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Multi-phase computed tomography angiography combined with inflammation index to predict clinical functional prognosis in patients with acute ischemic stroke

H. Yang [a,b,c,d], T. Han [b,c,d], Y. Han [a,c,d], X. Liu [b,c,d], Y. She [a,c,d], Y. Xu [b,c,d], L. Bai [a,b,c,d,**], J. Zhou [a,b,c,d,*]

[a] *Department of Radiology, The Second Hospital of Lanzhou University, Cuiyingmen No. 82, Chengguan District, Lanzhou 730030, China*
[b] *The Second Clinical Medical School, Lanzhou University, Lanzhou 730030, China*
[c] *Key Laboratory of Medical Imaging of Gansu Province, Lanzhou 730030, China*
[d] *Gansu International Scientific and Technological Cooperation Base of Medical Imaging Artificial Intelligence, Lanzhou, China*

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AIM: In this study, we investigated the feasibility of the Alberta Stroke Program Early CT Score (ASPECTS) and multiphase computed tomography angiography (mCTA) lateral branch circulation grading combined with clinical and laboratory indicators to predict the clinical prognosis of patients with acute ischemic stroke after 90 days.

MATERIALS AND METHODS: The clinical data of 80 patients with acute anterior circulation ischemic stroke were retrospectively analyzed and divided into the good prognosis (37 cases) and poor prognosis groups (43 cases) according to their clinical function score at 90 days after discharge. Various factors, including basic imaging parameters (ASPECTS), occluded vessel location, affected side location and clinical indicators (time from onset to computed tomography examination, height, weight, body mass index, previous hypertension, and degree of hypertension and diabetes mellitus), laboratory blood rutine, and biochemical tests (white blood count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, hematocrit test, platelet count, international normalized ratio, blood glucose, triglycerides, uric acid, and D-dimer) were considered in the analysis.

RESULTS: Logistic regression analysis showed that the mCTA score, hypertension, and neutrophil count were significant independent predictors.

CONCLUSION: A nomogram of the mCTA score, hypertension, and neutrophil count may predict functional recovery after 90 days in patients with acute ischemic stroke.

* Guarantor and correspondent: J. Zhou, Department of Radiology, Lanzhou University Second Hospital, Cuiyingmen No. 82, Chengguan District, Lanzhou, 730030, PR China.
** Guarantor and correspondent: L. Bai
E-mail address: ery_zhoujl@lzu.edu.cn (J. Zhou).

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Introduction

With the increasing aging of the population, stroke is a serious threat to population health. Because of the high disability and mortality rates of stroke, the post-rehabilitation and nursing care brings a huge financial burden to the family and the society. Stroke and ischemic heart disease were the leading causes of death and disability-adjusted life-years at the national level in China.[1] Strokes are usually classified as ischemic or hemorrhagic, and approximately 87% of cases are ischemic.[2] In addition to applying alteplase within this time window, endovascular thrombectomy for treating acute ischemic stroke (AIS) caused by large vessel occlusion (LVO) is recommended as a standard treatment as per the guidelines.[3] AIS, resulting from anterior circulation LVO, including occlusions in the internal carotid artery and the middle cerebral artery, can be treated within 6 h using a combination of endovascular stent resection and aspiration and is the most effective method to achieve rapid and complete restoration of cerebral reperfusion. An 8–14% reduction in the chance of a good functional prognosis exists for every 30-min delay in recanalization.[4]

Even after timely intravenous thrombolysis (IVT), some patients do not experience neurological improvement, indicating ineffective recanalization, as reflected by a modified Rankin scale (mRS) score of 4–6 points, with inflammation playing a pivotal role in reperfusion.[5–7] Postischemic inflammation exacerbates stroke outcomes, with neutrophils being the first responders to cerebral ischemia.[8,9] Postischemic neutrophil influx can lead to microvascular occlusion, increased blood viscosity, and vascular resistance, resulting in microcirculatory failure.[10,11] It is now well established that mechanisms such as endothelial adhesion of leukocytes, endothelial adhesion of platelets, and ultimately thrombosis influence progressive infarction in the penumbra region at the level of the ischemic microcirculation. It has been suggested that the ratio of the neutrophil count to the lymphocyte count in the blood is associated with long-term prognosis and collateral growth in patients with stroke.[12,13] The clinical prognosis of patients with AIS depends, in part, on the degree of collateral circulation. Good collateral circulation at baseline neuroimaging is associated with better clinical outcomes and may improve the effectiveness of IVT and endoscopic vacuum therapy. However, the lack of a unified and fairly independent grading of collateral circulation in the scientific literature limits its usefulness in emergency departments.[14] In patients with acute anterior circulation ischemic stroke and atrial fibrillation, the prohormone N-terminal pro-BNP levels were inversely correlated with the collateral status.[15]

Therefore, we anticipate that an increase in the neutrophil ratio will lead to collateral circulation failure and therefore poorer AIS clinical prognosis. This study established a comprehensive model that linked the grading of multiphase computed tomography angiography (mCTA) collateral circulation with the ratio of neutrophil count and baseline clinical data. This model aims to predict neurological recovery after 90 days and accurately judge the overall prognosis.

