JACC: ASIA VOL. 2, NO. 7, 2022

ORIGINAL RESEARCH

Prediction of Acute Myocardial Infarction in Asian Patients With Acute Ischemic Stroke

The CTRAN Score

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ABSTRACT

BACKGROUND Patients with acute ischemic stroke (AIS) are susceptible to acute myocardial infarction (AMI), which would lead to a dramatic increase of in-hospital mortality.

OBJECTIVES The authors established and validated an easy-used model to stratify the risk of in-hospital AMI among patients with AIS.

METHODS We consecutively included patients with AIS who were admitted within 7 days from symptom onset in our prospectively maintained database (NCT04487340) from January 2016 to December 2020. In the derivation cohort from 70 centers, we developed a score to predict in-hospital AMI by integrating the bedside-accessible predictors identified via multivariable logistic regression. Then in the validation cohort from 22 centers, we externally evaluated the performance of this score.

RESULTS Overall, 96,367 patients were included. In-hospital AMI occurred in 392 (0.41%) patients. The final model, named CTRAN, incorporated 5 predictors including the history of coronary heart disease, malignant tumor, renal insufficiency, age, and baseline National Institutes of Health Stroke Scale score. The CTRAN score was confirmed in the validation cohort using receiver operating characteristic curve, which yielded an area under the curve of 0.758 (95% CI: 0.718-0.798).

CONCLUSIONS The CTRAN score could be a good tool for clinicians to identify patients with AIS at high in-hospital AMI risk. (JACC: Asia 2022;2:845-852) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Acute myocardial infarction (AMI) has been reported to occur in 1.67% to 2.2% of patients with acute ischemic stroke (AIS),[1,2] predominantly within the first 2 to 3 days.[3] The occurrence of AMI after AIS is associated with a 3-fold increase of in-hospital mortality and a 50% increase in the cost and length of hospitalization, calling for early recognition and timely secondary prevention in this population.[4]

Certain variables, such as age, history of coronary artery disease, renal insufficiency, hypertension, and undergoing mechanical thrombectomy have been

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Sun Uck Kwon, PhD, served as Guest Associate Editor for this paper. Nathan Wong, PhD, served as Guest Editor-in-Chief for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 8, 2022; revised manuscript received July 13, 2022, accepted August 4, 2022.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.08.008

ABBREVIATIONS AND ACRONYMS

AC = anterior circulation

AIS = acute ischemic stroke

AMI = acute myocardial infarction

AUC = area under the curve

CTRAN = the history of Coronary heart disease, malignant Tumor, Renal insufficiency, Age, and baseline NIHSS score

ICD = International Classification of Diseases

NIHSS = National Institutes of Health Stroke Scale

PC = posterior circulation

reported as predictors of AMI after AIS.[4,5] However, previous studies paid no attention to the predictive value of AIS severity, evaluated by National Institutes of Health Stroke Scale (NIHSS) score, in the identification of AMI risk. As it is well acknowledged that the severity of AIS could play a critical role in the occurrence of AMI via so-called brain-heart intervention, NIHSS might also have potential predictive value of AMI in patients with AIS. To date, an instrument predicting the specific risk of AMI in an individual diagnosed with AIS is still lacking. Thus, to promptly identify patients with high risk of AMI at the bedside, a score based on easily accessible clinical characteristics is in need.

Therefore, in this research, we aimed to investigate whether a simple risk score based on bedside-accessible information could effectively identify patients with high risk of in-hospital AMI in Asian patients with AIS.

