Clinical- and Imaging-Based Prediction of Stroke Risk After Transient Ischemic Attack

The CIP Model

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Background and Purpose—Predictive instruments based on clinical features for early stroke risk after transient ischemic attack suffer from limited specificity. We sought to combine imaging and clinical features to improve predictions for 7-day stroke risk after transient ischemic attack.

Methods—We studied 601 consecutive patients with transient ischemic attack who had MRI within 24 hours of symptom onset. A logistic regression model was developed using stroke within 7 days as the response criterion and diffusion-weighted imaging findings and dichotomized ABCD² score (ABCD² ≥4) as covariates.

Results—Subsequent stroke occurred in 25 patients (5.2%). Dichotomized ABCD² score and acute infarct on diffusion-weighted imaging were each independent predictors of stroke risk. The 7-day risk was 0.0% with no predictor, 2.0% with ABCD² score ≥4 alone, 4.9% with acute infarct on diffusion-weighted imaging alone, and 14.9% with both predictors (an automated calculator is available at http://cip.martinos.org). Adding imaging increased the area under the receiver operating characteristic curve from 0.66 (95% CI, 0.57 to 0.76) using the ABCD² score to 0.81 (95% CI, 0.74 to 0.88; P=0.003). The sensitivity of 80% on the receiver operating characteristic curve corresponded to a specificity of 73% for the CIP model and 47% for the ABCD² score.

Conclusions—Combining acute imaging findings with clinical transient ischemic attack features causes a dramatic boost in the accuracy of predictions with clinical features alone for early risk of stroke after transient ischemic attack. If validated in relevant clinical settings, risk stratification by the CIP model may assist in early implementation of therapeutic measures and effective use of hospital resources. (Stroke. 2009;40:181-186.)

Key Words: diffusion-weighted imaging ■ stroke risk ■ transient ischemic attack

Transient ischemic attack (TIA) poses an increased risk of subsequent cerebral infarction. The 7-day risk of stroke after a TIA ranges from 0% to 12.8%.¹ Independent predictors of subsequent stroke after TIA include older age, high blood pressure at admission, history of diabetes mellitus, prolonged symptom duration, and focal weakness and/or speech impairment at presentation.²⁻³ The recently described ABCD² score integrates these clinical predictors in a simple and useful way that allows patients to be stratified into various risk groups according to their early risk of stroke.⁴ The ABCD² score identifies a moderate- or high-risk TIA with high sensitivity (92% for 7-day risk). High sensitivity is desirable in population-based settings because it can prevent unnecessary referrals for assessment on an emergency basis. However, the specificity of the ABCD² score suffers at high sensitivity (33% specificity at sensitivity of 92%), hampering its usefulness in clinical decisions that are resource-intensive or involve risk.

Diffusion-weighted MRI (DWI) reveals brain infarction in a clinically relevant location in approximately one third of patients with the clinical diagnosis of TIA.⁵ Patients with TIA with positive DWI findings (so-called “transient symptoms with infarction”) have increased risk of clinical stroke in both the short- and long-term.⁶⁻¹⁰ The finding of acute infarction on DWI is also a strong predictor of developing asymptomatic infarcts during the ensuing month after the TIA.¹¹ Thus, algorithms that combine imaging and clinical factors might assess the early risk of stroke after TIA with higher sensitivity and specificity. We, therefore, sought to combine imaging and clinical features together, and to do this formally, we aimed to construct and validate a clinical- and
imaging-based predictive algorithm (the “CIP” model) to quantify the early risk of stroke after a TIA.

Methods

Study Population

This was a retrospective study of consecutively admitted patients to the Massachusetts General Hospital with a clinical diagnosis of TIA during a 7-year period between January 2000 and December 2006. All patients diagnosed as having TIA according to The National Institute of Neurological Disorders and Stroke Report Criteria by a neurologist in the emergency room were identified from a registry that listed consecutive admissions. An administrative database that coded discharge diagnoses was used to ascertain diagnoses in the emergency room. We excluded patients with isolated transient monocular blindness and patients who did not have MRI performed within the first 24 hours of symptom onset. All patients with presumed diagnosis of TIA underwent basic blood tests, electrocardiogram, and brain and vascular imaging studies. The study protocol was approved by the local review board.

