Early prediction of the 3-month outcome for individual acute ischemic stroke patients who received intravenous thrombolysis using the N2H3 nomogram model

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Abstract

Background: The aim of this study was to establish a nomogram model for individualized early prediction of the 3-month prognosis in patients with acute ischemic stroke (AIS) who were treated with intravenous recombinant tissue plasminogen activator (rt-PA) thrombolysis.

Methods: A total of 691 patients were included in this study; 564 patients were included in the training cohort, while 127 patients were included in the test cohort. The main outcome measure was a 3-month unfavorable outcome (modified Rankin Scale 3–6). To construct the nomogram model, stepwise logistic regression analysis was applied to select the significant predictors of the outcome. The discriminative performance of the model was assessed by calculating the area under the receiver operating characteristic curve (AUC-ROC). A decision curve analysis was used to evaluate prognostic value of the model.

Results: The initial National Institutes of Health Stroke Scale [NIHSS, odds ratio (OR), 1.35; 95% confidence interval (CI), 1.28–1.44; $p < 0.001$], delta NIHSS (changes in the NIHSS score from baseline to 24 h, OR, 0.75; 95% CI, 0.70–0.79; $p < 0.001$), hypertension (OR, 2.07; 95% CI, 1.32–3.31; $p = 0.002$), hyperhomocysteinemia (Hhcy, OR, 2.18; 95% CI, 1.20–4.11; $p = 0.013$), and the ratio of high-density lipoprotein cholesterol (HDL-C) to low-density lipoprotein cholesterol (LDL-C) (HDL-C/LDL-C, OR, 3.29; 95% CI, 1.00–10.89; $p = 0.049$) (N2H3) were found to be independent predictors of a 3-month unfavorable outcome from multivariate logistic regression analysis and were incorporated in the N2H3 nomogram model. The AUC-ROC of the training cohort was 0.872 (95% CI, 0.841–0.902), and the AUC-ROC of the test cohort was 0.900 (95% CI, 0.848–0.953).

Conclusion: The study presented the N2H3 nomogram model, with initial NIHSS score, delta NIHSS, hypertension, Hhcy, and HDL-C/LDL-C as predictors. It therefore provides an individualized early prediction of the 3-month unfavorable outcome in AIS patients treated with intravenous rt-PA thrombolysis.

Keywords: acute ischemic stroke, intravenous thrombolysis, nomogram, prognosis

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Introduction

Ischemic stroke is highly prevalent worldwide. As one of the leading causes of disability and mortality, ischemic stroke places a significant burden on patients and caregivers. Thrombolysis has been found to be the most effective medical treatment for acute ischemic stroke (AIS) patients. The primary thrombolytic agent, recombinant tissue plasminogen activator (rt-PA), is the most widely used thrombolytic drug worldwide.[1–4] Unfortunately, some patients still experience functional deficits after rt-PA thrombolysis. Accurate and early prediction of the clinical outcome for individual AIS patients who receive rt-PA treatment is needed to provide a reasonable approach to patient management.[5]

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A series of prognostic models established using various statistical methods have been reported in the past few decades with the aim of predicting long-term patient outcome after intravenous thrombolysis.[6–11] As a graphical statistical instrument, nomograms make it possible to individually predict outcomes by calculating the scores of each individual based on their own characteristics. The nomogram has been used widely for clinical decision making in multiple clinical conditions, including ischemic stroke, myocardial infarction, and cancer.[5,12–16] Nomograms have also been used to predict outcome of patients receiving thrombolysis, including the START (National Institutes of Health Stroke Scale score, age, pre-stroke mRS score, onset-to-treatment time) nomogram for prediction of unfavorable outcome and the STARTING-SICH (systolic blood pressure, age, onset-to-treatment time for thrombolysis, National Institutes of Health Stroke Scale score, glucose, aspirin alone, aspirin plus clopidogrel, anticoagulant with INR ≤1.7, current infarction sign, hyperdense artery sign) nomogram for prediction of symptomatic intracerebral hemorrhage.[5,17]

The aim of this present study was to develop and validate a simple and reliable nomogram model for early and individual prediction of 3-month prognosis in AIS patients who treated with intravenous thrombolysis. To obtain a stronger power of prediction, we use both clinical characteristics and laboratory tests as variables.

Methods

Study design and participants
The study was conducted according to the principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the First Hospital of Jilin University (approval code: 2015-156). This retrospective study, based on a prospective database, included consecutive patients with AIS who received intravenous thrombolysis with rt-PA at the China National Comprehensive Stroke Center between January 2016 and June 2019. Patients who were treated from January 2016 to December 2018 were included in the training cohort, while those who were treated from January 2019 to June 2019 were included in the test cohort. Intravenous thrombolysis was administrated within 4.5 h of onset for each patient according to the recommendations of current guidelines and the decision of the treating physicians.[18–20] All patients received standard medical treatment after thrombolysis. Patients with a pre-stroke mRS (modified Rankin Scale) >2, who were treated with endovascular procedure after intravenous thrombolysis, who died within 24 h, who were diagnosed with conditions mimicking stroke or hematopathy, had incomplete data, or who were lost to follow up were excluded from this study. The process of patient inclusion is shown in Figure 1.