Materials and methods

Clinical data

This study was approved by the institutional review board of our hospital (2022A-110). This was a retrospective study and required informed consent from patients. Data from patients diagnosed with AIS at our hospital from January 2018 to November 2021 and treated with mCTA were collected. The inclusion criteria were as follows: (1) age $\geq$18 years; (2) anterior circulation ischemic stroke; and (3) symptoms and signs of obvious ischemic stroke neurological deficits. The exclusion criteria were as follows: (1) previous history of cerebral hemorrhage, severe head trauma, or surgery; (2) patients with brain tumors; (3) posterior circulation disease; (4) patients who could not be scored due to image artifacts; and (5) patients without an mRS score for 30 days postoperatively. This study was approved by the institutional review board of our hospital (2022A-110).

Image acquisition and processing

Patients who were suspected of stroke onset, as diagnosed by neurologists within 48 h (or those visited while in a stable condition), that underwent computed tomography (CT) examination with GE Revolution (GE Healthcare, Chicago, IL, USA) were used for inspection. Noncontrast computed tomography (NCCT) was obtained using a voltage of 120 kV, current of 350 mAs, tube rotation time of 1.0 s, matrix size of 512 $\times$ 512, slice thickness of 0.625 mm, and reconstructed slice thickness of 5 mm. Following confirmation of no hemorrhagic stroke, the CTA scan program commenced simultaneously with the high-pressure syringe, with the first-phase scan completed under bolus-tracking software monitoring. The second-phase and third-phase scans were performed with delays of 8 s each. The scanning range for phase 1 was from the aortic arch upward to the top of the skull, while for phases 2 and 3, it was from the base of the skull up to the top. Layer thickness was set at 0.625 mm for continuous scanning. In the emergency situations, CTA images of at least three-phase mixed-integer programming were provided to show the responsible vessels and collateral circulation associated with stroke (Fig 1). Some patients underwent further CT evaluation of cerebral perfusion, but this part of the data is not covered in this study.

Image rating

The Alberta Stroke Program Early CT Score (ASPECTS) is a standardized semiquantitative CT grading system used by

many stroke centers to quantify early signs of ischemia in patients with acute anterior circulation ischemic stroke.[16,17] The scoring was conducted in the basal ganglia region (i.e., thalamic and striatal planes) and above the basal ganglia level (2 cm above the nuclear level). Each region, including M1-M6 (M1 = anterior middle cerebral artery (MCA) cortex; M2 = MCA cortex lateral to insular ribbon; M3 = posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to Ml, M2, and M3, rostral to basal ganglia, respectively), insula, lentiform nucleus, caudate nucleus, and posterior limb of the internal capsule, was assigned a score ranging from 0 to 10 points. A score of 10 points indicated a normal CT scan, while 0 points indicated extensive ischemia in the MCA blood supply area.

Concerning the CTA collateral score, lateral branch compensation was assessed using a 5-point method using mCTA or by reading the original scan images of perfusion[18]: 0, compared with the opposite hemisphere, no blood vessels were found in the ischemic region at any time; 1, blood vessels were visible in any phase of the ischemic region compared with the opposite hemisphere; 2, compared with the contralateral hemisphere, the filling of the pial blood vessels was delayed in two phases, and the number of filling vessels was reduced, or there was a delay in one phase, and some areas were not filled; 3, compared with the contralateral hemisphere, the filling of pial vessels was delayed by two phases or by one phase, but the number of filling vessels was significantly reduced; 4, compared to the contralateral hemisphere, the degree of filling of the pial vessels was normal, and there was a delay of one phase; and 5, normal filling of the pial blood vessels with no delay compared with the contralateral hemisphere.

Table 1
Characteristic of patient.

