Prediction of Early Stroke Risk in Transient Symptoms With Infarction
Relevance to the New Tissue-Based Definition

E. Murat Arsava, MD; Karen L. Furie, MD; Lee H. Schwamm, MD; A. Gregory Sorensen, MD; Hakan Ay, MD

Background and Purpose—The risk of stroke shortly after transient ischemic attack with infarction on diffusion-weighted images, also known as transient symptoms with infarction (TSI), is substantially higher than is the risk after imaging-normal transient ischemic attack. We sought to assess the utility of a Web-based recurrence risk estimator (RRE; http://www.nmr.mgh.harvard.edu/RRE/) originally developed for use in patients with ischemic stroke for predicting 7-day risk of stroke in patients with TSI.

Methods—We calculated RRE and ABCD² scores in a retrospective series of 257 consecutive patients with TSI diagnosed by diffusion-weighted images within 24 hours of symptom onset. We defined subsequent stroke as clinical deterioration associated with new infarction spatially distinct from the index lesion. We assessed the predictive performance of each model by computing the area under receiver-operating characteristics curve.

Results—Over 7-day follow-up, 16 patients developed a recurrent stroke (6.2%). The sensitivity and specificity of an RRE score of ≥2 for predicting 7-day stroke risk were 87% and 73%, respectively. The area under the receiver-operating characteristics curve was 0.85 (95% CI, 0.78–0.92) for RRE and 0.57 (95% CI, 0.45–0.69) for ABCD² score (z-test; P<0.001).

Conclusions—The RRE score seems to predict 7-day risk of stroke after a TSI. If further validated in larger data sets, the RRE score could be useful in identifying high-risk patients with TSI who may benefit from early intervention with targeted stroke prevention strategies. (Stroke. 2011;42:2186-2190.)

Key Words: brain infarction ▪ diffusion-weighted imaging ▪ MRI ▪ transient ischemic attack ▪ stroke risk

The new tissue-based definition endorsed by the American Heart Association/American Stroke Association proposes to classify transient ischemic attack (TIA) as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction.¹ All remaining neurological events, regardless of whether symptoms are transient or permanent, are called “ischemic stroke,” as long as they are associated with brain infarction. The tissue-based definition is an important step in the right direction because it is no longer based on the arbitrary 24-hour duration criterion; more importantly, this definition is compatible with the pathophysiology (ie, based on objective evidence of ischemia).¹ Categorizations based on pathophysiology are crucial for accurate diagnosis and treatment of diseases with a certain level of complexity. Categorizations are likely to serve even more ideally when they are also consonant with prognosis. Prognostic information allows individualization of timing and optimal method of diagnostic evaluation and treatment. Although appealing from a pathophysiologic point of view, the tissue-based definition might have negative impact from a prognostic point of view. Specifically, it is now known that the early risk (7-day) of stroke after imaging-positive TIA (transient symptoms with infarction [TSI])² is substantially higher—as much as 15 times higher—than is the risk after ischemic stroke³-⁷; the 7-day risk of stroke ranges from 4% and 16% after TSI,⁴-⁹ whereas the corresponding risk after ischemic stroke is between 1% and 3%.²-⁴,⁶,¹⁰ Classifying “TSI” and “stroke” in the same category may unintentionally obscure the clinical importance of identifying TSI as the warning sign of an impending stroke within the lower-risk pool of strokes. We sought to develop a means to retain the prognostic information in the familiar TIA terminology while using the new definition. For this, we assessed the utility of a prognostic score (recurrence risk estimator [RRE]) for predicting 7-day risk of stroke in TSI.¹⁰ The RRE tool was originally devel-

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ected to predict 14- and 90-day risk of recurrence in patients with ischemic stroke (not TSI) per the conventional definition. If validated in TSI, the score could be used to identify patients with imminent risk of developing another stroke among the overall population of strokes regardless of whether the new definition or earlier definitions are used; this allows a way for practitioners to identify the highest-risk subjects regardless of whether they have become familiar with current terminology.