Data collection
Demographic features, vascular risk factors, laboratory test, as well as clinical and follow-up information of patients were collected from the database. Vascular risk factors included hypertension [defined as taking oral antihypertensive drugs, systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at discharge], diabetes mellitus (defined as previous use of glucose-lowering medication or having a clinical diagnosis of diabetes mellitus during hospitalization), hyperlipidemia (defined as previous use of lipid-lowering medication, total cholesterol ≥5.18 mmol/l, triglycerides ≥1.70 mmol/l, low-density lipoprotein cholesterol ≥3.37 mmol/l, or high-density lipoprotein cholesterol <1.04 mmol/l), smoking (current or ex-smoker), hyperhomocysteinemia (Hhcy, defined as total homocysteine level ≥10 μmol/l at discharge), and atrial fibrillation.[21,22] Clinical information included initial National Institutes of Health Stroke Scale (NIHSS) score (NIHSS score before thrombolysis), delta NIHSS (changes in the NIHSS score from baseline to 24 h), admission SBP, admission DBP, and onset to rt-PA bolus time. Laboratory information collected on admission included serum glucose level, white blood cell (WBC) count, neutrophil to lymphocyte ratio (NLR), platelet to neutrophil ratio (PNR), platelet count, international normalized ratio (INR), prothrombin time (PT), and prothrombin time activity (PTA). Laboratory information collected after thrombolysis included homocysteine level, total cholesterol level, triglyceride level, the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol (HDL-C/LDL-C), and serum uric acid level, all of which were collected in the morning following admission after overnight fasting.

Outcomes
The clinical outcome was assessed at 3 months using the mRS. While mRS scores of 3–6 were
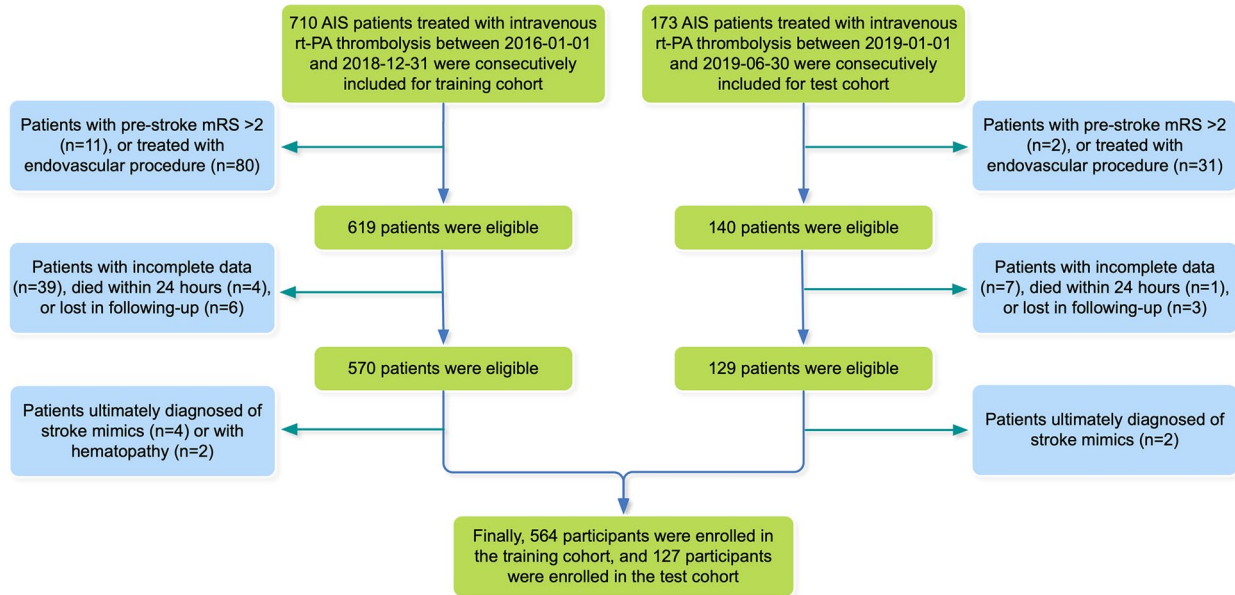
Figure 1. Study flowchart.
AIS, acute ischemic stroke; mRS, modified Rankin Scale; rt-PA, recombinant tissue plasminogen activator.

defined as an unfavorable outcome, mRS scores of 0–2 were defined as a favorable outcome.

Statistical analysis

Statistical analysis was performed using R statistical software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as means [standard deviation (SD)] or medians [interquartile range (IQR)], while categorical variables were expressed as n (%), as appropriate. Normality of distribution for continuous variables was evaluated using the Kolmogorov–Smirnov goodness-of-fit test.

To construct the nomogram, binary logistic regression analysis was applied to select the significant predictors of outcome. Variables with a $p < 0.1$ in the univariate analysis were included in multivariate logistic regression analysis using a backward-selection method. The variables with a $p < 0.05$ in the binary logistic regression analysis were considered statistically significant. The nomogram was developed based on the results obtained using the binary logistic regression model. The nomogram was externally validated using the test cohort. The model was also internally validated using all data of the training and test cohorts by preforming 10-fold cross-validation. Discriminative performance was measured by calculation of the area under the

receiver operating characteristic curve (AUC-ROC). Calibration was tested using a calibration plot with bootstraps of 1000 resamples, which described the degree of fit between actual and nomogram-predicted outcome. Decision curve analysis was used to evaluate the validity of the nomogram.