Characteristic	Functional outcome			
	Favorable (n=37)	Poor (n=43)	Chi-square/t value	*p*
Demographics				
Age (years)	57.95 ± 11.02	59.67 ± 13.18	-0.630	0.530
Sex/Male	9/28	11/32	0.017	0.090
Body mass index	21.37 ± 3.10	23.56 ± 2.60	-0.605	0.502
Risk factors, n (%)				
Diabetes mellitus	11 (26)	12 (31)	0.032	0.857
Hypertension			12.294	0.006
None	18 (22.5%)	12 (15%)		
Hypertension grade I	5 (6.25%)	0 (0)		
Hypertension grade II	4 (5%)	10 (12.5%)		
Hypertension grade III	10 (12.5%)	21 (26.25%)		
Smoking	6 (7.5%)	3 (3.75%)	1.700	0.192
Treatments, n (%)			2.464	0.116
IVT	22 (27.5%)	18 (22.5%)		
Conservative treatment	15 (18.75%)	25 (31.25%)		
Responsible vessels, n(%)			2.918	0.405
ACA	0 (0)	1 (1.25%)		
MCA	25 (31.25%)	26 (32.5%)		
ICA	9 (11.25%)	8 (10%)		
ICA + MCA	3 (3.75%)	8 (10%)		
Location of perfusion lesion, right vs left hemisphere, left/right brain	26/11	23/20	2.360	0.124
Onset to CT time	25.62	24.49	3.108	0.108
NIHSS, median (IQR)	2 (1–4)	5 (4–15)	-3.564	0.006
mCTA score, median (IQR)	4 (3–5)	2 (1–3)	8.441	0.041
ASPECTS score, median (IQR)	8 (1–10)	7 (2–9)	3.108	0.005
Baseline laboratory examination				
WBC (10^9/L)	7.14 ± 1.84	7.74 ± 1.98	-1.403	0.165
Neutrophils (10^9/L)	4.52 ± 1.59	5.59 ± 1.90	-2.687	0.009
Lymphocytes (10^9/L)	1.89 ± 0.68	1.53 ± 0.59	2.574	0.012
NLR	2.72 ± 1.88	4.27 ± 3.11	-2.635	0.010
HCT	0.45 ± 0.05	0.43 ± 0.06	2.140	0.035
Platelet	193.24 ± 58.48	213.14 ± 56.45	-1.548	0.954
Blood sugar content	6.70 ± 4.28	6.07 ± 1.77	0.877	0.395
Triglyceride	1.60 ± 0.75	1.49 ± 0.79	1.071	0.578
Uric acid	337.03 ± 81.62	296.28 ± 86.87	2.151	0.504
D-dimer	0.39 ± 0.23	0.95 ± 1.29	-2.6	< 0.001
INR	1 ± 0.09	1.02 ± 0.11	-0.935	0.139

ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; INR, international normalized ratio; MCA, middle cerebral artery; mCTA, multiphase computed tomography angiography; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; HCT, hematocrit.

Clinical score definition

A. Baseline neurological deficit score: The National Institutes of Health Stroke Scale (NIHSS) was used to assess the severity of neurological deficits upon admission for all patients with AIS, with scores ranging from 0 to 42 points. Higher scores indicate more severe clinical symptoms.
B. Neurological function score of the mRS at 90 days: The mRS score was determined via telephone follow-up, categorizing patients into two groups: those with scores of 0–2 points, indicating favorable prognosis, and those with scores of 3–6, indicating a poor prognosis.

CT image analysis

Two experienced neuroradiologists retrospectively examined the patients' NCCT and multistage CTA images. First, ASPECTS scores were obtained. Then, the mCTA scores were obtained based on the third-stage CTA images. Differences between radiologists were resolved through discussion and consensus.

Statistical analysis

IBM SPSS Statistics (version 25.0; IBM Corp.) and R software (version 4.2.1; R Foundation for Statistical Computing) were used for statistical analysis. Measurements that fit the normal distribution are expressed by ($x \pm s$). Measurements that did not fit the normal distribution are represented as medians (interquartile ranges [IQRs]) or medians (ranges). Percentages were utilized for statistical representation. Prognostic predictions were conducted through univariate and multivariate analyses using binary logistic regression. All hypothesis tests were two-tailed, with a significance level set at $p < 0.05$, indicating statistical significance.