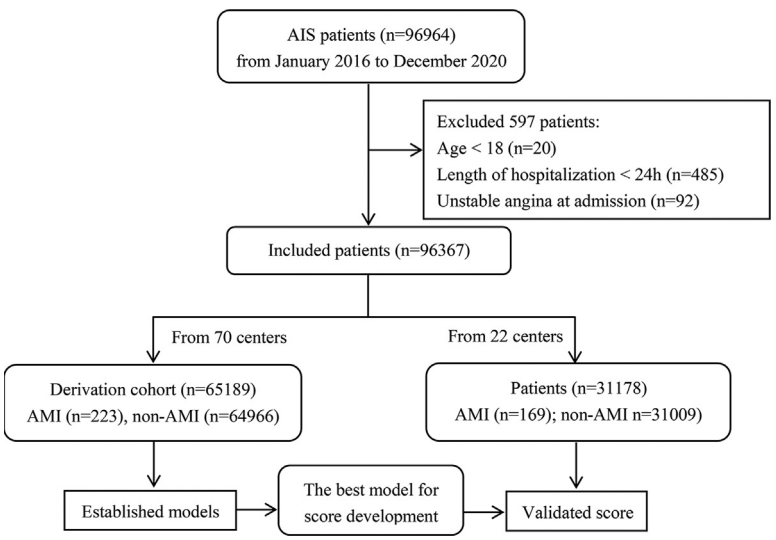
METHODS

STUDY POPULATION. The data for analyses were obtained from a multicenter registry, CASE-II (Computer-based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation, NCT04487340). We retrospectively reviewed the CASE-II database for patients with AIS who were consecutively admitted from January 2016 to December 2020 at 92 centers in China. We divided the centers into derivation cohort from 70 centers for score derivation and validation cohort from 22 centers for score validation. We excluded the following patients: 1) age <18 years; 2) hospital length of stay <24 hours; or 3) diagnosed as unstable angina at admission.

We obtained the bedside-accessible characteristics recorded by trained study personnel, including age, gender, medical history (hypertension, diabetes mellitus, atrial flutter/fibrillation, coronary artery disease, heart failure, cardiac valvular disease, anemia, malignant tumor, renal insufficiency, prior stroke, smoking, and drinking), baseline NIHSS score, initial and peak troponin levels, whether undergoing reperfusion therapy (intravenous thrombolysis and/or endovascular treatment), and presumed stroke cause (according to the TOAST [Trial of Org 10172 in Acute Stroke Treatment] classification).[6] Stroke cause by TOAST criteria was determined by the in-hospital treating physician based on routine workup.

DEFINITION. The primary outcome, in-hospital AMI, was adjudicated in accordance with the Fourth

FIGURE 1 Study Flowchart



Study flowchart of patient enrollment, model derivation, and validation are shown. A total of 96,367 patients were included in this study from the CASE-II (Computer-based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation), multivariable logistic regression analysis and area under the curve (AUC) from receiver operating characteristic curve analysis were applied for model derivation and validation. AIS = acute ischemic stroke; AMI = acute myocardial infarction.

Universal Definition of Myocardial Infarction.[7] Specifically, AMI was defined by acute myocardial injury (with detection of an elevation and/or fall of troponin values with at least 1 value above the 99th percentile upper reference limit) plus any of the following: symptoms or signs of myocardial ischemia, such as presence of chest pain, dyspnea, and new-onset heart failure; the electrocardiogram including new ischemic electrocardiographic changes and development of pathological Q waves.[7] In addition, the participants were also defined as patients with AMI if the clinical diagnoses were determined by the specialist physicians before discharge.

Medical history was collected from face-to-face interviews and cross-referenced with previous care records. History of coronary heart disease was defined based on known myocardial infarction, stable or unstable angina, and history of percutaneous coronary intervention or coronary artery bypass graft surgery.[8] History of renal insufficiency was defined based on known measurement (estimated glomerular filtration rate <60 mL/min/1.73 m^2), previous doctor diagnosis, and history of renal transplant or dialysis.[9,10] History of malignant tumor was confirmed if an International Classification of Diseases (ICD) code (140-208 according to ICD-8 and ICD-9; C00-C97 according to ICD-10) was recorded in the medical history. We excluded basal cell carcinomas and in situ lesions, as they are considered to be with noninvasive features.[11]

The severity of AIS was measured with the NIHSS score at admission and stratified into mild (≤3), moderate (4-10), moderate and severe (11-19), and severe (≥20).[12,13]

STATISTICAL ANALYSIS. Descriptive statistics were presented as frequencies with percentages for categorical variables and as mean ± SD for continuous variables. Fisher exact test was used to compare the dichotomous variables between groups, and independent samples 2-tailed *t*-test, or Mann-Whitney *U* test was used for the continuous variables, depending on the normality of the distribution.