Results

In total, 691 patients were included in this study, 564 patients (median age, 63 years; 72.52% male) were included in the training cohort, while 127 patients (median age, 62 years; 71.65% male) were included in the test cohort. The proportion of patients with 3-month unfavorable outcome was 36.17% ($n = 204$) in the training cohort and 30.71% ($n = 39$) in the test cohort.

Table 1 shows the comparison of baseline characteristics between patients with favorable outcome and unfavorable outcome in the training cohort. Variables with $p < 0.1$ were considered potential predictors of outcome and were included in the multivariate logistic regression analysis. These included age, hypertension, atrial fibrillation, Hhcy, admission SBP, admission DBP, initial NIHSS score, delta NIHSS, serum glucose level, WBC count, PNR, INR, PT, PTA, triglyceride level, HDL-C/LDL-C, and serum uric acid level.

Table 1. Comparison of baseline characteristics between patients with 3-month favorable outcome and unfavorable outcome in the training cohort.

Variables	Total patients $n = 564$	Favorable outcome $n = 360$	Unfavorable outcome $n = 204$	*p* value
Age, years	63 (54–70.75)	62 (54–69.5)	63.5 (55.5–72)	0.023
Male, *n* (%)	409 (72.5%)	258 (71.7%)	149 (73.0%)	0.685
Vascular risk factors				
Smoking, *n* (%)	327 (58.0%)	216 (60.0%)	111 (54.4%)	0.196
Hypertension, *n* (%)	310 (55.0%)	185 (51.4%)	125 (61.3%)	0.023
Diabetes mellitus, *n* (%)	131 (23.2%)	81 (22.5%)	50 (24.5%)	0.587
Previous stroke, *n* (%)	120 (21.3%)	80 (22.2%)	40 (19.6%)	0.466
Hyperlipidemia, *n* (%)	353 (62.6%)	231 (64.2%)	122 (59.8%)	0.304
Ongoing statin intake, *n* (%)	9 (1.6%)	5 (1.4%)	4 (2.0%)	0.729
Hhcy, *n* (%)	459 (81.4%)	281 (78.1%)	178 (87.3%)	0.007
Atrial fibrillation, *n* (%)	120 (21.3%)	64 (17.8%)	56 (27.5%)	0.007
Clinical data				
Initial NIHSS score, points	8 (5–12)	6 (4–10)	11 (8–15)	<0.001
Delta NIHSS, points	2 (0–4)	3 (1–5)	0 (–1–2)	<0.001
Admission SBP, mm Hg	155 (139–168)	152 (137.5–167)	160 (143.5–171)	0.005
Admission DBP, mm Hg	89 (80–99)	88 (79–97)	91 (82–100)	0.001
Onset to rt-PA bolus time, min	182 (143–230)	182.5 (143–229.5)	180 (137–230.5)	0.841
Laboratory tests				
Serum glucose, mmol/l	7.09 (6.14–8.77)	6.87 (5.99–8.74)	8.38 (6.40–9.07)	0.036
WBC counts $\times 10^9$/l	7.75 (6.40–9.52)	7.6 (6.2–9.34)	8.17 (6.68–9.96)	0.004
NLR, ratio	3.08 (1.94–5.08)	3.08 (1.96–4.82)	3.07 (1.87–5.82)	0.203
PNR, ratio	38.39 (26.95–51.28)	38.99 (28.68–52.45)	37.10 (23.85–48.92)	0.100
Platelet counts $\times 10^9$/l	200 (167–230)	200 (168.5–229)	199.5 (165–234.5)	0.741
INR, ratio	0.93 (0.9–0.98)	0.93 (0.9–0.98)	0.94 (0.91–0.98)	0.002
PT, s	10.9 (10.5–11.5)	10.9 (10.5–11.45)	11 (10.6–11.5)	0.003
PTA, s	107 (98–116)	108 (99–106.5)	105 (97–104)	0.002
Homocysteine, mmol/l	13.8 (10.6–21.05)	12.95 (10.23–18.88)	15.5 (11.43–25.78)	0.001
Total cholesterol, mmol/l	4.85 (4.14–5.55)	4.86 (4.14–5.51)	4.83 (4.14–5.65)	0.672
Triglyceride, mmol/l	1.36 (0.95–2.01)	1.42 (1.03–2.23)	1.24 (0.9–1.86)	0.055
HDL-C/LDL-C, ratio	0.42 (0.34–0.54)	0.41 (0.34–0.53)	0.44 (0.37–0.56)	0.014
Serum uric acid, mmol/l	340.5 (287–399.75)	339 (285–394.5)	348.5 (283.5–414.5)	0.023

DBP, diastolic blood pressure; Delta NIHSS, changes in the NIHSS score from baseline to 24h; HDL-C/LDL-C, the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol; Hhcy, hyperhomocysteinemia (defined as total homocysteine level ⩾10μmol/l); INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil to lymphocyte ratio; PNR, platelet to neutrophil ratio; PT, prothrombin time; PTA, prothrombin time activity; rt-PA, recombinant tissue-type plasminogen activator; SBP, systolic blood pressure; WBC, white blood cell.