Data Collection

Data were collected by review of all inpatient and outpatient reports by a neuroradiologist and included age, risk factors, time of TIA onset, duration of transient symptoms, admission blood pressure, history of TIA within the preceding week, and the type of TIA symptoms. In each patient, the ABCD² score was calculated as previously described. For the purpose of this study, subsequent stroke was defined as sudden disturbance of cerebral function that lasted more than 24 hours and was associated with a clinically appropriate new infarct on brain imaging. The validation of a subsequent stroke from medical records was done without knowledge of clinical and imaging characteristics of index TIA and required a confirmatory note by a neurologist involved in the medical care of the patient. One of the study investigators (H.A.) visually assessed the brain MRI in patients with clinical diagnosis of subsequent stroke to confirm the presence of a relevant acute infarction.

Ischemic lesions characterized by increased signal intensity on DWI and decreased or normal signal intensity on the apparent diffusion coefficient maps were classified as acute infarct in patients with TIA by one of the investigators (E.M.A.) blinded to the patient’s recurrence status. MRI was performed on 1.5-T whole body scanners (GE Signa; GE Medical Systems or Siemens Sonata; Siemens Medical Solutions). Average DWI maps as well as apparent diffusion coefficient maps were obtained as previously described.

Statistics

Baseline characteristics of patients with or without subsequent stroke were compared by Mann-Whitney U test or Student t test for continuous variables and by χ² test for categorical variables. Spearman rank correlation coefficient was calculated to describe an association between ABCD² score and the presence of acute infarct on DWI. Logistic regression analysis was used to test for independence of the ABCD² score and acute infarct on DWI as a predictor of subsequent stroke. The logistic regression model included subsequent stroke within 7 days as the response and ABCD² score and acute infarct on DWI as covariates. Because of limited statistical power, the ABCD² score was included in the model as a dichotomous variable to discriminate moderate or high risk (≥4) from low risk (<4) as defined by the original publication. Standard regression diagnostics were used to assess logistic regression assumptions. The shrinkage coefficient of the regression model was calculated as described by van Houwelingen and le Cessie to calculate the noise coming from overfitting. All numeric variables were expressed as mean ± SD or median (interquartile range). Associations were presented as ORs with corresponding 95% CIs. A level of P < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 11.5.

Development and Evaluation of the Predictive Model

The primary goal was to develop a model to predict 7-day risk of ischemic stroke after TIA. The risk of subsequent stroke in a given patient was calculated by summing up the independent dichotomous predictors weighted by their corresponding β coefficients from the logistic regression model. To evaluate the overall predictive ability of the risk score, we computed receiver operating characteristic curves. The area under the receiver operating characteristic curve (AUC) was used as a scalar measure to assess the performance of prognostic risk scores. An AUC of 1.00 indicated perfect prediction, whereas 0.50 designated prediction no better than chance. A secondary analysis was performed using multiple imputation (10 imputations) to incorporate uncertainty due to incomplete follow-up information into the receiver operating characteristic curve.

To provide an unbiased internal assessment of the model’s accuracy, we used crossvalidation, in which the whole data set was randomly partitioned into 2 halves 1000 times, each time testing half of the population using coefficients trained by the other half. The 95% prediction interval of resulting AUCs was calculated to provide the extent to which the model is likely to be useful for prediction on external data.

