IER-SICH Nomogram to Predict Symptomatic Intracerebral Hemorrhage After Thrombectomy for Stroke

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Abstract

Background and Purpose-: As a reliable scoring system to detect the risk of symptomatic intracerebral hemorrhage after thrombectomy for ischemic stroke is not yet available, we developed a nomogram for predicting symptomatic intracerebral hemorrhage in patients with large vessel occlusion in the anterior circulation who received bridging of thrombectomy with intravenous thrombolysis (training set), and to validate the model by using a cohort of patients treated with direct thrombectomy (test set).

Methods

We conducted a cohort study on prospectively collected data from 3714 patients enrolled in the IER (Italian Registry of Endovascular Stroke Treatment in Acute Stroke). Symptomatic intracerebral hemorrhage was defined as any type of intracerebral hemorrhage with increase of >=4 National Institutes of Health Stroke Scale score points from baseline <=24 hours or death. Based on multivariate logistic models, the nomogram was generated. We assessed the discriminative performance by using the area under the receiver operating characteristic curve.

Results

National Institutes of Health Stroke Scale score, onset-to-end procedure time, age, unsuccessful recanalization, and Careggi collateral score composed the IER-SICH nomogram. After removing Careggi collateral score from the first model, a second model including Alberta Stroke Program Early CT Score was developed. The area under the receiver operating characteristic curve of the IER-SICH nomogram was 0.778 in the training set (n=492) and 0.709 in the test set (n=399). The area under the receiver operating characteristic curve of the second model was 0.733 in the training set (n=988) and 0.685 in the test set (n=779).

Conclusions

The IER-SICH nomogram is the first model developed and validated for predicting symptomatic intracerebral hemorrhage after thrombectomy. It may provide indications on early identification of patients for more or less postprocedural intensive management.

TEXT

Endovascular thrombectomy is the new standard of care for ischemic stroke patients with large vessel occlusion (LVO) in the anterior circulation.1,2 Intravenous thrombolysis (IVT) plus mechanical thrombectomy is recommended within 6 hours of stroke onset.1,2 Direct thrombectomy is recommended within 6 hours in patients with contraindications for IVT and up to 24 hours in patients selected according

to strict clinical and radiological criteria. Nevertheless, symptomatic intracerebral hemorrhage (sICH) remains one of the most feared complications.

Several scores based on clinical and radiological pretreatment variables have been applied in the last few years to predict the risk of sICH after IVT.3 The STARTING-SICH (Systolic Blood Pressure, Age, Onset-to-Treatment Time for IVT, National Institutes of Health Stroke Scale [NIHSS] Score, Glucose, Aspirin Alone, Aspirin Plus Clopidogrel, Oral Anticoagulant With International Normalized Ratio <=1.7, Current Infarction Sign, Hyperdense Artery Sign) nomogram has also been recently developed and validated in a large Italian cohort for individualized prediction of the probability of sICH in stroke patients undergoing IVT alone.4 By converting the total score into a continuum of individual probability of sICH, the STARTING-SICH nomogram reclassifies better the risk of sICH from current low- to average-risk and from average- to high-risk categories, and vice versa, compared with previous prognostic scores. However, while remaining a rare adverse event, the incidence of sICH after IVT is variable in real-world practice, and generally agreed risk thresholds are not currently available.

Although a scoring system with enough power to detect the risk of sICH after thrombectomy has yet to be designed, recent studies have identified some potential pre- and posttreatment predictors of sICH.5-8 Higher NIHSS score, lower Alberta Stroke Program Early CT (ASPECT) score,9 poor collateral circulation, and delayed and unsuccessful recanalization were often associated with sICH after thrombectomy. The risk of sICH does not seem to be different between bridging therapy and direct thrombectomy 10; nevertheless, IVT-eligible patients are inherently different from IVT-ineligible patients.

The present study was aimed to develop a nomogram for predicting sICH in patients with LVO in the anterior circulation who received bridging therapy within 6 hours of stroke onset, and to validate the model by using a cohort of patients who received direct thrombectomy.

Methods

Study Design, Participants, and Procedures

We conducted a cohort study on prospectively collected data of patients enrolled in the IER (Italian Registry of Endovascular Stroke Treatment in Acute Stroke). The IER is a multicenter, observational internet-based registry (Table I in the online-only Data Supplement). All acute ischemic stroke patients with LVO who received endovascular procedures between January 2011 and December 2016 were included in the present study. All participating centers were required to accept the rules of the IER, including consecutive registration of all stroke patients receiving endovascular procedures irrespective of whether treatment was according to guidelines. Our analysis was conducted according to the STROBE criteria for observational studies.11

Data Collection

The collected data are provided in the online-only Data Supplement.