According to multivariate logistic regression analysis, the initial NIHSS score [odds ratio (OR), 1.35; 95% confidence interval (CI), 1.28–1.44; $p < 0.001$], delta NIHSS (OR, 0.75; 95% CI, 0.70–0.79; $p < 0.001$), hypertension (OR, 2.07; 95% CI, 1.32–3.31; $p = 0.002$), Hhcy (OR, 2.18; 95% CI, 1.20–4.11; $p = 0.013$) and HDL-C/LDL-C level (OR, 3.29; 95% CI, 1.00–10.89; $p = 0.049$) (N2H3) were independent predictors of unfavorable outcome. The results of multivariable analyses for the 3-month outcome in the training cohort are shown in Table 2.

Figure 2 shows the N2H3 nomogram established based on the variables that enabled researchers to predict outcome independently after the multivariable analyses. The total points calculated from the sum of points of the 5 predictors in N2H3 nomogram were found to be positively correlated with the risk of unfavorable outcome.

The discriminative performance of the model was assessed by calculating the AUC-ROC of the training cohort (AUC, 0.872; 95% CI, 0.841–0.902). The model was validated externally using the AUC-ROC of the test cohort (AUC, 0.900; 95% CI, 0.848–0.953). After 10-fold cross-validation was performed on all data of the training and test cohorts, the max AUC value was found to be 0.944 (95% CI, 0.894–0.993) (Figure 3).

Figure 4 shows the calibration plot of the nomogram, which compares the prediction of unfavorable outcome between the nomogram prediction and actual observation. The calibration plot suggested good predictive accuracy of the nomogram in both training cohort (A) and test cohort (B).

A decision curve analysis (DCA) was performed to evaluate prognostic value of the current prediction model. DCA estimates the net benefit of a model based on the difference between the number of true and false-positive results. As shown in Figure 5, using the N2H3 nomogram for outcome prediction processed greater net benefit than baseline NIHSS score alone.

Discussion

The study found that initial NIHSS score, delta NIHSS, hypertension, Hhcy, and HDL-C/LDL-C were independent predictors of 3-month unfavorable outcome in AIS patients treated with intravenous rt-PA thrombolysis from multivariate

Table 2. Independent risk factors associated with the 3-month outcome after intravenous thrombolysis in the training cohort.

Variable	Odds ratio (95% CI)	*p* value
Initial NIHSS score	1.35 (1.28–1.44)	<0.001
Delta NIHSS	0.75 (0.70–0.79)	<0.001
Hypertension	2.07 (1.32–3.31)	0.002
Hhcy	2.18 (1.20–4.11)	0.013
HDL-C/LDL-C	3.29 (1.00–10.89)	0.049

Delta NIHSS, changes in the NIHSS score from baseline to 24 h; HDL-C/LDL-C, the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol; Hhcy, hyperhomocysteinemia (defined as total homocysteine level ≥10 µmol/l); NIHSS, National Institutes of Health Stroke Scale.
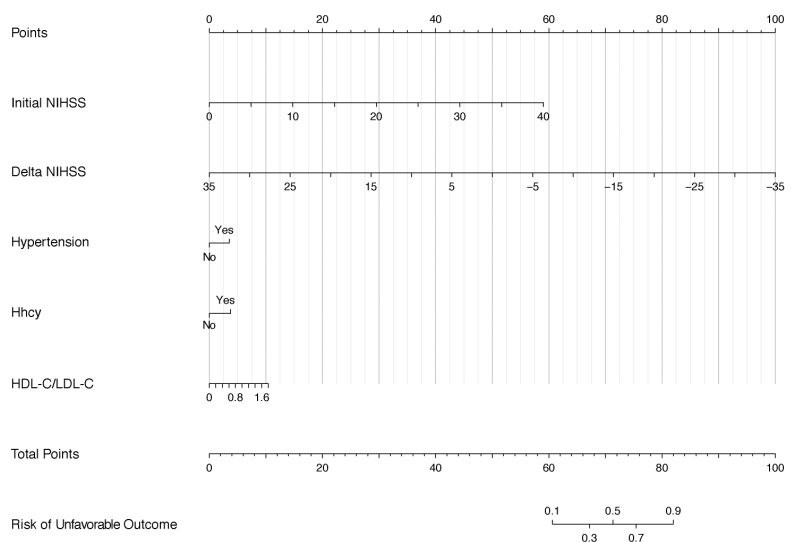

Figure 2. The N2H3 Nomogram for predicting the 3-month outcome. Points were assigned for initial NIHSS score, delta NIHSS, hypertension, Hhcy, and HDL-C/LDL-C by drawing a line upward from the corresponding values to the "points line." The "total points" are calculated as the sum of the individual score of each of the five variables included in the nomogram. Delta NIHSS, changes in the NIHSS score from baseline to 24 h; HDL-C/LDL-C, the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol; Hhcy, hyperhomocysteinemia; NIHSS, National Institutes of Health Stroke Scale.

logistic regression analysis. Using these five predictive factors, the N2H3 nomogram was developed to assess the probability of 3-month unfavorable outcome in these patients.