Results

Study Population and Follow-Up Events

Overall, 904 consecutive patients with TIA were admitted during the study period. Of these, 838 were within the first 24 hours of symptom onset. We excluded a total of 235 patients secondary to a missing MRI. The reasons for inability to obtain MRI included late scanning in 94 (>24 hours of onset), contraindications in 90 (metal implants/foreign body, cardiac pacemaker, excessive body weight), MRI not deemed to be necessary by the treating physician in 24, MRI performed at an outside center in 17, and MRI declined by 10 patients. Of the remaining 603 patients, follow-up data for Day 7 were available in 479 patients. Overall, 25 patients (5.2%) developed a subsequent stroke within 7 days of the index TIA; 16 of the 25 strokes occurred within the first 2 days. Two patients developed a subsequent stroke before an MRI study was done and were, therefore, excluded from further analyses; the ABCD² score was 3 in one and 4 in the other patient. Table 1 summarizes the baseline characteristics and clinical and imaging features of the remaining 477 patients. The median time to MRI was 8.2 hours. Eight percent of all patients were scanned while they still had TIA symptoms. None of the baseline characteristics, particularly the individual components of the ABCD² score, was statistically different between the target study population (477 patients) and the population excluded for various reasons (427 patients).

Patients with subsequent stroke were more likely to have ABCD² ≥4 and acute infarct on DWI (Table 1). Table 2 shows the proportion of positive DWI corresponding to each ABCD² score. There was a poor but statistically significant correlation between ABCD² score and the presence of acute infarct on DWI (r = 0.17, P < 0.001). The OR and 95% CI for positive DWI for ABCD² scores ≥4 compared with <4 was 1.67 (1.10 to 2.55). The logistic regression model with dichotomized ABCD² score and acute infarct on DWI showed that both covariates were independent predictors of 7-day stroke risk (Table 3). The log-likelihood statistic for the overall model was significant (P < 0.001). The shrinkage
The coefficient of the model was 94%, suggesting that only 6% of the information provided by this model was due to nonreplicable noise arising from overfitting the model.

An alternative regression model that also included the etiologic subtype of large artery atherosclerosis (LAA) as an additional covariate showed that both dichotomized ABCD² score and DWI (P = 0.050 and P = 0.001, respectively) but not LAA (P = 0.112) were independent predictors of stroke risk after TIA. Patients with TIA with LAA were more likely to have acute infarct on DWI in the current study; 39.1% of the patients with LAA presented had a positive DWI compared with 30.4% in other subtypes (P = 0.081). This suggested that DWI conveyed the prognostic information provided by LAA in the multivariable model. The number of outcome events for the number of covariates in this model was, however, lower than recommended (23 outcome events for 3 covariates).

Prognostic Models

The ABCD² score was a significant predictor of 7-day stroke risk after TIA (P for linear trend = 0.010). The AUC for the ABCD² score was 0.66 (95% CI, 0.57 to 0.76). The AUC for the model that was based on DWI information alone was 0.76 (95% CI, 0.67 to 0.86). There was a borderline improvement in predictions by DWI as compared with the ABCD² score (P = 0.115). The AUC for the model that combined dichotomized ABCD² score and DWI was 0.81 (95% CI, 0.74 to 0.88). The crossvalidated AUC of the combined model (the CIP model) was 0.79 (95% prediction interval, 0.72 to 0.86). Thus, the bias coming from predicting on the same data set used for fitting was approximately 0.02. The AUC of the CIP model was significantly higher than the AUC of the ABCD² score (P = 0.003).

The risk of stroke at 7 days was 0.0% with no predictor, 2.0% with ABCD² score alone, 4.9% with acute infarct on DWI alone, and 14.9% with both predictors (Table 4; an automated risk calculator is available at http://cip.martinos.org). Thus, the presence of an acute infarct on DWI increased the likelihood of subsequent stroke by approximately 7-fold in high-risk patients per the ABCD² score (score ≥ 4). The 7-day risk was 1.2% in the absence (low risk) and 12.3% in the