Criteria for Development of the Model

To develop the model, 3 neurologists with clinical expertise in stroke management have chosen a priori to include only patients with complete data on age, baseline NIHSS score, ASPECT score, pretreatment with IVT, occlusion site, symptom onset-to-groin puncture time, symptom onset-to-end procedure time, Thrombolysis in Cerebral Infarction grading system,12 and clinical/radiological data to determine sICH. Because data on possible predictors of sICH, such as platelet count, international normalized ratio, and activated partial thromboplastin time values, are not available in the IER, and major alterations of coagulation measures are contraindications for IVT but not for direct mechanical thrombectomy, we chose a priori to develop the prediction model by using the cohort of patients who received bridging therapy, and to validate the model by using the cohort of patients treated with direct mechanical thrombectomy.

Inclusion and Exclusion Criteria

We included only patients with complete data on all the variables generating the nomogram, and with clinical and radiological data to determine sICH. Age >=18 years was selected in agreement with the current guidelines.1,2

Patients who received intraarterial fibrinolysis or started mechanical thrombectomy after 360 minutes of stroke onset were excluded from the analyses in agreement with the current guidelines.1,2 In addition, we excluded stroke patients with LVO in the posterior circulation.

Outcome

The outcome measure was sICH defined as any type of ICH with an increase of >=4 NIHSS score points from baseline within 24 hours or leading to death.6

Statistical Analysis

We performed all statistical analyses using statistical software STATA 13.0.1 (StataCorp, College Station, TX). Differences between the cohorts were explored using the Mann-Whitney U test for continuous variables. Differences between proportions were assessed by Fisher exact test or [chi]2 test, where appropriate. Continuous variables were reported as median and interquartile range values. Proportions were calculated for categorical variables, dividing the number of events by the total number excluding missing/unknown cases.

To identify the independent predictors of sICH, a logistic regression model was performed using a forward stepwise method that included all variables with a probability value <0.10 in the univariate analysis. Collinearity of combinations of variables in the training set was evaluated by the variation inflation factors (<2 being considered nonsignificant) and condition index (<30 being considered nonsignificant). Regression coefficients and odds ratios (OR) with 2-sided 95% CIs for each of the variables included in the model were finally calculated.

The nomogram was created by assigning a graphic preliminary score to each of the predictors with a point range from 0 to 10, which was then summed to generate a total score, finally converted to the logit and then to an individual probability (from 0% to 100%) of sICH. Discrimination of the nomogram model was assessed by calculation of the area under the receiver operating characteristic curve (AUC-ROC). Calibration of the risk prediction model was assessed in the test cohort by the plot comparing the observed probability of sICH according to the total score of the nomogram against the predicted probability based on the nomogram, and by using the Hosmer-Lemeshow test which assesses whether or not the observed event rates matched the expected rates in subgroups of patients.

Additional analyses are provided in the online-only Data Supplement.

Standard Protocol Approvals, Registrations, and Patient Consents

Need for ethical approval or patient consent for participation in the IER varied among participating hospitals. Ethical approval and informed consent were obtained when required.

Data Availability Statement

Anonymized data will be shared by request from any qualified investigator.

Results

Among 3714 patients registered in the IER cohort by 44 centers (Table II in the online-only Data Supplement), 1767 patients were included in the study. Flow diagram of patient inclusion and exclusion is provided in Figure 1. The clinical characteristics of the included and excluded patients are provided in Table III in the online-only Data Supplement.

The clinical characteristics of the patients undergoing bridging therapy (training set; n=988) and direct mechanical thrombectomy (test set; n=779) are provided in the Table. The corresponding proportions of patients with sICH were 11.1% in the training cohort and 12.2% in the test cohort.

Thirteen variables (age, diabetes mellitus, previous stroke or transient ischemic attack, atrial fibrillation, coronary heart disease, prestroke modified Rankin Scale score, baseline NIHSS score, ASPECT score, Careggi collateral score,13 symptom onset-to-groin procedure time, symptom onset-to-end procedure time, unsuccessful recanalization,12 and no first pass 14) entered the logistic regression model. NIHSS score (OR, 1.073; 95% CI, 1.006-1.144 per point; P=0.032), onset-to-end procedure time (OR, 1.006; 95% CI, 1.002-1.010 per minute; P=0.008), age (OR, 1.031; 95% CI, 1.004-1.060 per year; P=0.024), unsuccessful recanalization (OR, 2.029; 95% CI, 1.069-3.851; P=0.030), and Careggi collateral score (OR, 0.638; 95% CI, 0.491-0.828 per point; P=0.001) remained independent predictors of sICH in the first model composed by a training set of 492 patients with complete data for generating the IER-SICH nomogram (Table IV in the online-only Data Supplement). No significant statistical collinearity was observed for any of the 5 variables included in the model (Tables V and VI in the online-only Data Supplement).