The predictors involved in this model are all routine and easy to obtain; moreover, most of them have previously been reported to be linked with
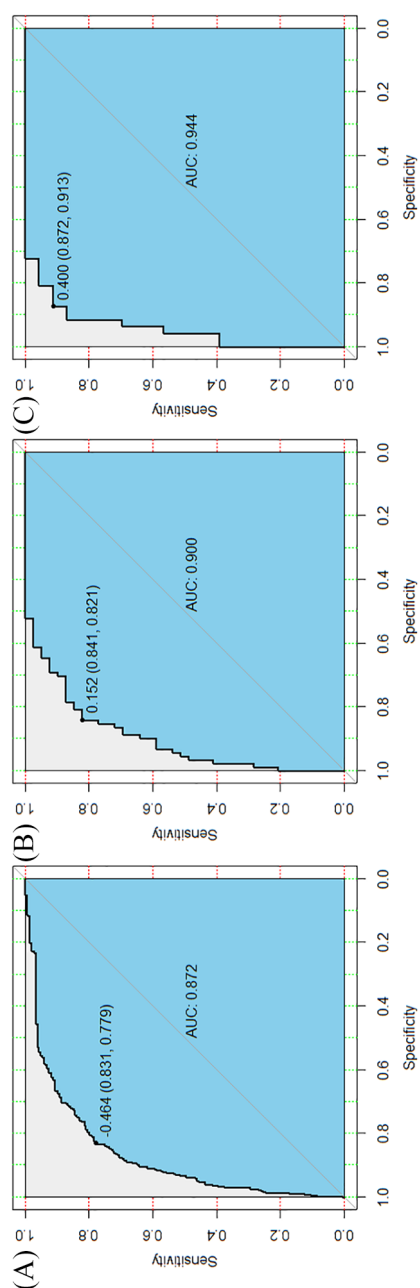
Figure 3. Receiver operating characteristic (ROC) curve of the training cohort (A), test cohort (B), and the 10-fold cross-validation (C).

unfavorable outcomes in AIS patients. Initial stroke severity evaluated using the NIHSS score on admission is a primary determinant of clinical outcome among patients with AIS and often be used in prognosis prediction models. Early response after thrombolysis may explain much of the long-term outcomes. Post-treatment markers of stroke severity that included changes in NIHSS and 24-h NIHSS have been shown to be better predictors of subjects' clinical and functional outcomes than the initial NIHSS score.[23–27] Changes in post-treatment NIHSS over the first 24h may be a reflection of reperfusion, partly distinguishing patients with clinically effective reperfusion from those with futile or no reperfusion.[26] Since we did not collect vascular examination data before and after treatment, the relation between reperfusion status and NIHSS score changes could not be analyzed. Nevertheless, delta NIHSS is the strongest predictor of outcome in our model, which is in accordance with the results of previous studies.

In addition to stroke severity, age is one of the major determinants of stroke outcomes.[11,28] Elderly patients were prone to have poorer outcomes compared with young patients after rt-PA thrombolysis treatment in early clinical trials.[29,30] However, recent studies have provided inconsistent findings.[31–33] Recently, a pooled analysis of seven randomized clinical trials by Bluhmki and colleagues showed that the odds of a good outcome following rt-PA treatment in AIS patients were independent of age.[34] The differences in the measurement of outcome could be an explanation of those inconsistent results. Besides, elderly patients were more likely to have complications such as atrial fibrillation and hypertension, as well as higher NIHSS score, all of which may influence stroke outcomes.[30] In the present study, although patients with an unfavorable outcome had a higher median age than those with a favorable outcome, the effect of age on outcome was not significant after adjusting for confounding variables.

Higher LDL-C level is a risk factor of ischemic stroke; this has been proven in previous studies to be associated with patient outcomes.[35] HDL-C level is also attributed to the prognosis in AIS patients treated with thrombolysis.[36] The ratio of the two variables was found to be an even better predictor of cardiovascular events and atherosclerotic burden.[37,38] Given the fact that both higher

LDL-C and lower HDL-C levels are related with unfavorable outcomes in patients with ischemic stroke, the HDL-C/LDL-C may be a stronger predictor. In the present study, we found that a higher HDL-C/LDL-C was independently associated with 3-month unfavorable outcome, which was opposite from the result of previous studies. In fact, evidence of relation between serum cholesterol level and stroke outcome is inconsistent. Several studies have reported lipid paradox, that is, elevated cholesterol levels improved short-term functional outcome and long-term survival,[39–41] while lower cholesterol levels contributed to short-term mortality.[42] However, the potential mechanism of this paradox observation remains unknown. The observation of the HDL-C/LDL-C paradox has not been reported yet. Considering the small sample of our study, this result needs further study to be verified.

In our study, hypertension, rather than the level of blood pressure, was found to be an independent predictor of outcome. Blood pressure values vary considerably during the whole process. Previous studies have revealed that both high and low blood pressure were independent prognostic factors for poor outcome in ischemic stroke patients.[43,44] Hypertension has been included in previous AIS prognostic models, such as the THRIVE score.[10] Another variable of our nomogram, Hhcy, is also a proved predictor of outcome in ischemic stroke.[45] A higher level of homocysteine was reported to be associated with an increased risk of poor outcome after thrombolysis in AIS patients.[46–48] Although found to be independent predictors after multivariable logistic analysis, hypertension and Hhcy are only a small proportion of our model.