### Table 1. Baseline Clinical and Imaging Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Subsequent Event Within 7 Days (n=454)</th>
<th>Subsequent Stroke Within 7 Days (n=23)</th>
<th>Overall (n=477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>67.7±14.8 years</td>
<td>67.4±11.5 years</td>
<td>67.7±14.7 years</td>
</tr>
<tr>
<td>Gender, female/male*</td>
<td>240 (52.9%)/214 (47.1%)</td>
<td>6 (26.1%)/17 (73.9%)</td>
<td>246 (51.6%)/231 (48.4%)</td>
</tr>
<tr>
<td>Time from symptom onset to MRI, median (IQR)*</td>
<td>8.3 (5.2–12.0) hours</td>
<td>5.4 (2.5–14.6) hours</td>
<td>8.2 (5.0–12.0) hours</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>331 (72.9%)</td>
<td>17 (73.9%)</td>
<td>348 (73.0%)</td>
</tr>
<tr>
<td>Admission blood pressure systolic ≥140 mm Hg and/or diastolic ≥90 mm Hg*</td>
<td>282 (62.1%)</td>
<td>21 (91.3%)</td>
<td>303 (63.5%)</td>
</tr>
<tr>
<td>Focal weakness*</td>
<td>207 (45.6%)</td>
<td>19 (82.6%)</td>
<td>226 (47.4%)</td>
</tr>
<tr>
<td>Speech difficulty*</td>
<td>251 (55.3%)</td>
<td>16 (69.6%)</td>
<td>267 (56.0%)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 minutes</td>
<td>87 (19.2%)</td>
<td>3 (13.0%)</td>
<td>90 (18.9%)</td>
</tr>
<tr>
<td>10–59 minutes</td>
<td>151 (33.3%)</td>
<td>8 (34.8%)</td>
<td>159 (33.3%)</td>
</tr>
<tr>
<td>≥60 minutes</td>
<td>216 (47.6%)</td>
<td>12 (52.2%)</td>
<td>228 (47.8%)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>93 (20.5%)</td>
<td>2 (8.7%)</td>
<td>95 (19.9%)</td>
</tr>
<tr>
<td>Treatment after TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>365 (80.4%)</td>
<td>15 (65.2%)</td>
<td>380 (79.7%)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>89 (19.6%)</td>
<td>8 (34.8%)</td>
<td>97 (20.3%)</td>
</tr>
<tr>
<td>Statin</td>
<td>155 (34.1%)</td>
<td>6 (26.1%)</td>
<td>161 (33.8%)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>25 (5.5%)</td>
<td>3 (13.0%)</td>
<td>28 (5.9%)</td>
</tr>
<tr>
<td>ABCD² score ≥4*</td>
<td>294 (64.8%)</td>
<td>21 (91.3%)</td>
<td>315 (66.0%)</td>
</tr>
<tr>
<td>Acute ischemic lesion on DWI*</td>
<td>136 (30.0%)</td>
<td>19 (82.6%)</td>
<td>155 (32.5%)</td>
</tr>
<tr>
<td>Large artery atherosclerosis*</td>
<td>105 (23.1%)</td>
<td>10 (43.5%)</td>
<td>115 (24.1%)</td>
</tr>
</tbody>
</table>

*P<0.05 for comparisons between patients with TIA with and without subsequent event.