For model development, candidate variables that were associated with in-hospital AMI in univariable analysis ($P < 0.10$) were entered into the multivariable logistic regression analysis. A backward stepwise procedure was applied in the multivariable logistic regression to remove non-statistically significant variables and calculated an adjusted β-coefficient. The final integer-based scoring system was developed by dividing the adjusted β-coefficient of the remaining items in the derivation cohort by the median of the lowest 3 values (ie, 0.721) and rounding to the nearest integer.[14] To account for differential statistical dependencies for patients within centers vs between centers, as a sensitivity analysis, a random intercept for center was added in the mixed effect logistic regression. Because the proportion of AMI is small in the population, a control model was built without any covariate information to predict "No AMI" for every patient. Troponin I or troponin T were measured in each center using either contemporary or high-sensitivity assays. These tests yielded results in different measurable ranges, with unique cutoff points for the 99th centile of the upper limit of normal, the standardized troponin was yielded by using the ratio of the observed troponin value divided by the upper limit of normal for each troponin assay.[15] To further explore[16] whether the combination of troponin could better predict the risk of in-hospital AMI, the standardized troponin was entered into multivariable logistic regression along with the former established score. Model discrimination was assessed by area under the curve (AUC) from receiver operating characteristic curve analysis. We then computed the established score (named CTRAN [history of Coronary heart disease; malignant Tumor, Renal insufficiency, Age, and baseline NIHSS score] score) for each patient, the predicted probability of

TABLE 1 Baseline Characteristics of Patients in Derivation and Validation Cohorts

	Derivation Cohort (n = 65,189)	Validation Cohort (n = 31,178)
Age, y	69 ± 12	68 ± 12
Female	26,364 (40.4)	12,235 (39.2)
In-hospital AMI	223 (0.34)	169 (0.54)
Medical history		
Hypertension	42,387 (65)	19,921 (63.9)
Diabetes mellitus	13,383 (20.5)	6,567 (21.1)
Atrial flutter/fibrillation	7,084 (10.9)	3,169 (10.2)
Coronary artery disease	3,187 (4.9)	1,531 (4.9)
Heart failure	633 (1)	210 (0.7)
Valvular disease	586 (0.9)	586 (0.9)
Anemia	367 (0.6)	153 (0.5)
Malignant tumor	2,236 (3.4)	1,272 (4.1)
Renal insufficiency	1,101 (1.7)	526 (1.7)
Smoking	22,159 (34.2)	10,956 (35.3)
Drinking	9,240 (14.2)	3,833 (12.3)
Prior stroke	14,435 (22.1)	6,513 (20.9)
Clinical presentation of stroke		
Baseline NIHSS, median (IQR)	2 (1-5)	2 (1-5)
Undergoing intravenous thrombolysis	6,354 (9.7)	2,891 (9.3)
Undergoing thrombectomy	496 (0.8)	319 (1)

Values are mean ± SD, n (%), or median (IQR).
AMI = acute myocardial infarction; NIHSS = NIH Stroke Scale.