### Patients and Methods

#### Study Population and Data Acquisition

This was a retrospective study of consecutive patients with TIA defined according to time-based traditional definition (symptoms lasting <24 hours)11 who were admitted during a 6-year period between 2003 and 2009. Patients were identified from a prospectively maintained database that included all admissions to the emergency department with possible diagnosis of TIA. The current study included patients with TIA who had a clinically relevant acute infarction on diffusion-weighted imaging (DWI) obtained within 24 hours of symptom onset. DWI was performed as a routine piece of diagnostic evaluation in all TIA patients who did not have contraindication to magnetic resonance imaging (MRI). As previously stated, we used the term TSI to designate TIA with DWI evidence of acute infarction.2

Data on TSI characteristics, patient demographics, vascular risk factors, ABCD² score, etiologic stroke subtype, and treatment for secondary prevention were collected from the database. The stroke etiology was classified using the automated Causative Classification of Stroke system based on information available from clinical history, electrocardiography, brain imaging, and brain vascular imaging within the first 24 hours of symptom onset. The study protocol was approved by the local institutional review board.

The RRE score was computed for each patient by a stroke neurologist blinded to the patient’s recurrence status. RRE is a Web-based (http://www.nmr.mgh.harvard.edu/RRE/) 7-point score composed of 2 clinical and 4 imaging predictors.10 These predictors are prior TIA or stroke within the month preceding TSI (1 point), etiologic Causative Classification of Stroke subtype (1 point for large artery atherosclerosis and other uncommon causes, and 0 points for all other subtypes), the presence of multiple acute infarcts (1 point), simultaneous acute infarcts in both hemispheres or in both anterior and posterior circulations (1 point), multiple infarcts of different ages (combination of acute and subacute infarcts, 1 point), and isolated cortical location (1 point). The RRE provides estimates for 14-day and 90-day risk of recurrence after an ischemic stroke based on information available to physicians immediately after initial stroke evaluation in typical clinical practice (based on clinical history, electrocardiography, and baseline brain and vascular imaging). The RRE score has demonstrated adequate calibration and good discrimination in the prior derivation and validation data sets.10 The current study aims to validate RRE in a different patient population (TSI instead of stroke) and outcome window (7 days instead of 14 or 90 days).

#### Follow-Up Assessment

The outcome parameter was recurrent ischemic stroke within 7 days of index TSI. Follow-up information was collected retrospectively by an investigator blinded to RRE scores; this was achieved through inspection of inpatient medical record notes, as well as from routine 1- to 3-month outpatient assessment notes by the treating neurologist. These notes included a detailed description and timing of the follow-up event. Recurrent stroke was defined as a clinical incident that was clearly attributable to a new area of brain infarction visualized by imaging as spatially distinct from the index lesion. Each clinically suspected recurrent event was adjudicated by a separate investigator using pertinent brain images without the knowledge of clinical and imaging characteristics of the index TSI.

### Results

A total of 302 consecutive patients with TSI were admitted during the study period. Seven-day follow-up information was available in 257 patients. Patients with incomplete follow-up (n=45) had lower RRE scores compared with patients with complete follow-up (n=257; median [IQR] RRE score 1 (0–2) versus 2, (1–3); P=0.001). Other baseline clinical predictors of stroke risk (etiologic stroke mechanism, recent history of stroke or TIA, and ABCD² score) were similar between patients with and without complete follow-up. Overall, 24 patients (9.3%) developed a recurrent clinical event within 7 days of TSI. In 8 of these 24 patients, recurrent events were not associated with a new infarction on DWI. All 8 patients with clinical recurrence unconfirmed by imaging had lacunar infarcts at baseline; the recurrent event was stereotypical for the index TSI in all 8 (stuttering lacunar syndrome). The remaining 16 patients (6.2%) who developed a subsequent event associated with imaging evidence of a new infarct fulfilled the predefined criteria for recurrence.