After removing Careggi collateral score from the first model because of a large number of missing data (n=496), a second logistic regression model was performed. NIHSS score (OR, 1.089; 95% CI, 1.042-1.137 per point; P<0.001), onset-to-end procedure time (OR, 1.004; 95% CI, 1.001-1.007 per minute; P=0.003), age (OR, 1.028; 95% CI, 1.010-1.046 per year; P=0.002), unsuccessful recanalization (OR, 2.046; 95% CI,

1.319-3.173; P=0.001), and ASPECT score (OR, 0.885; 95% CI, 0.790-0.992 per point; P=0.036) remained independent predictors of sICH in the second model composed by the entire training set (n=988; Table VII in the online-only Data Supplement). No significant statistical collinearity was observed for any of the 5 variables included in the second model (Tables VIII and IX in the online-only Data Supplement).
The IER-SICH nomogram is shown in Figure 2 taking into account the approximation of all the variables that are graphed without decimal. Each predictor was assigned points on the preliminary score by drawing a vertical line between predictor line and preliminary score line. The total score is the cumulative sum of the points assigned to each of the predictors. Probability of sICH is obtained by drawing a vertical line between total score line and probability line. Details for the construction of the IER-SICH nomogram are provided in the online-only Data Supplement. An example of how to use the nomogram is provided in Figure II in the online-only Data Supplement.
The AUC-ROC of the IER-SICH nomogram for predicting the probability of sICH was 0.778 (95% CI, 0.719-0.838) in the training cohort (n=492). The model was internally validated using 2000 bootstrap samples to calculate the discrimination with accuracy of 0.778 (95% CI, 0.719-0.837). The model was validated in the test cohort (n=399) with AUC-ROC value of 0.709 (95% CI, 0.630-0.788). Figure 3 displays a calibration plot for the model, comparing the predicted proportion of patients who developed sICH per nomogram with the proportions observed according to IER-SICH total score point in the test set. The Hosmer-Lemeshow goodness-of-fit test comparing predicted and observed rates of sICH showed good calibration of the total score (2.326; P=0.969).
The second nomogram is shown in Figure II in the online-only Data Supplement. The AUC-ROC of the second nomogram for predicting the probability of sICH was 0.733 (95% CI, 0.685-0.781) in the training cohort (n=988). The model was internally validated using 2000 bootstrap samples to calculate the discrimination with accuracy of 0.733 (95% CI, 0.684-0.781). The model was validated in the test cohort (n=779) with AUC-ROC value of 0.685 (95% CI, 0.631-0.738). Figure III in the online-only Data Supplement displays a calibration plot for the second model. The Hosmer-Lemeshow goodness-of-fit test showed good calibration of the total score (8.653; P=0.372).
The AUC-ROC values of the IER-SICH nomogram across different subgroups of patients identified according to several variables are provided in Table X in the online-only Data Supplement.

Discussion

We presented here the IER-SICH nomogram based upon the NIHSS score, onset-to-end procedure time, age, unsuccessful recanalization, and Careggi collateral score to predict the probability of sICH for stroke patients with LVO in the anterior circulation treated with mechanical thrombectomy. The model was developed by using a cohort of patients undergoing bridging of thrombectomy with IVT and validated by using a cohort of patients receiving direct thrombectomy according to the current guidelines.1,2
To our knowledge, the present study should represent the first attempt to develop a prognostic model for predicting the probability of sICH after thrombectomy, but its accuracy is still limited. Discriminative performance of the IER-SICH nomogram including the Careggi collateral score was higher than that of the second nomogram including the ASPECT score in both training and test cohorts. Nevertheless, a significant correlation between the Careggi collateral score and the ASPECT score for all computed tomography perfusion parameters has been reported.15 Moreover, the ASPECT score has been universally used since the prethrombectomy era as a pragmatic, reliable, and easily applicable scoring template for early ischemic changes on computed tomography and has drawn a lot of attention because of its use for patient exclusion in the randomized controlled trials (RCTs) on mechanical thrombectomy.16-18
Our study confirms that the incidence of sICH after thrombectomy is higher in real-world practice than in RCTs.6 After the publication of 5 RCTs showing the benefit of thrombectomy,19,20 the number of endovascular procedures has rapidly increased in real-world practice. However, the clinical and radiological eligibility criteria used in RCTs were more strict compared with the current guidelines.21 Additional imaging selection criteria could lead to a reduction of the risk of sICH, but also to a drastic reduction of the number of procedures. Plots of our models for prediction of sICH risk in the validation cohort showed a good calibration up to the highest values observed on the total scores (ie, 22 points in the IER-SICH nomogram and 24 points in the second nomogram model), corresponding to a maximum probability of sICH of [almost equal to]50% predicted by both nomograms. The strongest predictor of sICH included in the IER-SICH

