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Imaging predictors of progressive infarction in patients with anterior circulation small subcortical infarction

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Abstract

Background The purpose of the present study is to investigate the association between imaging characteristics and progressive infarction (PI) in patients with anterior circulation single subcortical infarction (ACSSI).

Methods Between January 2020 and October 2022, we retrospectively enrolled 638 ACSSI patients admitted to the Stroke Unit of First Affiliated Hospital of Nanchang University within 48 h after symptom onset. Demographic characteristics, clinical information, laboratory data, and imaging features (the number of infarct slices and the maximal diameter of infarcts) were collected.

Results There were 121 patients with PI, accounting for 18.9% of the total. In univariate analysis, the infarct slice number tended to be higher in the PI group ($P < 0.05$). Additionally, patients with PI had a higher frequency of infarct diameter≥ 10 mm and infarct slices≥3 than patients without PI ($P < 0.05$). Patients diagnosed with branch atheromatous disease (BAD) were more likely to develop PI compared to lacunar infarction (LI) when BAD was defined as axial slices of infarcts ≥ 3 and the infarct diameter ≥10 mm ($P < 0.05$). Multivariate logistic analysis revealed that slice number ≥ 3 remained slightly significant after adjusting all variables with $P < 0.05$. Finally, receiver operating characteristic curves were used to compare discriminative abilities and suggested slices of infarcts ≥ 3 were superior to other imaging variables to predict PI in ACSSI patients.

Conclusion The present study suggests a lesion visible ≥3 slices is independently correlated with PI in ACSSI patients. The slice number of infarcts in ASCCI is a superior indicator to predict PI than other imaging markers.

Keywords Anterior circulation single subcortical infarction, Progressive infarction, Predict, Slices of infarct, Diameter of infarct

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Introduction

Single subcortical infarction (SSI) is commonly defined as a single small deep infarction in the territory of perforating arteries [1]. Anterior circulation single subcortical infarction (ACSSI), the most common type of SSI, is usually caused by the occlusion of perforating arteries including lenticulostriate artery supplying from the middle cerebral artery (MCA), Heubner's artery originating from the anterior cerebral artery (ACA) and anterior choroidal artery (AchA) arising from the internal carotid artery (ICA) [2]. The etiological heterogenicity of SSI could be divided into two main types: lacunar infarction (LI) and branch atheromatous disease (BAD) [3, 4]. LI is pathologically characterized by lipohyalinotic degeneration in the distal area of the perforating branches, while BAD is caused by atherosclerotic plaque in the parental artery or the proximal area of the perforating branches [3, 4]. Currently, distinguishing between LI and BAD mainly relies on imaging rather than pathology. BAD is usually defined as an infarct diameter ≥ 15 mm and extending 3 or more axial slices, while LI is usually considered as a single lesion of < 15 mm in the greatest diameter [5]. However, BAD is also defined as an infarct more than 10 mm in diameter on the axial slice and visible for 3 or more axial slices [6]. Thus there is inconsistency in the definition of BAD covering size, location, and slice through radiologic methods [2].

Recent studies have revealed a higher possibility of progressive infarction (PI) in BAD compared to LI, which has a negative effect on functional prognosis [2, 5]. In our previous study, we tried not to distinguish between BAD and LI to investigate the relationship between imaging markers and progressive infarction in patients with ACSSI, and demonstrated ≥ 3 infarct slices as a predictor of progressive infarction [7]. However, clinical studies regarding the predictive significance of infarct slices and infarct diameter in PI also remain inconsistent [8–11].

Therefore, in the present study, we aim to verify the findings of our previous study by expanding the sample size, and further investigating the association between imaging characteristics and PI in ACSSI patients.

Methods

Study populations

Between January 2020 and October 2022, we retrospectively recruited patients who were admitted to the Stroke Unit of First Affiliated Hospital of Nanchang University within 48 h after symptom onset. Inclusion criteria were as follows: (1) completed the first diffusion-weighted imaging (DWI) within 48 h of onset; (2) diagnosed as ACSSI on DWI consistent with the clinical deficits; (3) PI should be confirmed by DWI or computerized tomography (CT). Patients were excluded if they (1) received intravenous thrombolysis or endovascular therapy; (2) were identified of cardiogenic embolism, arterial to arterial embolism, other determined etiology (moyamoya disease, arterial dissection, vasculitis and so on); (3) neurological deficits worsening occurring before the first DWI; (4) lacked complete imaging, laboratory, or follow-up data. The study was approved by the Ethics Committee of First Affiliated Hospital of Nanchang University.