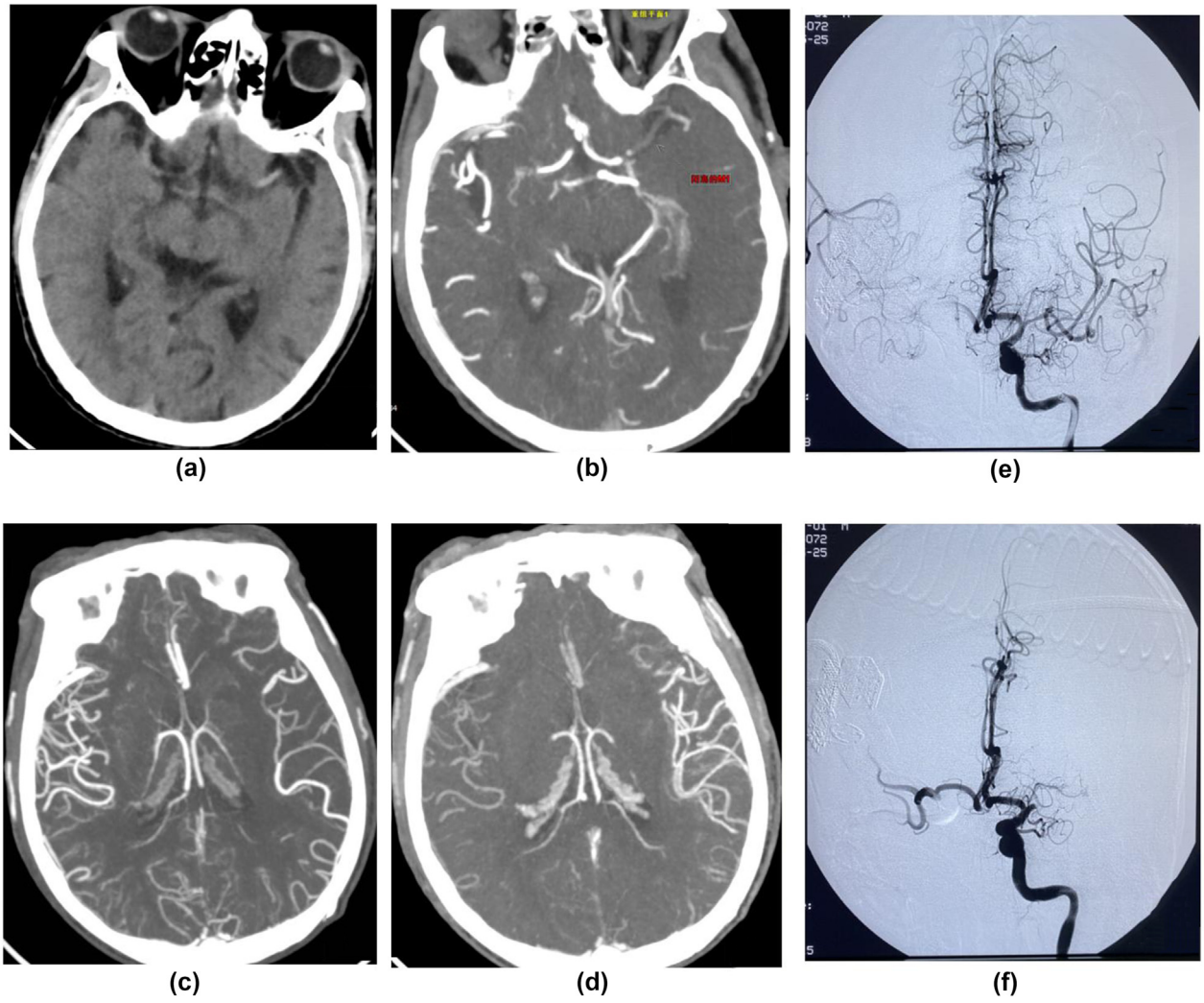

Figure 1 The patient was a 73-year-old male with speech impairment and right limb weakness for 5 hours. His NIHSS score was 19. A, NCCT scan showed high-density thrombosis in the left middle cerebral artery. B, CTA clearly shows the responsible vessels. C and D, Multistage CTA has good collateral compensation. The patient underwent arterial thrombectomy. E, Preoperative DSA angiography was consistent with CTA. F, Postoperative recanalization was good, TICI 3 grade. NIHSS, National Institutes of Health Stroke Scale; NCCT, Noncontrast computed tomography; CTA, computed tomography angiography; mTICI, modified Thrombolysis in Cerebral Infarction; DSA, Digital subtraction angiography.

Results

Patient characteristics

Eighty patients (60 men and 20 women; Table 1) were analyzed; the median time from onset to imaging was 25 h. The number and proportion of patients with hypertension, diabetes, and smoking were 30 (37.5%), 23 (28.8%), and nine (11.3%), respectively. Half of the patients received symptomatic medical treatment, and the other half received endovascular thrombolysis or thrombectomy (Fig 1). The MCA at the infarct site was 51 (63.75%): one (1.25%) for the anterior cerebral artery (ACA), 17 (21.25%) for the internal carotid artery (ICA), and 11 (13.75%) for the ICA and MCA.

The median baseline NIHSS score was 6 (IQR, 3–9) points, and the mCTA collateral circulation and 90-day mRS scores were 4 (IQR, 3–5) and 2 (IQR, 1–3) points, respectively. There were 37 good neurological cases (46.25%) (90-day mRS score of 0–2 points) and 43 (53.75%) with poor prognosis (90-day mRS score of 3–5 points).

The laboratory tests showed no significant differences in routine blood platelet count, biochemical lipid content, triglyceride levels, uric acid levels, or international normalized ratio.