The AUC value of the N2H3 nomogram was 0.872 (95% CI, 0.841–0.902), which is higher than the value of the START nomogram (AUC, 0.766; 95% CI, 0.707–0.826).[5] The variables of the START nomogram could be collected before thrombolysis. Patients in whom a high probability of unfavorable outcome were predicted should be considered for further treatment, especially endovascular thrombectomy. In our nomogram, although several variables were derived from clinical examination and laboratory test results after thrombolysis, it is still possible to select patients with a high risk of unfavorable outcome. Further neuroprotective drugs such as
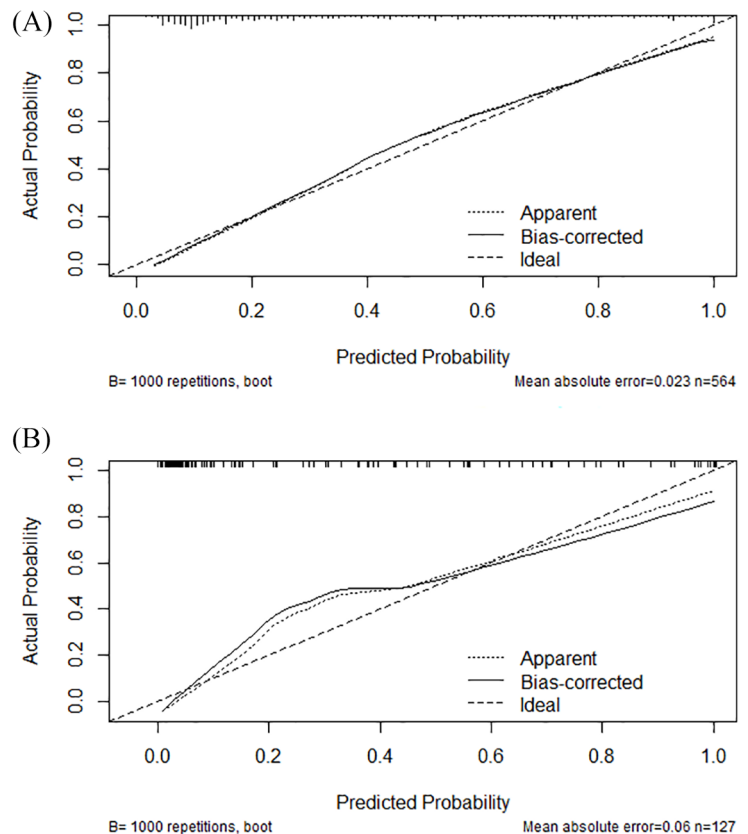
Figure 4. Calibration plot of the N2H3 nomogram in the training (A) and test cohorts (B). The dotted line represents the performance of the nomogram; the solid line corrects for any bias in the nomogram; and the dashed line represents the reference line where an ideal nomogram would lie.

edaravone and n-butylphthalide,[49,50] and intensive rehabilitation, should be considered for these patients. Of course, patients with a calculated prediction of a positive outcome should by no means withdraw from beneficial treatments. The most noteworthy strength of a nomogram is to serve as a useful tool for individualized prediction of the probability of unfavorable outcomes. From the clinicians' perspective, as a quantitative indicator, using a nomogram can make things easy when explaining the prognosis to patients and their families.

DCA is a method used to assess the prediction value and clinical usefulness of a model (like a nomogram).[51,52] Distinguishing patients with high and low risk of unfavorable outcome is the main purpose of this nomogram. For any given probability threshold, the nomogram with the greatest net benefit would be the most preferred model. In
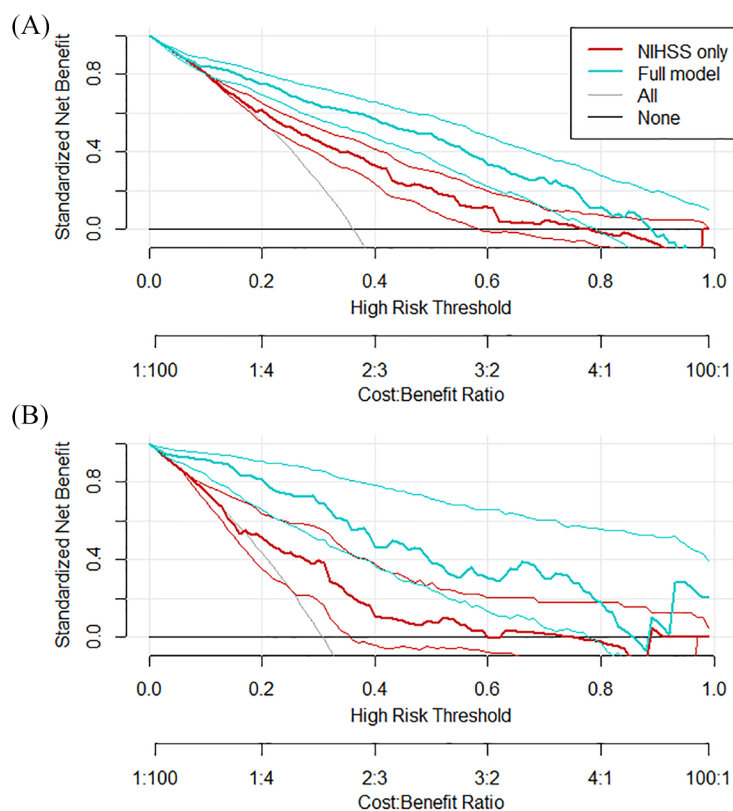
Figure 5. Decision curve analysis of the N2H3 nomogram of training cohort (A) and test cohort (B). The red line displays the net benefit of the prediction of NIHSS score only. The blue line displays the net benefit of the prediction of the full nomogram model. The gray line assures that all patients develop unfavorable outcome. The black line assures that no patients develop unfavorable outcome.
NIHSS, National Institutes of Health Stroke Scale.

the present study, DCA showed that using the N2H3 nomogram with limited variables for outcome prediction was better than using the initial NIHSS score alone. The N2H3 nomogram was found to be clinically useful in predicting outcome and could facilitate the early identification of patients who are candidates for further therapy.