### Table 2. Clinical and Imaging Covariates Stratified by the ABCD² Score

<table>
<thead>
<tr>
<th>ABCD² Score</th>
<th>0 (n=4) Patients (%)</th>
<th>1 (n=18) Patients (%)</th>
<th>2 (n=45) Patients (%)</th>
<th>3 (n=95) Patients (%)</th>
<th>4 (n=108) Patients (%)</th>
<th>5 (n=119) Patients (%)</th>
<th>6 (n=77) Patients (%)</th>
<th>7 (n=11) Patients (%)</th>
<th>Overall (n=477) Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infarct on DWI</td>
<td>1 (25.0%)</td>
<td>2 (11.1%)</td>
<td>14 (31.1%)</td>
<td>24 (25.3%)</td>
<td>29 (26.9%)</td>
<td>41 (34.5%)</td>
<td>40 (51.9%)</td>
<td>4 (36.4%)</td>
<td>155 (32.5%)</td>
</tr>
<tr>
<td>Subsequent stroke in 7 days</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.2%)</td>
<td>1 (1.1%)</td>
<td>5 (4.6%)</td>
<td>9 (7.6%)</td>
<td>7 (9.1%)</td>
<td>0 (0.0%)</td>
<td>23 (4.8%)</td>
</tr>
</tbody>
</table>
presence of acute infarct on DWI (high risk). The risks in these low- and high-risk strata were comparable to those reported for the ABCD² score (low risk: 1.2%, moderate and high risk: 7.7%).

The sensitivity of 80% on the receiver operating characteristic curve corresponded to a specificity of 73% for the CIP model and 47% for the ABCD² score. The high specificity for a given sensitivity caused substantial alterations in risk assignments. For instance, 201 of the 315 patients (63.8%) who had moderate or high risk of subsequent stroke per the ABCD² score⁴ (scores ≥4, estimated risk = 6.7%) were classified low risk by the CIP model (estimated risk = 1.2%; Tables 2 and 4). Likewise, 41 of the 162 low-risk patients (25.3%) according to the ABCD² score (scores <4, estimated risk = 1.2%) were classified high risk by the CIP model (estimated risk = 12.3%). The use of the CIP model displaced 50.0% of the patients within the highest risk category according to the ABCD² score (scores 6 and 7, estimated risk = 8.0%) into the low-risk group (risk = 1.2%).

Of the 601 patients with acute imaging, 124 patients had been excluded because of incomplete follow-up. An exploratory analysis with multiple imputation that also included these 124 patients revealed an AUC of 0.81 (95% CI, 0.74 to 0.87). This was exactly the same as the AUC of the original CIP model (P = 0.940). We performed a second exploratory analysis to assess the usefulness of the CIP model for predicting the 2-day risk of stroke. Follow-up data were available in all 601 patients for 2 days. Subsequent stroke occurred in 14 patients (2.3%). The ABCD² score was a borderline predictor of 2-day risk of stroke (P for linear trend = 0.148). DWI, on the other hand, was a significant predictor (P < 0.001). The AUC was 0.61 (95% CI, 0.51 to 0.71) for the ABCD² score, 0.74 (95% CI, 0.62 to 0.87) for DWI, and 0.79 (95% CI, 0.69 to 0.89) for the CIP model for predicting the 2-day risk of stroke. The AUC of the CIP model was significantly higher than the AUC of the ABCD² score (P = 0.001).

**Discussion**

Although approximately half of the population aged between 45 and 64 years reports a brief episode of acute focal neurological dysfunction during their lifetime,¹⁸ after expert assessment, only a small fraction of them turn out to have had an ischemic attack. The prevalence of TIA in the United States ranges from 1% to 6%.¹⁸,¹⁹ Therefore, it is critical to identify the subset of patients presenting with transient symptoms that are most likely caused by brain ischemia in primary care settings. The ABCD² and other clinical scores accomplish this to some extent by stratifying patients according to their risk of developing a subsequent stroke.²⁴ The current study confirms that the ABCD² score is a significant predictor of 7-day stroke risk after a TIA. We found that if one selects 2 patients with TIA, one with and one without subsequent stroke, the probability will be 0.66 (95% CI, 0.57 to 0.76) that the patient with a subsequent stroke will have a predicted risk different than zero using only the ABCD² score. This is consistent with the reported range of AUC values in prior emergency-based cohort studies (0.63 to 0.66).⁴