Predictors of poor outcome

There were significant differences between the two groups in terms of hypertension ($p = 0.006$); baseline NIHSS score at admission between the two groups ($p = 0.006$); baseline multistage CTA collateral circulation score and ASPECTS score ($p = 0.041$, 0.005); and neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, hematocrit levels, and D-dimer levels at baseline laboratory examination (p values were 0.009, 0.012, 0.010, 0.035, and <0.001, respectively).

The mRS score at 90 days was negatively correlated with the mCTA collateral circulation score ($r = -0.720$, $p < 0.01$) and negatively associated with the ASPECTS score ($r = -0.321$, $p = 0.004$). There was a low correlation with baseline NIHSS score ($r = 0.366$, $p = 0.001$), weak correlation with baseline neutrophils count ($r = 0.291$, $p = 0.009$), and weak correlation with baseline D-dimer content ($r = 0.313$, $p = 0.005$), and degree of hypertension ($r = -0.231$, $p = 0.015$) (Table 2).

Multivariate regression analysis determined the neurological outcome

Patient univariable binary logistic regression showed that the mCTA score (odds ratio [OR], −3.717; $p = 0.001$), hypertension (OR, 1.152; $p = 0.010$), and neutrophil count in baseline laboratory examination (OR, 0.891; $p = 0.043$) could be used to determine neurological outcomes in patients with AIS after 90 days (Table 3). We developed a clinico-radiological nomogram for visualizing the model results (Fig 2). The calibration curve for the probability of 90-day outcomes showed favorable predictive performance satisfactorily consistent with the ideal curve (Fig 3). The decision curve analysis revealed that the nomogram had good clinical utility in predicting poor 90-day outcomes in patients with AIS (Fig 4).

Table 2
Linear correlation analysis.

Variables	r	*P*
mCTA score	-0.720	P < 0.01
ASPECTS score	-0.321	0.004
Baseline NIHSS	0.366	0.001
D-dimer	0.313	0.005
Hypertension	0.231	0.015
Neutrophil	0.291	0.009

ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale.

Discussion

The study results revealed that functional recovery in patients with large-vessel occlusive ischemic stroke after treatment was negatively associated with baseline mCTA, ASPECTS, baseline NHISS, and 90-day mRS scores, and the degree of hypertension was positively correlated with the 90-day mRS score. The serum D-dimer levels were negatively correlated with the mRS scores at 90 days. In patients with AIS with a history of hypertension, approximately 26.25% of those with poor functional recovery were classified into the tertiary extremely high-risk group. There was no correlation between IVT or conservative medical treatment and clinical function recovery in patients, and macrovascular recanalization failed to improve the clinical outcomes in nearly half of the patients. Disease location (left or right brain) and obstruction site were not associated with clinical function recovery.[19] Stroke severity and age independently affected the odds of good functional outcomes in patients with circulating LVO before AIS.[20]

CTA is the most common follow-up study after non-contrast head CT and is mainly used to identify intracranial large-vessel occlusion and carotid or vertebral artery disease.[17] This technique is highly sensitive and can improve the accuracy of endovascular treatment. Moreover, the mCTA score can predict the clinical, functional prognosis of patients with stroke after 90 days. Higher collateral score on mCTA corresponded to better compensation for ischemic stroke; lower mRS scores after 90 days corresponded to better clinical functional recovery. This aligns with previous study findings.[21,22]

Table 3
Application of univariate binary logistic regression to determine the neurological prognosis of patients.

Variables	B value	OR (95% CI)	*p*
mCTA score	-3.717	0.024 (0.002–0.239)	0.001
Hypertension	1.152	3.163 (1.310–7.640)	0.010
Neutrophils (10^9/L)	0.891	2.437 (1.029–5.770)	0.043

CI, confidence interval;
mCTA, multiphase computed tomography angiography; OR, odds ratio.