Definition

ACSSI is defined as the single subcortical infarct supplied from the lenticulostriate artery, Heubner's artery or anterior choroidal artery [2]. PI was defined as an increase in the NIHSS score by ≥1 point in motor power or ≥2 points on the total NIHSS within 7 days after admission, and extension of the original infarction was further confirmed by DWI or CT [7].

Clinical information and laboratory parameters

Clinical data that included demographic characteristics (age and sex), history of hypertension, diabetes, and stroke, initial National Institutes of Health Stroke Scale (NIHSS), and discharge NIHSS were recorded. We recruited laboratory parameters within 24 h of admission including white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), platelet (PLB), blood urea nitrogen (BUN), creatinine, uric acid, fasting glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fibrinogen and D-dimer.

Imaging procedures and evaluation

All patients underwent magnetic resonance imaging (MRI) on a 3.0 Tesla scanner (MAGNETOM Trio, Siemens, Erlangen, Germany). The protocol included T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery (FLAIR), DWI (TR/TE of 3100/91 ms; Field of view $230 \times 230 mm^2$; 19 slices with slice thickness of 5 mm; voxel size = $1.2 \times 1.2 \times 5 mm^3$; 2b values of 0 and 1000 s/mm^2; scan time of 1.16 min) and three-dimensional time-of-flight MRA (TR/TE of 22/3.86 ms; Field of view $235 \times 235 mm^2$; voxel size = $0.9 \times 0.6 \times 0.6 mm^3$; 2b values of 0 and 1000 s/mm^2; scan time of 3.12 min). Imaging data were evaluated by two trained neurologists who were blind to patients' information. We collected the number of infarct slices and the maximal diameter of infarcts on axial DWI. BAD [1] was defined as axial slices of infarcts≥3 and the infarct diameter ≥10 mm; LI [1] was defined as axial slices of infarcts < 3 or the infarct diameter < 10 mm [6]. BAD [2] was defined as axial slices of infarcts ≥3 and the infarct diameter ≥ 15 mm; LI [2] was defined as axial slices of infarcts < 3 or the infarct diameter < 15 mm [5].

Statistical analysis

SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Continuous variables were compared using the Student's t-test or Mann–Whitney U test and described by mean ± SD or median [interquartile range (IQR)]. Categorical variables were presented as frequency (percentages) and compared using the Chi-square test or Fisher exact test. Univariable and multivariable logistic regression models were performed to identify risk factors for progressive infarction. Receiver operating characteristic (ROC) curves were constructed for slices and diameter of infarcts, and the area under the curve (AUC) and Youden's index were further calculated to determine the cutoff value. To further compare the predictive abilities of four categorical variables (diameter of infarcts ≥10 mm or < 10 mm, axial slices of infarcts ≥ 3 or < 3, BAD [1] or LI [1], and BAD [2] or LI [2]), ROC curves were used based on predictive probability. All variables with a *P*-value < 0.05 were considered statistically significant.

Results

From January 2020 and October 2022, a total of 638 eligible patients diagnosed with ACSSI were enrolled in the analysis according to the inclusion criteria and exclusion criteria, including 121 patients with PI and 519 patients with non-PI. As shown in Table 1, there were no significant differences in age, sex, history of hypertension, diabetes and stroke, infarction location, WBC, RBC, HGB, PLB, BUN, creatinine, uric acid, fasting glucose, HDL-c, fibrinogen, and D-dimer between patients with PI and non-PI ($P > 0.05$). However, patients in the PI group had a higher initial NIHSS score, a higher discharge NIHSS score, a higher TG, a higher TC, and a higher LDL-c ($P < 0.05$). The baseline neuroimaging characteristics were presented in Table 1. Infarct diameter was not significantly different and infarct with diameter ≥ 15 mm was comparable between the two groups ($P > 0.05$). However, patients with PI more frequently had a diameter of infarcts ≥ 10 mm and axial slices of infarcts ≥ 3 ($P < 0.05$). In addition, the infarct slice number (slice thickness of 5 mm) tended to be higher in the PI group ($P < 0.05$). On the other hand, the percentage of BAD was higher in patients with PI when BAD was defined as axial slices of infarcts ≥ 3 and the infarct diameter ≥ 10 mm ($P < 0.05$), but equally when BAD was defined as axial slices of infarcts ≥ 3 and the infarct diameter ≥ 15 mm between the two groups ($P > 0.05$).