There are several limitations that need to be addressed in this study. First, the clinical data was collected retrospectively. Second, this is a single-center study with a relatively small sample size, some variables (like serum glucose and onset to rt-PA bolus time) that were reported in previous studies to be associated with AIS outcomes were not observed in our study.[6,53] In addition, the test cohort comes from the same stroke center from where the training cohort was derived. This nomogram needs to be tested in other centers in future studies.

Conclusion

Our study developed and validated a reliable N2H3 nomogram model, which is composed of history of initial NIHSS, delta NIHSS, hypertension, Hhcy, and HDL-C/LDL-C. The N2H3 nomogram could provide individualized early prediction of the 3-month unfavorable outcome in AIS patients who were treated with intravenous rt-PA thrombolysis, and thus facilitate the early identification of patients who are candidates for further therapy.

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Supplemental material
Supplemental material for this article is available online.

Reference
1. Wardlaw JM, Sandercock PAG and Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. *Stroke* 2003; 34: 1437–1442.

2. Wahlgren N, Ahmed N, Dávalos A*, et al.* Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. *Lancet* 2007; 369: 275–282.

3. Hacke W, Kaste M, Bluhmki E*, et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317–1329.

4. Wardlaw JM, Murray V, Berge E, *et al.* Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; 2014: CD000213.

5. Cappellari M, Turcato G, Forlivesi S, *et al.* The START nomogram for individualized prediction of the probability of unfavorable outcome after intravenous thrombolysis for stroke. *Int J Stroke* 2018; 13: 700–706.

6. Kent DM, Selker HP, Ruthazer R, *et al.* The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. *Stroke* 2006; 37: 2957–2962.

7. Ntaios G, Faouzi M, Ferrari J, *et al.* An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. *Neurology* 2012; 78: 1916–1922.

8. Strbian D, Meretoja A, Ahlhelm FJ, *et al.* Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. *Neurology* 2012; 78: 427–432.

9. Saposnik G, Fang J, Kapral MK, *et al.* The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke. *Stroke* 2012; 43: 1315–1322.

10. Flint AC, Faigeles BS, Cullen SP, *et al.* THRIVE score predicts ischemic stroke outcomes and thrombolytic hemorrhage risk in VISTA. *Stroke* 2013; 44: 3365–3369.

11. Saposnik G, Guzik AK, Reeves M, *et al.* Stroke prognostication using age and NIH stroke scale: span-100. *Neurology* 2013; 80: 21–28.

12. Zhang X, Yuan K, Wang H, *et al.* Nomogram to predict mortality of endovascular thrombectomy for ischemic stroke despite successful recanalization. *J Am Heart Assoc* 2020; 9: e014899.

13. Gong P, Zhang X, Gong Y, *et al.* A novel nomogram to predict early neurological deterioration in patients with acute ischemic stroke. *Eur J Neurol*. Epub ahead of print 20 May 2020. DOI: 10.1111/ene.14333.

14. Hathaway WR, Peterson ED, Wagner GS, *et al.* Prognostic significance of the initial electrocardiogram in patients with acute myocardial infarction. GUSTO-I Investigators. Global utilization of streptokinase and t-PA for occluded coronary arteries. *JAMA* 1998; 279: 387–391.

15. Califf RM, Pieper KS, Lee KL, *et al.* Prediction of 1-year survival after thrombolysis for acute myocardial infarction in the global utilization of streptokinase and TPA for occluded coronary arteries trial. *Circulation* 2000; 101: 2231–2238.

16. Jehi L, Yardi R, Chagin K, *et al.* Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurol* 2015; 14: 283–290.

17. Cappellari M, Turcato G, Forlivesi S, *et al.* STARTING-SICH nomogram to predict symptomatic intracerebral hemorrhage after intravenous thrombolysis for stroke. *Stroke* 2018; 49: 397–404.

18. Jauch EC, Saver JL, Adams HP Jr, *et al.* Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke* 2013; 44: 870–947.

19. Powers WJ, Derdeyn CP, Biller J, *et al.* 2015 American heart association/American stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke* 2015; 46: 3020–3035.

20. Powers WJ, Rabinstein AA, Ackerson T, *et al.* 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke* 2018; 49: e46–e110.

21. Wang Y, Cui L, Ji X, *et al.* The China national stroke registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke* 2011; 6: 355–361.

22. Sacco RL, Adams R, Albers G, *et al.* Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American heart association/American stroke association council on stroke: co-sponsored by the council on cardiovascular radiology and intervention: the American academy of neurology affirms the value of this guideline. *Circulation* 2006; 113: e409–e449.

23. Broderick JP, Lu M, Kothari R, *et al.* Finding the most powerful measures of the effectiveness of tissue plasminogen activator in the NINDS tPA stroke trial. *Stroke* 2000; 31: 2335–2341.

24. Al-Ajlan FS, Goyal M, Demchuk AM, *et al.* Intra-arterial therapy and post-treatment infarct

volumes: insights from the ESCAPE randomized controlled trial. *Stroke* 2016; 47: 777–781.

25. Sajobi TT, Menon BK, Wang M, *et al.* Early trajectory of stroke severity predicts long-term functional outcomes in ischemic stroke subjects: results from the ESCAPE trial (endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times). *Stroke* 2017; 48: 105–110.