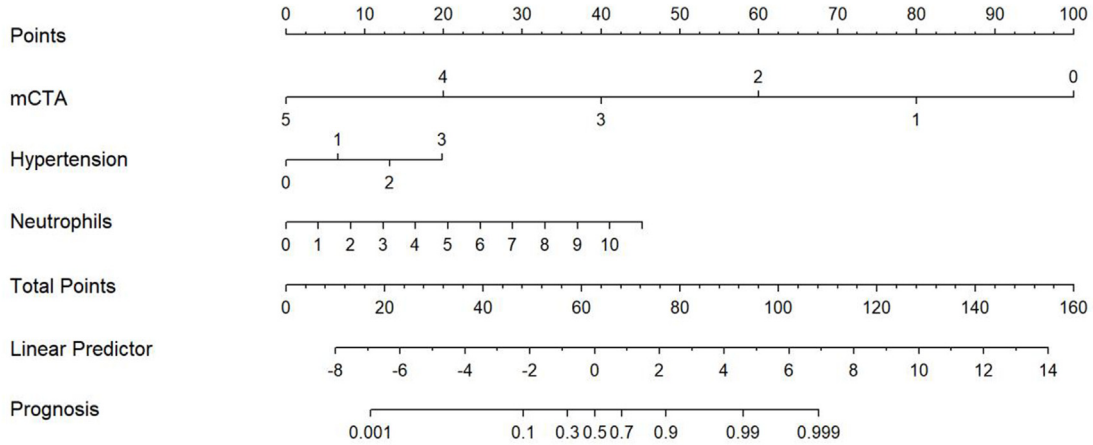

Figure 2 The clinico-radiological nomogram for assessing 90-day clinical functional outcome.

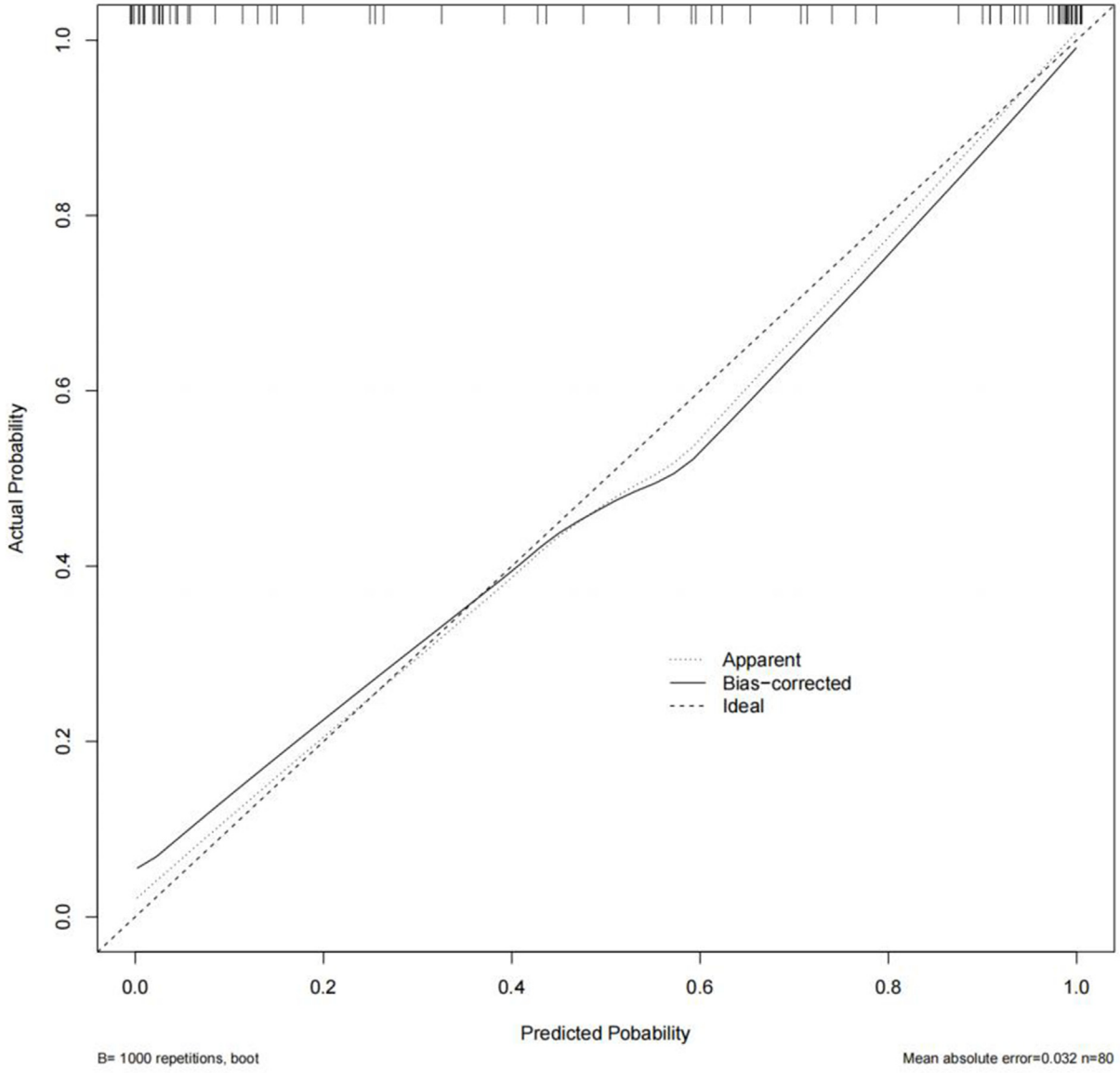

Figure 3 The calibration curves for the clinico-radiological nomogram.

mCTA can be used to evaluate the establishment of meningeal collateral circulation and provide new options for patient treatment. A large patient cohort study of proximal artery occlusion[18] found that collateral compensation increased over time, ischemic penumbra volume remained constant, and tissue vitality was maintained over the time window (0–6 h). The Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE-3) derived criteria suggest that patients with favorable collaterals in the MR CLEANLATE trial[23] may not require immediate endovascular treatment based solely on core and penumbra volumes. Instead, selecting patients for endovascular treatment guided by collateral circulation is important for clinical guidance.