As shown in Table 2, the initial NIHSS score, TC, TG, LDL-c, diameter of infarcts ≥ 10 mm and axial slices of infarcts ≥3 showed significant associations with PI in the univariate analysis ($P < 0.05$). However, after adjusting all variables with $P < 0.05$, TG, LDL-c, and slice number ≥3 remained slightly significant in the multivariate analysis ($P < 0.05$).

ROC curves were used to estimate the overall discriminative ability of two imaging markers (diameter and axial slices of infarcts) (Fig. 1A). We observed that the AUC of diameter and slices to discriminate PI were 0.557 (95% CI 0.503–0.610) and 0.604 (95% CI 0.552–0.656), respectively. Additionally, the optimal cutoff values of diameter and slices were 11.1 mm and 2.5 axial slices. To further compare the predictive value of diameter and slices on PI, we established four categorical variables (diameter of infarcts ≥ 10 mm or < 10 mm, axial slices of infarcts ≥ 3 or < 3, BAD [1] or LI [1], and BAD [2] or LI [2]) based on infarct diameter and slice number. ROC curves based on predictive probability revealed that the AUC of diameter of infarcts ≥ 10 mm or < 10 mm, axial slices of infarcts ≥ 3 or < 3, BAD [1] or LI [1], and BAD [2] or LI [2] were 0.553 (95% CI 0.499–0.607), 0.602 (95% CI 0.547–0.656), 0.583 (95% CI 0.527–0.638) and 0.543 (95% CI 0.486-0.600). Of note, the AUC of axial slices of infarcts ≥ 3 was superior to other categorical variables to predict PI in ACSSI patients (Fig. 1B).

Discussion

In this study, we evaluated imaging markers predicting PI in patients with ACSSI and explored the association between the etiology and PI based on imaging characteristics. The main findings in our study are that a lesion visible ≥ 3 slices is correlated with PI, and a lesion visible ≥ 3 slices is shown to predict PI in a better performance compared to other imaging markers.

Early neurological deterioration (END) could be caused by mutiple mechanisms including PI representing an extension of the infarction in situ, increased intracranial pressure, recurrent cerebral ischemia, and secondary parenchymal bleeding [12]. Many previous studies have used END as an outcome variable, however, the relevant factors that contribute to the different mechanisms of END may be different, just as lacunar syndrome does not fully represent lacunar infarction, and lacunar syndrome not due to lacunar infarction are found in 16.6% of cases [12, 13]. Therefore, we investigated the predictors of PI rather than END in our present study. We defined the PI combining symptoms with imaging, and PI was defined as an increase in the NIHSS score, and extension of the original infarction was further confirmed by DWI or CT.

Although the term BAD was originally created by pathological changes, the definitions of BAD relied on imaging features [3, 14]. Currently, BAD is usually defined as an infarction ≥15 mm in diameter, and the slices of infarcts ≥3 [5, 15]. It has been reported that BAD is more likely to develop neurological worsening in acute ischemic stroke, compared to LI [5, 6, 16]. Nevertheless, the neuroimaging features used to define BAD-related