The median age of the study population was 67 years (IQR, 55–76 years), the median time to MRI was 9.4 hours (IQR, 5.5–15.2 hours), the median ABCD² score was 4 (IQR, 3–5), and the median RRE score was 2 (IQR, 1–3). Table 1 summarizes baseline characteristics and clinical and imaging features with respect to subsequent stroke status. Patients with recurrence were more likely to have prior TIA or stroke within the month preceding the index TSI (P=0.004) and large artery atherosclerosis and “other uncommon causes” (dissection, vasculitis, etc.) as the underlying TSI mechanism (P<0.001; Table 1). There was no difference in mean and median ABCD² scores between patients with and without subsequent stroke. There were 8 patients with and 28 patients without subsequent stroke who were eligible for carotid intervention. Five of the 8 patients (62.5%) with and 16 of the 28 patients (57.1%) without subsequent stroke eventually underwent carotid endarterectomy or stenting (Fisher exact test, P=1.000).

Table 2 shows the distribution of RRE scores in patients with and without recurrent stroke. The risk of subsequent stroke at 7 days continuously rose with increasing RRE scores (P<0.001, log rank test; Figure 1); the risk was 0% (95% CI, 0%–3%) with no or 1 predictor, 3% (95% CI, 0%–3%) with 2 predictors, 15% (95% CI, 5%–25%) with 3 predictors, and 22% (95% CI, 7%–35%) with 4 or more predictors. Both mean and median RRE score were higher in patients with subsequent stroke. For scores ≥3, the sensitivity and specificity for predicting 7-day risk of subsequent stroke were 87% and 73%, respectively.

### Statistics

All numeric variables were expressed as mean±SD or median (interquartile range [IQR]). Fisher exact test, Mann-Whitney U test, and Kruskal-Wallis tests were used to explore the relationship between baseline categorical variables and recurrent stroke status as of day 7. We quantified the predictive validity of RRE and ABCD² scores by computing the receiver-operating characteristic curve and calculated the area under the curve (AUC). We compared the AUC for different scores using the z-test.13 Statistical analyses were performed using SPSS 16.0.
Figure 2 shows the receiver-operating characteristic curve for predicting 7-day risk of stroke in patients with TSI. The AUC was 0.85 (95% CI, 0.78–0.92; \(P=0.001\)). The AUC for the ABCD2 score was 0.57 (95% CI, 0.45–0.69; \(P=0.331\)). The improvement in diagnostic performance as measured by AUC by the RRE score over the ABCD2 score was both clinically meaningful (from 0.57–0.85) and statistically significant (\(P=0.001\), z-test). The AUC remained essentially unchanged (0.86; 95% CI, 0.80–0.93) when analyses included the 45 patients with incomplete follow-up by carrying forward the available follow-up information.

Discussion

TIA, when using the tissue-based definition, should be thought of as an extremely low-risk condition. According to a recent pooled analysis of 4574 patients with conventionally defined TIA from 12 centers, \(9\), the 7-day risk of stroke after a “TIA with no infarction” is 0.4%. In contrast, TSI (that is, TIA with infarction) is a high-risk condition; the 7-day risk of stroke ranges from 4% and 16%. \(5–8\) In settings where brain imaging is available and feasible, the fundamental question is, therefore, no longer about whether a patient with a traditionally defined TIA will develop a subsequent stroke, but rather, which patient with TSI is at imminent risk of developing a stroke. Our results indicate that the RRE criteria segregate the TSI population into different risk groups with a high degree of predictive power (AUC \(=0.85\)). Using RRE, approximately two thirds of patients with TSI can be classified as low-risk (risk \(\leq 1\%\); score \(\leq 2\)) and one third as high-risk (risk \(>18\%\); score \(>2\)). The implication of these findings for the practitioner is that the RRE tool can allow determination of who is at high short-term risk and therefore may need urgent intervention.