In AIS, automatic assessment of noncontrast CT X-line attenuation changes within the ASPECTS score area can serve as an imaging alternative to the ischemic core defined by CT perfusion.[16] For many basic hospitals that do not have CTA or Computed tomography perfusion (CTP), ischemic cerebral infarction early brain parenchymal density reduction, shallow groove fission disappearance, fuzzy, island zone or high density of middle cerebral artery,[16] and certain visibility can be shown by other early signs in determining the degree of ischemic cerebral infarction and prognosis. Moreover, a lower ASPECTS score and higher mRS scores after 90 days are associated with poorer clinical functional recovery in the affected area.

In this study, the number of male patients with stroke was three times that of female patients, which may be attributed to the inclusion and exclusion criteria; less baseline data were collected and could be related to geography, environment, and cognitive factors. Studies have

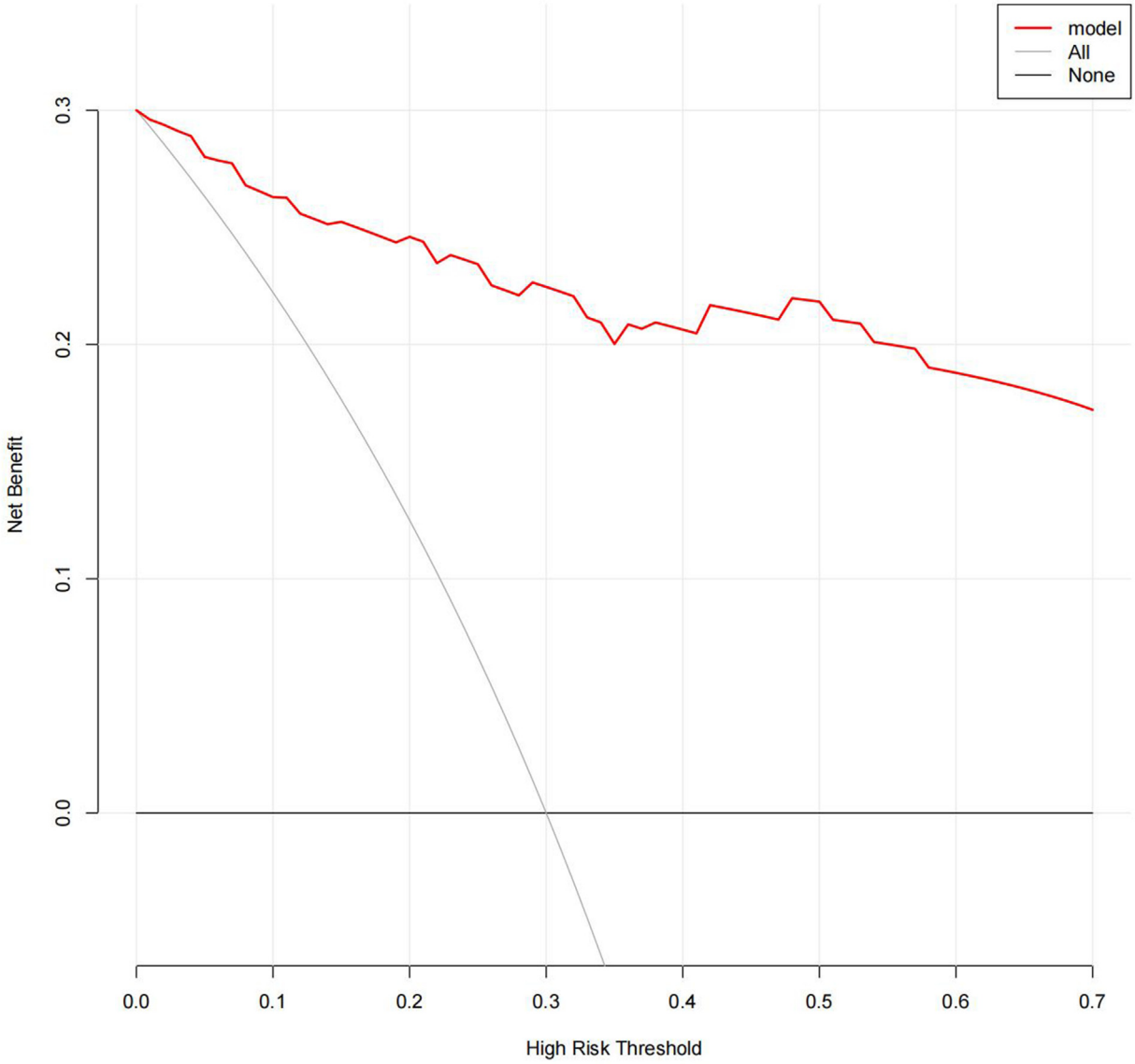

Figure 4 The decision curve for the clinico-radiological nomogram.