We found that the incorporation of DWI into the ABCD² score significantly improved the accuracy of predictions for 7-day stroke risk after TIA; the AUC increased from 0.66 with the ABCD² score to 0.81 in the combined model (CIP model). We also found that predictions for 2-day risk of stroke with the CIP model (AUC, 0.79) were more accurate as compared with the ABCD² score (AUC, 0.61). The improvement in predictions with the CIP model primarily resulted from achieving greater specificity while maintaining or increasing high sensitivity. Improved overall predictive ability indicates that there should be fewer false-positive and false-negative predictions with the use of CIP model compared with the ABCD² score. Hence, we found that 25% of the patients classified low risk for Day 7 by the ABCD² score were in fact high risk according to the CIP model. Likewise, 64% of the patients graded moderate or high risk per the ABCD² score were classified low risk by the CIP model. The magnitude of displacement across the risk categories with the use of CIP method depends on the definition of the risk used to prompt a change in clinical practice. The added benefit of the CIP model at each risk level must be carefully weighed against the cost of brain imaging in different hospital settings. It should, however, be noted that imaging of all patients with TIA is already recommended to rule out intracranial pathologies that can mimic TIA.²¹ The CIP model only requires that the imaging study be done early enough to allow risk stratification. There is no advantage to postponing the TIA workup. Although CT is more readily accessible in most emergency settings and less expensive than MRI, published data suggest that even conventional MRI (not DWI) can miss or misidentify the acute infarction on DWI in approximately half of the patients with TIA.⁸ DWI is the preferred technique of evaluation in the CIP model because of its high sensitivity to visualize acute small infarcts (typical TIA-related infarct is <1 mL) and its ability to differentiate acute infarcts from chronic small lesions.⁷,²²,²₃ MRI, on the other hand, is not fully immune from limitations. Contraindications to MRI limit its widespread applicability in patients

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**Table 3. Logistic Regression Analysis of Predictors of Stroke After a TIA**

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Coefficient</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ischemic lesion on DWI</td>
<td>2.31</td>
<td>10.10 (3.36–30.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dichotomized ABCD² score</td>
<td>1.54</td>
<td>4.65 (1.06–20.44)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**Table 4. Seven-Day Risk of Stroke After a TIA According to the CIP Model**

<table>
<thead>
<tr>
<th>ABCD² Score ≥4</th>
<th>DWI</th>
<th>No. of Patients</th>
<th>Subsequent Stroke</th>
<th>Stroke Risk</th>
<th>Risk Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>−</td>
<td>121</td>
<td>0</td>
<td>0.0%</td>
<td>Low risk</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>201</td>
<td>4</td>
<td>2.0%</td>
<td>(1.2%; 95% CI, 0.0%–2.5%)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>41</td>
<td>2</td>
<td>4.9%</td>
<td>High risk</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>114</td>
<td>17</td>
<td>14.9%</td>
<td>(12.3%; 95% CI, 7.1%–17.4%)</td>
</tr>
</tbody>
</table>
with TIA; approximately 10% of patients with stroke and TIA cannot have an MRI because of contraindications.24

Patients with TIA with acute infarct on DWI are more likely to have an established etiologic mechanism of stroke, presentation with motor symptoms or aphasia or disturbance of other higher brain function, and prolonged spell duration (≥30 minutes).6,25 Most of these features are also the components of the ABCD2 score. We found a statistically significant correlation between positive DWI and the ABCD2 score; yet, the magnitude of this correlation was small (r=0.17). It is, therefore, plausible that ABCD2 score and DWI convey different prognostic information. We suggest that the dichotomized ABCD2 score identifies a population with high burden of stroke risk factors. DWI adds specificity to the ABCD2 score due to its ability to differentiate a true ischemic attack from TIA mimics such as migraine, seizures, and syncope. In addition, DWI identifies patients who are more likely to harbor a major stroke etiology6 and characterize the underlying mechanism of TIA as active and unstable with high risk of imminent stroke.6–10 It should be noted, however, that early after the onset of transient symptoms, DWI can miss lacunar infarcts in the brainstem or internal capsule.26 This hampers the predictive value of emergency department DWI-based algorithms. Three of the 4 patients with normal DWI who developed subsequent stroke in the current data set had lacunar infarct.