TABLE 2 Univariate Analysis for In-hospital AMI in the Derivation Cohort

	No AMI (n = 64,966)	AMI (n = 223)	*P* Value
Age, y	69 ± 13	76 ± 13	**<0.001**
Female	26,249 (40.4)	115 (51.6)	**0.001**
Onset time of AMI, d	–	1.25 (1-4)	
Medical history			
Hypertension	42,232 (65)	155 (69.5)	0.159
Diabetes mellitus	13,339 (20.5)	44 (19.7)	0.767
Atrial flutter/fibrillation	7,023 (10.8)	61 (27.4)	**<0.001**
Coronary artery disease	3,153 (4.9)	34 (15.2)	**<0.001**
Heart failure	628 (1)	5 (2.2)	0.068
Valvular disease	584 (0.9)	2 (0.9)	1.000
Anemia	362 (0.6)	5 (2.2)	**0.009**
Malignant tumor	2,216 (3.4)	20 (9)	**<0.001**
Renal insufficiency	1,090 (1.7)	11 (4.9)	**<0.001**
Prior stroke	14,373 (22.1)	62 (27.8)	**0.041**
Clinical presentation of stroke			
Baseline NIHSS score	2 (1-5)	7 (3-15)	**<0.001**
Undergoing intravenous thrombolysis	6,323 (9.7)	31 (13.9)	**0.036**
Received thrombectomy	493 (0.8)	3 (1.3)	0.241
Antithrombotic agents in hospital	63,106 (97.1)	205 (91.9)	**<0.001**
TOAST classification			
Large artery atherosclerosis	13,447/35,231 (38.1)	41/119 (34.4)	0.405
Cardioembolism	4,569/35,231 (12.9)	42/119 (35.2)	**<0.001**
Small artery occlusion	12,042/35,231 (34.1)	12/119 (10.0)	**<0.001**
Other determined cause	785/3,5231 (2.22)	4/119 (3.36)	0.343
Undetermined	4,388/35,231 (12.4)	20/119 (16.8)	0.151

Values are mean ± SD, n (%), or median (IQR). Values in **bold** indicate $P < 0.05$.
TOAST = Trial of Org 10172 in Acute Stroke Treatment; other abbreviations as in Table 1.

AMI was the mean value of ρ based on the logistic regression model:

$$\rho = \frac{e^{L}}{1 + e^{L}}$$

Where ρ = the probability of in-hospital AMI, L = β-coefficient of the constant + [(β-coefficient of each CTRAN items) × (the score of each item)]. All statistical analyses were performed in SPSS 26.0 and R (version 4.1.2). Two-sided probability values < 0.05 were considered significant.

ETHICS STATEMENT. The study was approved by the human ethics committee of the Second Affiliated Hospital of Zhejiang University, School of Medicine. Clinical investigation had been conducted in accordance with the principles expressed in the Declaration of Helsinki.

RESULTS

STUDY POPULATION. During the period, 96,964 patients met the inclusion criteria and 96,367 patients were finally enrolled in the analysis (Figure 1). A total of 392 (0.41%) patients suffered from in-hospital AMI, and 49 of 392 (12.5%) patients were identified according to the diagnosis of specialist physicians before discharge. Data of troponin were available in 6,634 patients, and the troponin of patients with AMI is shown in Supplemental Table 1.

SCORE DERIVATION AND VALIDATION. To derive the risk score, the pooled cohort was split into the derivation cohort (n = 65,189, from 70 centers) and the validation cohort (n = 31,178, from 22 centers). The flowchart is depicted in Figure 1 and the clinical characteristic distributions of derivation and validation cohorts are described in Table 1.

Univariate analyses (Table 2) shows that older age, female sex, history of atrial flutter/fibrillation, coronary artery disease, anemia, malignant tumor, renal insufficiency, prior stroke, intravenous thrombolysis, and higher baseline NIHSS score correlated with the occurrence of AMI.

For model establishment, all variables with *P* value <0.10 in the univariate analysis were entered into the multivariable analysis, finding that 5 variables were independently associated with in-hospital AMI in model 2, including history of coronary heart disease, malignant tumor, renal insufficiency, age, and baseline NIHSS score (Table 3). There were no missing data in model 2 of the derivation cohort. Based on the results of multivariable analysis, the point values were assigned to the items to develop an integer-based estimation system, which was termed as CTRAN score (Central Illustration). In the derivation cohort, the risk of in-hospital AMI increased with increasing CTRAN score (OR: 2.098; 95% CI: 1.926-2.285; $P < 0.001$) with an AUC of 0.777 (95% CI: 0.746-0.808, Central Illustration A).

In the validation cohort, the risk of in-hospital AMI increased with increasing CTRAN score (OR: 1.998, 95% CI: 1.809-2-208; $P < 0.001$) with an AUC of 0.753 (95% CI: 0.714-0.793) (Central Illustration A). The comparison of predictive abilities for CTRAN and the control model is shown in Supplemental Table 2.

