from 8.04% (for a 90-year-old woman with a moderate stroke), to 26.1% for a same age man, by adding hyperglycemia and dependency on admission (Figure 3B).

A more impressive increase is observed for higher risk categories. For example, for an 80-year-old patient with severe stroke (+65 points), the addition of stroke subtype (nonlacunar = +30 points) or on dialysis (+35 points) would
quadruple the estimated risk of death or institutionalization from 14.8% to 66.4% (not shown in Figure 3).

Discrimination and Calibration of the iScore for the Functional Outcomes

In the RCSN, the C-statistics were 0.830 for 30-day mortality or institutionalization at discharge and 0.787 for 30-day mortality or disability at discharge. There was a diminished discrimination in the OSA (C-statistics 0.743 and 0.679 for each outcome, respectively). The significance level of the Hosmer-Lemeshow test was 0.276 in the RCSN. Due to the diminished calibration in the OSA (Hosmer-Lemeshow test P<0.001 for both composite outcomes), we also plotted risk score observed versus predicted outcomes (Figure 2A for 30-day mortality/disability at discharge and Figure 2B for 30-day mortality/institutionalization at discharge).

Discussion

The findings of this study suggest that the iScore can be used to identify patients at high risk of death or disability and also death or institutionalization after ischemic stroke. The iScore showed a graded effect: the higher the score, the higher the risk of a poor
outcome. Predicted and observed mortalities in the validation cohort were in close agreement across the entire spectrum of risk, and the results were confirmed in an external sample.

Prior studies have been conducted to predict stroke outcomes. In 1 study, both clinical and imaging variables were combined, and the investigators were able to find good discrimination (receiver operating characteristic $>0.80$) and suboptimal calibration (Hosmer-Lemeshow $<0.05$) for a devastating outcome at 3 months (a composite outcome was defined as National Institutes of Health Stroke Scale (NIHSS) $\geq 20$ or death, Barthel Index $<60$ or death, or Glasgow Outcome scale $>2$). Predictor variables included initial NIHSS score, stroke subtype, history of diabetes or stroke, preadmission status, and infarct volume determined on CT 7 to 10 hours/day poststroke. However, the commonly used modified Rankin Scale was not included and a score was not developed.

Other studies have used age and the NIHSS to predict good functional recovery, defined as a Barthel Index $>95$ at 3
months. The Virtual International Stroke Trials Archive used a simple score to predict functional independence between 1 and 6 months in 5419 patients with an ischemic stroke and found that age and NIHSS score predicted good functional recovery at 3 months with an area under the curve of 0.80. Although there are obvious advantages to having fewer variables in this prediction score, the tool was created as a nomogram, making it difficult in its application, and the main outcome measure estimated good functional outcome using the Barthel Index,17 which is known to perform poorly in determining change in high-functioning individuals.

Furthermore, although previous simple prognostic models have been able to demonstrate good discrimination (C-statistics 0.70–0.80)17,19–21 in determining mortality, they have ignored the importance of discharge disposition (eg, institutionalization) as an outcome, which is useful for prognostic purposes, discharge planning, and rehabilitation course. In addition, some of these models omitted the
inclusion of relevant and prevalent conditions—atrial fibrillation, renal failure, cancer, congestive heart failure—which in our study had important influence on stroke outcomes (Figure 3).17,19–21

Our present model was designed to use clinical information that is readily available to clinicians in the early hours of hospital presentation for stroke and is independent of stroke volume, imaging, or specialized laboratory tests. Based on the number of variables required, our iScore has good face validity and greater parsimony than most other predictive risk models.

We demonstrated that the use of simple models only including age and stroke severity may over- or underestimate the risk of poor functional outcomes. For example, the inclusion of additional and relevant clinical information leads to very different estimates of 30-day mortality/disability or institutionalization at discharge (Figure 3) compared with those obtained when only age and stroke severity are used.17,19,20,22

Our study has some limitations that deserve comment. By using a score derived initially for a single outcome, 30-day mortality, it is possible that some prognostically important variables (eg, dementia, socioeconomic status, size and location of the infarcts, interventions) not included in the initial iScore may improve the estimated risks of each of the desired composite outcomes. Social factors influencing institutionalization were not considered in the iScore (eg, lack of spouse, social support). Together, differences in the probability of the occurrence of the composite outcomes and differences in baseline characteristics between the RCSN and OSA and lack of inclusion of other relevant variables may explain the suboptimal calibration in the external data set (OSA). Second, the present study only included hospitalized patients with an acute ischemic stroke; therefore, the findings may not be generalizable to ambulatory patients and those with other stroke types. Third, although several ethnic groups were included in the present study, the majority of patients were whites. As such, the predictive ability of the iScore for the studied outcomes needs to be validated in other ethnic groups. Fourth, similar regional or national factors influencing care may limit the iScore’s generalizability in hospitals outside the studied region. Fifth, we defined functional status using only 1 scale, the modified Rankin Scale, which was assessed at patient discharge in the RCSN. Finally, we used the CNS Scale,9 which is analogous to the more widely used NIHSS23 for assessing stroke severity. A recent study24 validated the ability to use the CNS and NIHSS interchangeably. As a result, the following conversion formula can be used: a CNS of 1 to 4 = a NIHSS score of 14 to 22 (severe), a CNS of 5 to 7 = a NIHSS score of 9 to 13 (moderate), a CNS of ≥8 = a NIHSS score of ≥8 (mild), and a CNS of 0 = an NIHSS score of >22. Thus, the iScore (www.sorcan.ca/iscore) may
be used by healthcare providers using either 1 of these scales for neurological assessment.

Notwithstanding these limitations, the strengths of our risk score include that it contains near complete stroke severity ascertainment, long-term follow-up for all cohorts, and only includes individual patient-level variables.

The iScore constitutes an objective tool to stratify and estimate the risk of a poor functional outcome after stroke. An online Web-based tool (www.sorcan.ca/iscore) and iPhone apps are currently available for practical use to facilitate the estimation of individual patient mortality at 30 days and 1 year, and the composite functional outcomes. This could be used not only to discuss prognosis and support rational decision-making, but also to guide end-of-life care and discharge planning. From the healthcare perspective, the iScore may be used to help policymakers plan resources, which may result in optimized access to stroke care and rehabilitation services.

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Disclosures

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References

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/10/02/STROKEAHA.111.623116.DC1

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Supplemental Table: Mean predicted mortality by quintiles of the iScore

<table>
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<tr>
<th>Outcome</th>
<th>RCSN (n=3818)</th>
<th>OSA (n=4635)</th>
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<tr>
<td></td>
<td>Dth or Institutional</td>
<td>Death or disability</td>
</tr>
<tr>
<td>Q1</td>
<td>2.58%</td>
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</tr>
<tr>
<td>Q2</td>
<td>5.45%</td>
<td>41.20%</td>
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<tr>
<td>Q3</td>
<td>10.00%</td>
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</tr>
<tr>
<td>Q4</td>
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<td>77.30%</td>
</tr>
<tr>
<td>Q5</td>
<td>51.40%</td>
<td>91.40%</td>
</tr>
</tbody>
</table>

References:
Q1 – Q5 represented the quintiles of the iScore
Dth: death at 30 days
Institutional: institutionalization at discharge
Differences in outcomes between the RCSN and OSA may be explained by differences in baseline characteristics (e.g. patients in the OSA had a less severe stroke).