shown that sex is associated with differences in the incidence of different stroke types.[24] Additionally, we found no correlation between the diseased location (left or right brain) and the obstruction site or recovery of clinical function. Although the baseline ischemic core is more predictive of the functional outcome than the occlusion location,[19] the relationship between the ischemic core and clinical outcome did not differ according to the occlusion location. In addition, the prevalence of hypertension in patients with stroke was associated with an increased risk of stroke, with the severity of pre-existing hypertension correlating with poorer prognosis. Long-term increases in the triglyceride glucose index in patients with hypertension are associated with an increased risk of stroke,[25] particularly ischemic stroke. Diabetes mellitus is a major risk factor for cerebrovascular disease, with increased stroke mortality in patients with diabetes. There are significant inconsistencies in the management of cardiovascular risk factors in patients with stroke, diabetes, and coronary artery disease. Improved clinical outcomes after stroke are associated with a reduction in recurrent vascular events, leading to better long-term prognosis and quality of life for patients.[26]

The functional outcome of the patients in this study was related to routine blood neutrophil count and did not correlate with the serum triglyceride levels. Ischemic stroke induces an immune response that contributes to neuronal loss and tissue repair.[27] This complex process involves a range of cell types and effector molecules, with interleukin playing bidirectional roles in ischemic stroke through information transmission, immune cell activation, and regulation, mediating the activation, proliferation, and differentiation of T and B cells and the inflammatory response.[28] Mutual communication among different immune cells can also affect the outcome of ischemic stroke. Depending on the severity of the injury, acute inflammation can begin within a few minutes and resolve within a few days.[29,30] In ischemic stroke, acute inflammation occurs immediately after vessel occlusion.[31] After IS, hypoxia, pure stress in the wall of the postcapillary venules, and the production of reactive oxygen species trigger the recruitment of leukocytes (including neutrophils, lymphocytes, and monocytes) to the site of injury. For example, hypoxia-pretreated bone marrow stromal cells promote endothelial cell proliferation and tubule formation by upregulating *Rabep2*. Recent studies have shown that the activation of peripheral immune cells, especially neutrophils, may lead to microcirculatory failure and ineffective recanalization. In addition, atherosclerosis and cardiovascular disease can develop in patients with hypercholesterolemia; however, hypercholesterolemia has a beneficial impact on outcomes after ischemic stroke, noncardiac stroke, and acute coronary artery disease. Possible explanations include the antioxidant effect of lipids and lower risk of infection. Stroke primarily affects the elderly population, and mortality after endovascular treatment is associated with advanced age.[32] Several patients use conservative treatments; natural drugs exhibit good neuroprotective properties during the acute phase of cerebral ischemia by inhibiting oxidative stress and reducing neuroinflammation and apoptosis.[33]

Our study had some limitations. First, this was a retrospective analysis of a single-center prospective database, which may have generated biases in self-reported socioeconomic status and variability in diagnostic testing. Second, we did not analyze medication data, such as the number and class of antihypertensive medications. Finally, a multicenter validation study is required to confirm the performance of our nomogram before it can be applied in clinical practice.

Conclusion

Our study successfully developed a clinical model employing laboratory indices and clinical factors, effectively predicting a poor 90-day prognosis within 48 h of AIS onset. The model demonstrated commendable predictive performance, combining objectivity with user-friendliness. These results hold the potential to facilitate the identification of patients at risk of poor outcomes and inform future research on effective treatments and prognosis improvement.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

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Author contribution

1. Guarantor of integrity of the entire study: Junlin Zhou.
2. Study concepts and design: Haiting Yang, Junlin Zhou.
3. Literature research: Haiting Yang, Yinping Han.
4. Clinical studies: Haiting Yang, Yuan Xu, Tao Han.
5. Experimental studies/data analysis: Haiting Yang, Yinping Han.
6. Statistical analysis: Haiting Yang, Tao Han, Xianwang Liu, Liangcai Bai.
7. Manuscript preparation: Haiting Yang, Liangcai Bai.
8. Manuscript editing: Haiting Yang, Yingxia She, Junlin Zhou.

Conflict of interest

The authors declare that they have no competing interest.

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