The prediction estimates of the CTRAN score in validation cohort are displayed in Central Illustration B. The lowest CTRAN value (0 points) predicts a 0.14% risk of AMI during hospitalization. The highest CTRAN value (8 points) predicts a 26.73% risk of AMI during hospitalization.

THE COMBINATION OF CTRAN SCORE AND TROPONIN TO PREDICT AMI. In patients with data of troponin (n = 6,634), the AUC could be elevated to 0.876 (95% CI: 0.855-0.896) (Supplemental Figure 1) by adding standardized troponin to the CTRAN score.

SUBGROUP ANALYSIS ACCORDING TO THE TERRITORY OF ISCHEMIC STROKE. In subgroup analysis, the trend of each CTRAN component in subgroups were

TABLE 3 Multivariate Logistic Analysis for In-hospital AMI in the Derivation Cohort

	Mode 1			Mode 2	
	OR (95% CI)	*P* Value	β	OR (95% CI)	*P* Value
The history of coronary heart disease	2.136 (1.460-3.125)	**<0.001**	0.755	2.127 (1.454-3.112)	**<0.001**
The history of malignant tumor	2.397 (1.505-3.819)	**<0.001**	0.874	2.395 (1.504-3.815)	**0.003**
The history of renal insufficiency	2.061 (1.105-3.843)	**0.023**	0.721	2.056 (1.102-3.834)	**0.027**
Age, y					
18-65	Ref.	Ref.	Ref.	Ref.	Ref.
66-84	1.965 (1.332-2.899)	**0.001**	0.687	1.988 (1.348-2.932)	**<0.001**
>84	3.563 (2.282-5.563)	**<0.001**	1.296	3.655 (2.346-5.694)	**<0.001**
Baseline NIHSS					
NIHSS ≤3	Ref.	Ref.	Ref.	Ref.	Ref.
NIHSS 4-10	2.096 (1.492-2.944)	**<0.001**	0.742	2.099 (1.495-2.948)	**<0.001**
NIHSS 11-19	5.777 (3.985-8.375)	**<0.001**	1.759	5.809 (4.035-8.363)	**<0.001**
NIHSS ≥20	8.696 (5.560-13.60)	**<0.001**	2.200	9.022 (5.847-13.92)	**<0.001**
Therapy of stroke					
Received intravenous thrombolysis	1.035 (0.698-1.533)	0.865	–	–	–
Received thrombectomy	0.591 (0.185-1.886)	0.374	–	–	–
Antithrombotic agents in hospital	0.658 (0.397-1.091)	0.104	–	–	–

Mode 1: Adjusted for the history of coronary heart disease, malignant tumor, renal insufficiency, age, baseline NIHSS score, received intravenous thrombolysis, received thrombectomy and antithrombotic agents in hospital. Mode 2: Adjusted for the history of coronary heart disease, malignant tumor, renal insufficiency, age, and baseline NIHSS score. Values in **bold** indicate $P < 0.05$.

Abbreviations as in Table 1.

consistent with the overall population (Supplemental Table 3). The AUCs were 0.765, 0.760, and 0.730, respectively, in patients with anterior circulation (AC) stroke, patients with both posterior circulation (PC) and AC stroke, and patients with PC stroke (Supplemental Figure 2). Sensitivity analyses with the mixed-effects model to account for institutional clustering of the patients were consistent with the primary analyses (Supplemental Table 4).