nomogram is the onset-to-end procedure time, which is not predictable before the endovascular procedure. The onset-to-end procedure time reflects the technical difficulty of the procedure itself, and it may be related to several factors such as occlusion site pattern (often associated with neurological severity), vessel tortuosity (often associated with old age), thrombus characteristics (often associated with onset-to-groin puncture time and stroke cause), distal embolization (often associated with procedure type), early vessel reocclusion (often associated with poor collateral circulation), and operator expertise. The AUC-ROC values of the IER-SICH nomogram were similar across subgroups of patients identified according to different occlusion sites, risk factors, onset-to-groin puncture intervals, and procedure types. Given the expected progressive increase of endovascular procedures in the next years, combinations of very long onset-to-end procedure time with very high NIHSS scores, very old age, and very poor collateral circulation should occur, the IER-SICH nomogram will be able to estimate a probability of sICH even higher than 50%. We recognize that the IER-SICH will need to be tested for predictive accuracy in a future population of stroke patients at very high risk of sICH; however, even more urgent seems to be the need for developing strategies to reduce the onset-to-end procedure time.

Our study also confirms that the incidence of sICH is similar in patients receiving bridging therapy and direct thrombectomy.10 Nevertheless, the underlying pathophysiological mechanisms may differ because IVT-eligible patients are inherently different from IVT-ineligible patients. For example, LVO-related stroke patients with platelet count <100 000/mm3 or severe liver disease, and LVO-related stroke patients taking warfarin with international normalized ratio >1.7, direct oral anticoagulants with therapeutic effect, or intravenous heparin in the previous 48 hours with activated partial thromboplastin time above laboratory normal upper limit are not eligible for IVT but are eligible for direct thrombectomy. Lack of data on major alterations of coagulation measures could explain the lowest discriminative performance of our nomograms in the validation cohort (ie, direct thrombectomy) than in the derivation cohort (ie, bridging therapy).

Nomograms are important components of modern medical decision-making and have been used extensively in cancer, surgery, and other specialties.22-24 Compared with classical scores, nomograms often provide better individualized disease-related outcome estimations that facilitate management-related decisions.25 This might stem from the fact that risk groups consist of patients with similar (albeit not identical) characteristics, resulting in heterogeneity within a risk group that reduces the predictive accuracy. In contrast to risk groups, a nomogram provides an individualized estimate of the predicted probability of the event of interest, which is entirely based on the individual's disease characteristics, without averaging or combining within a category.

By using the combination of few predictors easily available before and at the end of bridging therapy and direct thrombectomy, the IER-SICH nomogram may provide indications for early identification of patients who are candidates for a more or less postprocedural intensive management. In patients at high risk of sICH, monitoring and treatment of hypertension and hyperglycemia should be intensified, postprocedural imaging control should be anticipated, and early antithrombotic therapy should be avoided. In patients at low risk of sICH, weaning from sedation might be faster and patient transfer back to the referring hospital more rapid. The IER-SICH nomogram may also be useful for stratifying patients in RCTs designed to test new devices and new fibrinolytic or neuroprotective drugs.

Our study has several limitations. First, it is based on a retrospective analysis of prospectively collected data. Despite our belief that patient data in the entire Italian cohort are representative of a variety of demographics and stroke center types, for the risk score to be suitable in daily clinical practice, an external validation in a completely different cohort is warranted. Second, missing data for generating the nomogram and determining sICH might have influenced the final outcome. Third, only data on Careggi collateral score are available for the assessment of collateral circulation. Fourth, data on platelet count, international normalized ratio, and activated partial thromboplastin time values are not available in the IER to assess their possible association with sICH, especially in patients undergoing direct thrombectomy. Nevertheless, both models have been internally validated by using the cohort of patients treated with direct thrombectomy. Finally, biomarkers such as cerebral microbleeds are not included into the model because brain magnetic resonance imaging is not performed routinely before thrombolysis. Future prospective studies will have to assess whether the integration of novel biomarkers may help to improve the accuracy of the IER-SICH nomogram prediction.

Conclusions

The IER-SICH nomogram was developed to predict the probability of sICH in patients with LVO in the anterior circulation who received bridging therapy within 6 hours of stroke onset. The model was validated by using a cohort of patients who received direct thrombectomy. Our model may be easily and quickly applicable in the clinical setting if used on a computer or a handheld device with the related software.

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