26. Jeong H-G, Kim BJ, Choi JC, *et al.* Posttreatment national institutes of health stroke scale is superior to the initial score or thrombolysis in cerebral ischemia for 3-month outcome. *Stroke* 2018; 49: 938–944.

27. Wouters A, Nysten C, Thijs V, *et al.* Prediction of outcome in patients with acute ischemic stroke based on initial severity and improvement in the first 24 h. *Front Neurol* 2018; 9: 308.

28. König IR, Ziegler A, Bluhmki E, *et al.* Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke* 2008; 39: 1821–1826.

29. Heuschmann PU, Kolominsky-Rabas PL, Roether J, *et al.* Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. *JAMA* 2004; 292: 1831–1838.

30. Sylaja PN, Cote R, Buchan AM, *et al.*; Canadian Alteplase for Stroke Effectiveness Study Investigators. Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian alteplase for stroke effectiveness study. *J Neurol Neurosurg Psychiatry* 2006; 77: 826–829.

31. Mishra NK, Diener H-C, Lyden PD, *et al.* Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA). *Stroke* 2010; 41: 2840–2848.

32. Manawadu D, Bodla S, Keep J, *et al.* Influence of age on thrombolysis outcome in wake-up stroke. *Stroke* 2013; 44: 2898–2900.

33. Emberson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; 384: 1929–1935.

34. Bluhmki E, Danays T, Biegert G, *et al.* Alteplase for acute ischemic stroke in patients aged >80 years: pooled analyses of individual patient data. *Stroke.* Epub ahead of print 2 July 2020. DOI: 10.1161/STROKEAHA.119.028396.

35. Nardi K, Leys D, Eusebi P, *et al.* Influence of lipid profiles on the risk of hemorrhagic transformation after ischemic stroke: systematic review. *Cerebrovasc Dis Extra* 2011; 1: 130–141.

36. Nardi K, Engelter S, Strbian D, *et al.* Lipid profiles and outcome in patients treated by intravenous thrombolysis for cerebral ischemia. *Neurology* 2012; 79: 1101–1108.

37. Barter P, Gotto AM, LaRosa JC, *et al.* HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007; 357: 1301–1310.

38. Enomoto M, Adachi H, Hirai Y, *et al.* LDL-C/HDL-C ratio predicts carotid intima-media thickness progression better than HDL-C or LDL-C alone. *J Lipids* 2011; 2011: 549137.

39. Patel U, Malik P, Dave M, *et al.* The lipid paradox among acute ischemic stroke patients-a retrospective study of outcomes and complications. *Medicina (Kaunas)* 2019; 55: 475.

40. Vauthey C, de Freitas GR, van Melle G, *et al.* Better outcome after stroke with higher serum cholesterol levels. *Neurology* 2000; 54: 1944–1949.

41. Olsen TS, Christensen RHB, Kammersgaard LP, *et al.* Higher total serum cholesterol levels are associated with less severe strokes and lower all-cause mortality: ten-year follow-up of ischemic strokes in the Copenhagen Stroke Study. *Stroke* 2007; 38: 2646–2651.

42. Zuliani G, Cherubini A, Atti AR, *et al.* Low cholesterol levels are associated with short-term mortality in older patients with ischemic stroke. *J Gerontol A Biol Sci Med Sci* 2004; 59: 293–297.

43. Leonardi-Bee J, Bath PMW, Phillips SJ, *et al.*; IST Collaborative Group. Blood pressure and clinical outcomes in the international stroke trial. *Stroke* 2002; 33: 1315–1320.

44. Vemmos KN, Tsivgoulis G, Spengos K, *et al.* U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004; 255: 257–265.

45. Shi Z, Guan Y, Huo YR, *et al.* Elevated total homocysteine levels in acute ischemic stroke are associated with long-term mortality. *Stroke* 2015; 46: 2419–2425.

46. Yao E-S, Tang Y, Xie M-J, *et al.* Elevated homocysteine level related to poor outcome after thrombolysis in acute ischemic stroke. *Med Sci Monit* 2016; 22: 3268–3273.

47. Ling-Cong, Hong-Zhao, Yu- Wang, *et al.* The serum homocysteine level in patients with acute

ischemic stroke (AIS) after thrombolysis and its relationship with clinical outcomes. *Rev Assoc Med Bras (1992)* 2018; 64: 438–442.

48. Luo Y, Jin H, Guo Z-N, *et al.* Effect of hyperhomocysteinemia on clinical outcome and hemorrhagic transformation after thrombolysis in ischemic stroke patients. *Front Neurol* 2019; 10: 592.

49. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis* 2003; 15: 222–229.

50. Cui L-Y, Zhu Y-C, Gao S, *et al.* Ninety-day administration of dl-3-n-butylphthalide for acute ischemic stroke: a randomized, double-blind trial. *Chin Med J (Engl)* 2013; 126: 3405–3410.

51. Rousson V and Zumbrunn T. Decision curve analysis revisited: overall net benefit, relationships to ROC curve analysis, and application to case-control studies. *BMC Med Inform Decis Mak* 2011; 11: 45.

52. Vickers AJ and Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; 26: 565–574.

53. Yue Y-H, Li Z-Z, Hu L, *et al.* Clinical characteristics and risk score for poor clinical outcome of acute ischemic stroke patients treated with intravenous thrombolysis therapy. *Brain Behav* 2019; 9: e01251.

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