DISCUSSION

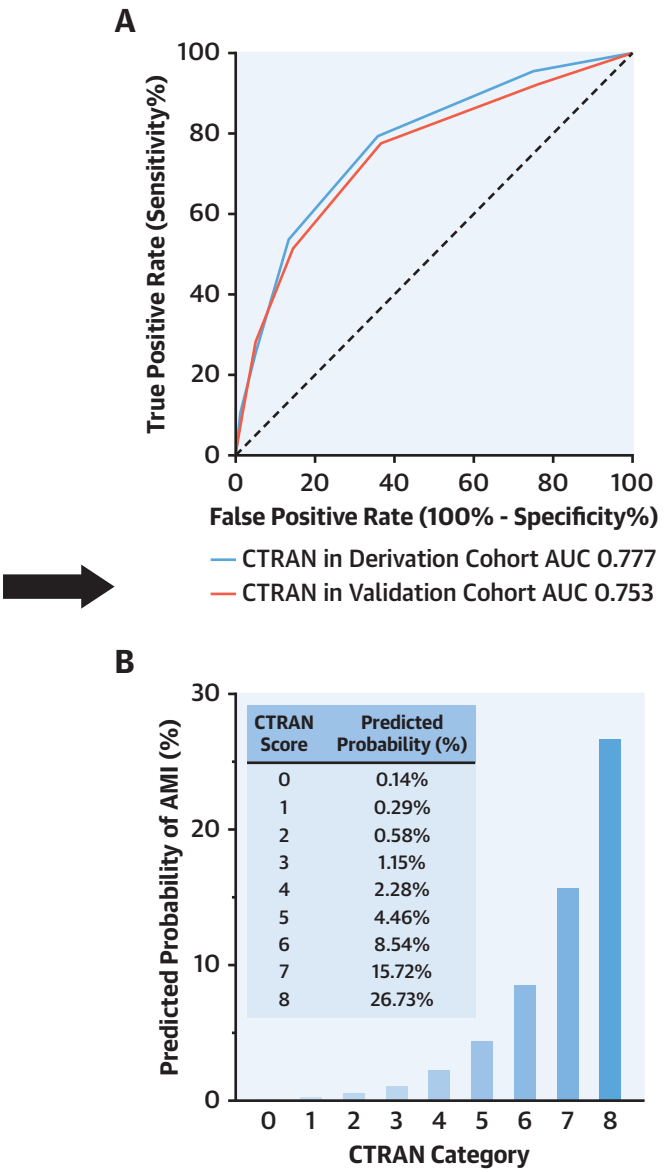
In this study, we derived a novel risk score, CTRAN score, based on the bedside-accessible information in a large AIS cohort in China to predict in-hospital AMI after AIS. Good discriminative ability of CTRAN score was demonstrated in the validation cohort. This score could be a good tool for clinicians to identify patients at high in-hospital AMI risk after AIS.

A previous study by Alqahtani et al[4] showed an in-hospital AMI risk of 1.6% in patients with AIS in the US cohort. In our Chinese cohort, the risk of in-hospital AMI after AIS (0.41%) was much lower than that in the United States, and more similar to the cohort from Korea, which reported a cumulative 30-day and 90-day myocardial infarction rate after stroke of 0.1% and 0.3%.[17] The possible reason might be that the population in the United States was mainly composed of White and Black men, whereas Asian race was generally reported with lower risk of myocardial infarction (2.6% for men; 0.7% for women) than the White (4.0% for men; 2.4% for women) and Black races (3.3% for men; 2.2% for women).[18]

Previous researchers have suggested that the items in the CTRAN score were associated with the occurrence of AMI. 1) The history of coronary heart disease was included in the score as it is universally accepted that AMI mostly results from spontaneous plaque rupture or erosion and subsequent thrombosis in patients with coronary heart disease.[19] 2) It was reported that 9.3% of patients with AMI had received care for malignant tumor in the 5 years before admission.[20] Patients with malignant tumor were reported to have higher risks of phlebitis, thrombophlebitis, and thromboembolism.[21] In addition, the oncotherapy could injure the vascular endothelial cells via radiation (radiotherapy)[22] or possess potential cardiotoxic effects (chemotherapy),[23] thus elevating the risk of AMI. 3) AMI is prevalent in the population with renal insufficiency.[24] Apart from the concordance of shared risk factors, the coronary arteriosclerosis in patients with renal insufficiency could be exacerbated by systemic inflammation, as well as by vascular calcification resulting from calcium and phosphate imbalances.[25] 4) The burden of cardiovascular disease, including AMI, is higher in patients with older age.[26] 5) After AIS, the brain-heart interactions, originating from the autonomic deregulation and catecholamine surge, might play a dominant role in the aggravation of underlying coronary artery, myocardial injury or stunning, and the occurrence of AMI (type II MI).[5,7] Thus, with the