Recent studies have shown that the risk of early recurrence after minor stroke is relatively comparable to the risk after TSI. \(14,15\) One could, thus, retain the prognostic information in TSI by adjusting the current tissue-based definition to accommodate for prognostically different categories (such as definit-

Table 1. Baseline Characteristics According to Recurrence Status

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>No Recurrence</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>16</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>Age (IQR), y</td>
<td>70 (61–82)</td>
<td>66 (55–76)</td>
<td>0.255</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>9 (56.2)</td>
<td>115 (47.7)</td>
<td>0.508</td>
</tr>
<tr>
<td>Hypertension no. (%)</td>
<td>13 (81.2)</td>
<td>158 (65.6)</td>
<td>0.276</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>3 (18.8)</td>
<td>44 (18.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial fibrillation, no. (%)</td>
<td>1 (6.2)</td>
<td>39 (16.2)</td>
<td>0.479</td>
</tr>
<tr>
<td>Prior TIA or stroke, no. (%)</td>
<td>11 (68.8)</td>
<td>80 (33.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Time (h) to MRI, no. (%)</td>
<td>9.6 (5.2–15.0)</td>
<td>9.4 (5.5–15.5)</td>
<td>0.907</td>
</tr>
<tr>
<td>CCS stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis, no. (%)</td>
<td>11 (68.8)</td>
<td>53 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Cardio-aortic embolism, no. (%)</td>
<td>1 (6.2)</td>
<td>35 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Small artery occlusion, no. (%)</td>
<td>0 (0.0)</td>
<td>21 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Other rare causes, no. (%)</td>
<td>4 (25.0)</td>
<td>15 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Undetermined, no. (%)</td>
<td>0 (0.0)</td>
<td>117 (48.5)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet treatment, no. (%)</td>
<td>12 (75.0)</td>
<td>196 (81.3)</td>
<td>0.533</td>
</tr>
<tr>
<td>Anticoagulation, no. (%)</td>
<td>11 (68.8)</td>
<td>116 (48.1)</td>
<td>0.110</td>
</tr>
<tr>
<td>Mean ABCD2 Score±SD</td>
<td>4.5±1.0</td>
<td>4.1±1.6</td>
<td>0.292</td>
</tr>
<tr>
<td>Median ABCD2 Score (IQR)</td>
<td>5 (3–5)</td>
<td>4 (3–5)</td>
<td>0.321</td>
</tr>
<tr>
<td>Mean RRE Score±SD</td>
<td>3.5±1.3</td>
<td>1.7±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median RRE Score (IQR)</td>
<td>3 (3–4)</td>
<td>2 (1–3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| IQR, interquartile range; TIA, transient ischemic attack; MRI, magnetic resonance imaging; SD, standard deviation; RRE, recurrence risk estimator.

Table 2. Distribution of RRE Score in Patients With and Without Recurrence

<table>
<thead>
<tr>
<th>RRE Score</th>
<th>Recurrence (N=16)</th>
<th>No Recurrence (N=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 (0.0%)</td>
<td>48 (19.9%)</td>
</tr>
<tr>
<td>1</td>
<td>0 (0.0%)</td>
<td>68 (28.2%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (12.5%)</td>
<td>61 (25.3%)</td>
</tr>
<tr>
<td>3</td>
<td>7 (43.8%)</td>
<td>39 (16.2%)</td>
</tr>
<tr>
<td>4</td>
<td>5 (31.2%)</td>
<td>20 (8.3%)</td>
</tr>
<tr>
<td>5</td>
<td>1 (6.2%)</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>6</td>
<td>1 (6.2%)</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

RRE indicates recurrence risk estimator.

Figure 1. Cumulative probability of 7-day risk of recurrence across the recurrence risk estimator (RRE) scores. The dotted lines represent 95% confidence intervals.