An important limitation of the current study is retrospective data collection. This may have caused information and follow-up bias because only the data that were available in the chart could be used. The stringent exclusion criteria may have also caused a selection bias. We found that baseline characteristics of our patients such as age,9,10 gender,2,4 and risk factors,4,9,27 as well as in-hospital treatment for stroke prevention,4,9,28 the proportion of early carotid revascularization,9,28,29 and early stroke risk1,4,30,31 were similar to other published hospital-based studies of stroke risk after TIA, arguing against significant selection and treatment bias. In addition, our study has a number of strengths to lessen the impact of this inherent limitation that includes consecutive recruitment, large sample size, blind assessment of clinical and imaging TIA features to outcome status, multiple imputation for the missing data, and crossvalidation.

The current study does not contain an external validation cohort as might typically be the case for such predictive tools. Although external validation is desirable, it requires a sample size that is comparable to the present study. The dramatic boost in diagnostic power that the addition of imaging brings to the prediction of stroke risk in patients with TIA indicates the necessity of a multicenter effort for external validation because no single-center study published to date have had more than one fourth of the sample size in the current study. Crossvalidation is an unbiased method of internal validation to evaluate the stability of regression coefficients, which predicts the extent to which a model is likely to be useful for prediction on external data.17 The 95% prediction interval for crossvalidated AUCs was 0.72 to 0.86. It is highly unlikely that an AUC from external validation will be out of this prediction interval in a properly powered data set.

Although our study is the largest ever reported DWI study of TIA, there were only 23 outcome events, which limited the ability of this study to assess the influence of additional variables such as individual components of the ABCD2 score or the size, location, and pattern of DWI lesions on the predictive value of the CIP model. Future studies with larger data sets could address whether incorporation of additional clinical and imaging features further improve predictions.

An important factor that determines the rate of detection of small brain infarcts is the spatial resolution of the imaging technique32; as the spatial resolution increases, the likelihood of detecting small lesions also increases. We used a standard scanning protocol (5-and 6-mm slice thickness with a 1-mm gap) in the current study because our goal was to develop a predictive tool for use in a typical clinical practice and typical patient population, not an idealized setting. It is, however, important to recognize that the CIP model, like all other imaging-based decision algorithms, requires validation as scanning protocols improve over time.

The CIP model integrates multiple aspects of routine diagnostic TIA evaluation to estimate the risk of subsequent stroke after a TIA. If validated externally, the CIP model may find usefulness as a tool to develop risk-based algorithms for use in several key stages in the management of TIA. First, risk stratification through the CIP model can be used for decision-making for admitting patients with TIA to a hospital. It has been shown that short-term hospitalization for high-risk patients with TIA (24-hour stroke risk >5%) can be cost-effective.33 Alternatively, benefit accrues if patients with TIA with low risk of developing subsequent stroke are not exposed to the risks, discomforts, and costs of hospitalization. Second, the use of CIP model may justify an urgent and comprehensive diagnostic evaluation in high-risk patients because the mechanism that underlies the index TIA may also operate in the genesis of subsequent stroke. Third, early initiation of preventive treatments is associated with reduction in the risk of early recurrent stroke29,34 and the length of hospital stay.29 It is therefore plausible to consider that the risk scores can be used to identify high-risk patients in whom urgent intervention is needed. Fourth, because treatments used for risk modification might exhibit different efficacy in different risk groups (expected to yield greater absolute benefit in high-risk population),34 a risk-based stratification may allow designing therapeutic trials with higher statistically power. Finally, a valid risk score can be used by physicians to reassure their patients that decisions made for the management of their TIA are evidence-based.

Acknowledgments

An automated CIP risk calculator is available at http://cip.martinos.org. We thank Thomas Benner for assistance in constructing the automated risk calculator.

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Disclosures

None.
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