CENTRAL ILLUSTRATION The Calculation and Performance of CTRAN Score

The Calculation of CTRAN Score	
(C) Coronary heart disease	
NO	0
YES	1
(T) Malignant tumor	
NO	0
YES	1
(R) Renal insufficiency	
NO	0
YES	1
(A) Age	
18-65	0
66-84	1
>84	2
(N) NIHSS score	
NIHSS ≤3	0
NIHSS 4-10	1
NIHSS ≥11-19	2
NIHSS ≥20	3



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The weight of CTRAN score (history of Coronary heart disease; malignant Tumor, Renal insufficiency, Age, and baseline NIHSS score) was based on multivariable logistic regression in the derivation cohort. **(A)** Receiver operating characteristic curves for in-hospital acute myocardial infarction (AMI) plotted according to CTRAN score in the derivation and validation cohorts. **(B)** Predicted risk of in-hospital AMI according to CTRAN score in the validation cohort. AUC = area under the curve; NIHSS = National Institutes of Health Stroke Scale.

increased severity of AIS (higher NIHSS), the risk of AMI would increase.

Previous studies have reported that undergoing intravenous thrombolysis and thrombectomy might be predisposing factors of AMI occurrence. However, their model for analyses had not adjusted for NIHSS score.[4] In the univariate comparison of our study, undergoing intravenous thrombolysis was found to be positively associated with the occurrence of AMI. However, neither intravenous thrombolysis nor thrombectomy remained significant in the multivariate model after adjusting for baseline NIHSS score.

Thus, the severity of stroke itself might be more relevant to the occurrence of AMI in comparison with reperfusion therapy. In our cohorts, the CTRAN score performed better in AC stroke than in PC stroke. The main reason might be that NIHSS, the most commonly used scale for neurological deficits, has relatively poor predictive value for vessel occlusion in PC stroke,[16] and patients with cancer-related stroke tend to have widely distributed infarct lesions in multiple territories, both AC and PC.[27]

This study has several strengths. First, the CTRAN score was derived from a large multicentric database with the inclusion of a broad spectrum of Chinese patients with AIS, which could support the application of this instrument in diverse clinical settings and populations. Second, the CTRAN score was validated in an independent external cohort and showed good discrimination. Furthermore, thanks to the easily measured and routinely available components of the CTRAN (which could be acquired from the self-report of patients and routine NIHSS assessment at admission), no data were missed in the process of score development and validation, suggesting a great availability of CTRAN to quickly identify the patients with high risk vs patients with relatively low risk, so as to prompt the clinicians to pay more attention to patients with high risk and help to screen patients for the enrollment of prospective studies.

STUDY LIMITATIONS. First, because of the lack of follow-up on AMI events, the predictive value of CTRAN score on AMI risk after discharge remains unknown. Second, not all patients with AIS without AMI have baseline troponin data, and the troponin was standardized for analysis because of the different measuring instruments in each center. Third, the CTRAN score was derived and validated in the Chinese cohort only, the generalizability of the CTRAN score warrants further validation in other Asian populations (eg, South Asian in particular).

CONCLUSIONS

CTRAN is a risk score based on clinical variables that were routinely evaluated at the bedside, thus can help clinicians quickly identify patients with high in-hospital AMI risk. Prospective study is expected to verify the value of the CTRAN score to predict the risk of in-hospital AMI in patients with AIS.

ACKNOWLEDGMENTS The authors thank the staff of the CASE-II registry, the other members at the participating centers, and the study coordinators for their efforts in collecting clinical data and ensuring the accuracy and completeness of the data.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the Science Technology Department of Zhejiang Province (2018C04011), the National Natural Science Foundation of China (81971101), and the National Key Research and Development Program of China (2016YFC1301503). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The CTRAN score might help clinicians stratify the risk of in-hospital AMI among Chinese patients with AIS at admission.

TRANSLATIONAL OUTLOOK: Future studies are expected to prospectively verify the predictive value of the CTRAN score, and establish an effective strategy for the prevention of AMI in patients with AIS with high risk.

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KEY WORDS myocardial infarction, natriuretic peptides, risk, stroke

APPENDIX For supplemental tables and figures, please see the online version of this paper.

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