Figure 2. Receiver operating characteristics curves for 7-day risk of recurrent stroke. RRE indicates recurrence risk estimator.
ing a separate minor stroke category). Nevertheless, we suspect that such an approach would not be practical and may even cause confusion, because prognostic categories in stroke are many (minor versus moderate versus major stroke, small versus large infarct, single versus multiple infarcts, etc) and most are definition dependent; at least 4 different definitions have been used in the literature to describe minor stroke (National Institutes of Health Stroke Scale score $\leq 1$, $\leq 3$, $\leq 5$, and $\leq 9$). $^{9,16,17}$ Here, we offer an alternative approach: a simple score that can be universally applied to anyone with “ischemic stroke,” as defined by the tissue-based definition, to identify prognostically similar subsets. After 1 internal and 1 independent validation, $^{10}$ this is another validation of RRE for a new application in a different population. The score has been previously shown to predict reliably short-term risk (14-day risk) of recurrence in patients with ischemic stroke per the conventional definition. The present study shows that RRE can also predict short-term risk (7-day risk) of stroke after a TSI (which is now called stroke per the tissue-based definition). Hence, if further validated for 7- and 14-day risk prediction, RRE could be applied to any patient with clinically relevant brain infarction, regardless of whether neurological symptoms are transient or persistent, to identify individuals at risk of early recurrence. By this way, RRE may complement the tissue-based definition by providing a prognostic component to it.

In contrast to RRE, the ABCD$^2$ score reveals little predictive value in patients with TSI; the point estimate of AUC (0.57) was not different from predictions based on chance alone, although a modest predictive value could not be excluded (95% CI, 0.45–0.69). The ABCD$^2$ score appears to predict stroke risk partly because of its ability to discriminate between a true TIA and a suspected TIA with eventual diagnosis of a nonvascular TIA-mimic. $^{18–20}$ The predictive value of the ABCD$^2$ score shows marked variation among studies with different methods of patient selection and case-mix (true and suspected TIA). $^{9,21}$ In contrast to the general TIA population, TSI represents a fairly homogenous subset consisting of definite cerebral infarctions. The prognostic value of a score in this homogenous group in large part relies on its ability to account for the underlying stroke mechanism. $^3$ All individual components of RRE directly relate to the underlying stroke mechanism. Etiologic stroke subtype itself is a predictor in RRE. Imaging predictors such as location, age, and number of infarcts, and their spatial relationship with respect to each other provide information on whether the underlying stroke mechanism is unstable with potential to cause another stroke. $^{10}$ Other predictors such as “recent history of TIA/stroke” and “multiple infarcts of different ages” further add to the system’s ability to mark an unstable etiology by providing the continuity information.

The complexity of stroke and current nomenclature require 1 additional clarification. Pragmatic definition of recurrent stroke includes any clinical incident that is associated with a new ischemic lesion spatially distinct from the initial infarct. Although in general this is straightforward, the special case of “stuttering lacunar infarction” causes some pause. In stuttering lacunar infarction, patients present with a cluster of repetitive, stereotypic, and short lasting events—which sometimes might be thought of as TIAs—and then subsequently develop a permanent deficit with no imaging evidence of a spatially distinct new lesion beyond the initial index lacunar infarct. This special case, then, consists of a TSI patient developing a subsequent clinical stroke without a new, spatially distinct infarct. The dissociation between the changing clinical symptoms and the stable imaging findings is important, and we propose the terminology, “lacunar infarct paradox,” to clarify this dissociation. Also, we point out that the RRE criteria should not be applied in this special case.

This study has several limitations. First, 7-day follow-up information was not available in approximately 15% of patients. Missing follow-up data, however, would not be expected to alter significantly the predictive performance of RRE unless patients with incomplete follow-up more often developed a recurrent stroke (hence, they had lower RRE scores). It is unlikely that the stroke rate was higher in the cohort with missing follow-up information because, in our practice, the primary neurologist taking care of TIA is often notified in an event of stroke occurring within days of TIA, and the data collection methods would have captured this. Second, the number of outcome events was small for reliable validation of a prognostic score, and therefore limited the power of the predictive model. $^{22}$ The 95% confidence intervals around the point estimate for AUC were large. Nevertheless, the lower confidence limit was still well above the threshold set for random prediction. Moreover, the predictive performance of RRE in this data set was comparable to those in prior validation and derivation data sets; this suggests that the current estimate for AUC reflects the true predictive capacity of the RRE score. Third, although MRI is recommended as the method of imaging in TIA, $^1$ approximately 5% to 10% of patients cannot be scanned because of contraindications; this may limit widespread applicability of RRE. Although the RRE requires an imaging study, the ABCD$^2$ score does not; the improved performance and widespread use of MRI in the evaluation of stroke reduce this concern for most practice settings. We note that current guidelines for the management for TIA already recognize the helpful role of imaging, and specifically state, “MRI can help to determine which TIA patients to admit to hospital and it may help in identifying patients to treat with more aggressive therapies.”  $^1$ Our current data support this recommendation and demonstrate the added value of imaging beyond the ABCD$^2$ score to identify patients for the most aggressive treatment. Finally, the predictive performance of RRE may be different in clinical settings where patient profile, and type and timing of preventive stroke treatments substantially differ from that reported in this study. Therefore, additional validation is critical for the generalizability of our results.

Our findings offer utility in clinical management of TSI. The major concept behind using prognostic tools in medicine is to identify individuals who are at risk of developing a potentially avoidable adverse event. Prognostic information becomes more critical if future events are prevalent and occur soon after the index disease so that acute care at specialized centers can be organized on an individual basis. TSI is an ideal condition for prognostic risk evaluation because the risk of subsequent stroke is high and imminent. The RRE score
may allow physicians to identify high-risk patients who benefit most from timely identification of the underlying etiology; early institution of specific preventive treatment, such as carotid endarterectomy; and care at specialized centers, where timely administration of acute treatments in the event of a subsequent stroke is possible.23

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Disclosures
None.

References
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梗塞を伴う一過性症状における初期脳卒中リスクの予測
—組織に基づく新たな定義との関連
Prediction of Early Stroke Risk in Transient Symptoms With Infarction
—Relevance to New Tissue-Based Definition

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Abstract

背景および目的：正常画像所見を示す一過性脳虚血発作に比べ、梗塞を伴う一過性症状（TSI）とも呼ばれる、拡散強調画像上の梗塞を伴う一過性脳虚血発作後期的には、脳卒中リスクが大幅に上昇する。本研究では、ウェブを利用した再発リスク推定値（Recurrence risk estimator：RRE、http://www.nmr.mgh.harvard.edu/RRE/）の有用性を検討した。RREは、無血性脳卒中患者を対象として、TSI患者の7日間脳卒中リスクを予測するために開発されたものである。

方法：症状発現から24時間以内に収集した拡散強調画像でTSIと診断された連続症例257例を対象に、後向き症例集積研究を行い、RREおよびABCD2スコアを算出した。初発病変は空間的に区別される新規梗塞を伴う臨床的悪化を脳卒中再発と定義した。受信者操作特性（ROC）曲線下面積を算出し、各モデルの予測性能を評価した。

結果：7日間の追跡調査期間に16例が脳卒中を再発した（6.2％）。RREスコアが2以上の場合、7日間脳卒中リスク予測段は87％、特異度は73％であった。ROC曲線下面積は、RREスコアが0.85（95% CI：0.78～0.92）、ABCD2スコアが0.57（95% CI：0.45～0.69）であった（z検定、p < 0.001）。

結論：RREスコアを用いれば、TSI後7日間の脳卒中リスクを予測できると考えられる。さらに大規模なデータセットで妥当性が確認されれば、RREスコアは、集中的な脳卒中予防戦略による早期介入が有益と思われる、高リスクのTSI患者を特定する有用な手段になる可能性がある。

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図1 各再発リスク推定値（RRE）スコアにおける7日間再発リスクの累積確率。点線は95%信頼区間を表す。

図2 7日間脳卒中再発リスクの受信者操作特性（ROC）曲線。RRE：再発リスク推定値。