Table 1 Comparison of baseline characteristics between PI and non-PI groups

Variable	PI (*n* = 121)	Non-PI (*n* = 517)	*P*
Demographic characteristics			
Age (y), median (IQR)	65 (55, 71)	64 (55, 72)	0.464
Male, n (%)	78 (64.5%)	347 (67.1%)	0.577
Clinical data			
Hypertension, n (%)	110 (90.9%)	461 (89.2%)	0.742
Diabetes, n (%)	38 (31.4%)	161 (31.1%)	0.955
History of stroke, n (%)			0.964
None	104 (85.9%)	445 (86.1%)	
Ischemic	15 (12.4%)	62 (11.9%)	
Hemorrhagic	2 (1.7%)	10 (1.9%)	
Initial NIHSS score, median (IQR)	4 (2, 6)	3 (2, 5)	0.003*
Discharge NIHSS score, median (IQR)	4 (2, 6)	2 (1, 3)	< 0.001*
Laboratory data			
WBC (10*9/L), median (IQR)	6.60 (5.22, 7.75)	6.45 (5.21, 7.56)	0.476
RBC (g/L), mean ± SD	4.46 ± 0.47	4.47 ± 0.54	0.828
HGB (g/L), median (IQR)	136 (127, 145)	135 (126, 145)	0.637
PLT (10*9/L), median (IQR)	200 (159.5, 238)	202 (170, 242)	0.454
BUN (mmol/L), median (IQR)	4.5 (3.7, 5.5)	4.8 (3.80, 5.6)	0.217
Creatinine (umol/L), median (IQR)	71.2 (56.65, 83.6)	74.5 (61, 88.05)	0.120
Uric acid (mmol/L), median (IQR)	344.5 (282.05, 418.0)	336 (279.85, 399.65)	0.207
Fasting glucose (mg/dL), median (IQR)	104.34 (89.92, 131.18)	98.57 (85.78, 128.57)	0.080
TC (mg/dL), median (IQR)	191.42 (171.31, 225.45)	183.3 (155.84, 205.92)	0.002*
TG (mg/dL), median (IQR)	150.62 (105.87, 196.25)	117.84 (87.71, 171.88)	< 0.001*
HDL-c (mg/dL), median (IQR)	43.7 (35.38, 50.47)	44.08 (36.74, 52.2)	0.332
LDL-c (mg/dL), median (IQR)	118.72 (98.61, 144.24)	110.6 (88.55, 130.31)	0.003*
Fibrinogen (g/L), median (IQR)	2.89 (2.52, 3.38)	2.89 (2.51, 3.33)	0.638
D-dimer (mg/L), median (IQR)	0.25 (0.14, 0.48)	0.28 (0.15, 0.48)	0.217
Imaging date			
Diameter of infarcts (mm), median (IQR)	15.6 (12.02, 21.12)	14.28 (10.16, 19.53)	0.052
Diameter of infarcts ≥ 15 mm, n (%)	64 (52.9%)	239 (46.2%)	0.190
Diameter of infarcts ≥ 10 mm, n (%)	106 (87.6%)	398 (76.9%)	0.009*
Axial slices of infarcts, mean ± SD	3.25 ± 1.21	2.8 ± 1.33	0.001*
Axial slices of infarcts ≥ 3, n (%)	88 (72.7%)	271 (52.4%)	< 0.001*
BAD[1]	79 (65.3%)	252 (48.7%)	0.001*
BAD[2]	57 (47.1%)	199 (38.5%)	0.082

PI: Progressive Infarction; NIHSS: National Institute of Health Stroke Scale; WBC: White Blood Cell; RBC: Red Blood Cell; HGB: Hemoglobin; PLT: Platelet; BUN: Blood Urea Nitrogen; TC: Total Cholesterol; TG: Triglyceride; HDL-c: High Density Lipoprotein cholesterol; LDL-c: Low Density Lipoprotein cholesterol; IQR: Interquartile Range. SD: Standard Deviation. *$p < 0.05$. BAD [1]: Branch atheromatous disease defined as axial slices of infarcts ≥ 3 and the infarct diameter ≥ 10 mm. BAD [2]: Branch atheromatous disease defined as axial slices of infarcts ≥ 3 and the infarct diameter ≥ 15 mm

Table 2 Univariate and multivariate logistic regression analysis of risk factors for progressive infarction

Covariate	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Initial NIHSS score	1.073 (1.009–1.141)	0.025*	1.040 (0.976–1.109)	0.222
TC	1.006 (1.001–1.010)	0.013*	0.990 (0.977–1.003)	0.133
TG	1.002 (1.000-1.004)	0.026*	1.003 (1.001–1.005)	0.013*
LDL-c	1.008 (1.002–1.013)	0.008*	1.018 (1.003–1.033)	0.021*
Diameter of infarcts ≥ 10 mm	2.113 (1.185–3.767)	0.011*	0.736 (0.394–1.375)	0.337
Axial slices of infarcts ≥ 3	2.421 (1.566–3.743)	< 0.001*	2.044 (1.276–3.273)	0.003*

NIHSS: National Institute of Health Stroke Scale; TC: Total Cholesterol; TG: Triglyceride; LDL-c: Low-Density Lipoprotein cholesterol; OR: odds ratio; CI: confidence interval. *$p < 0.05$

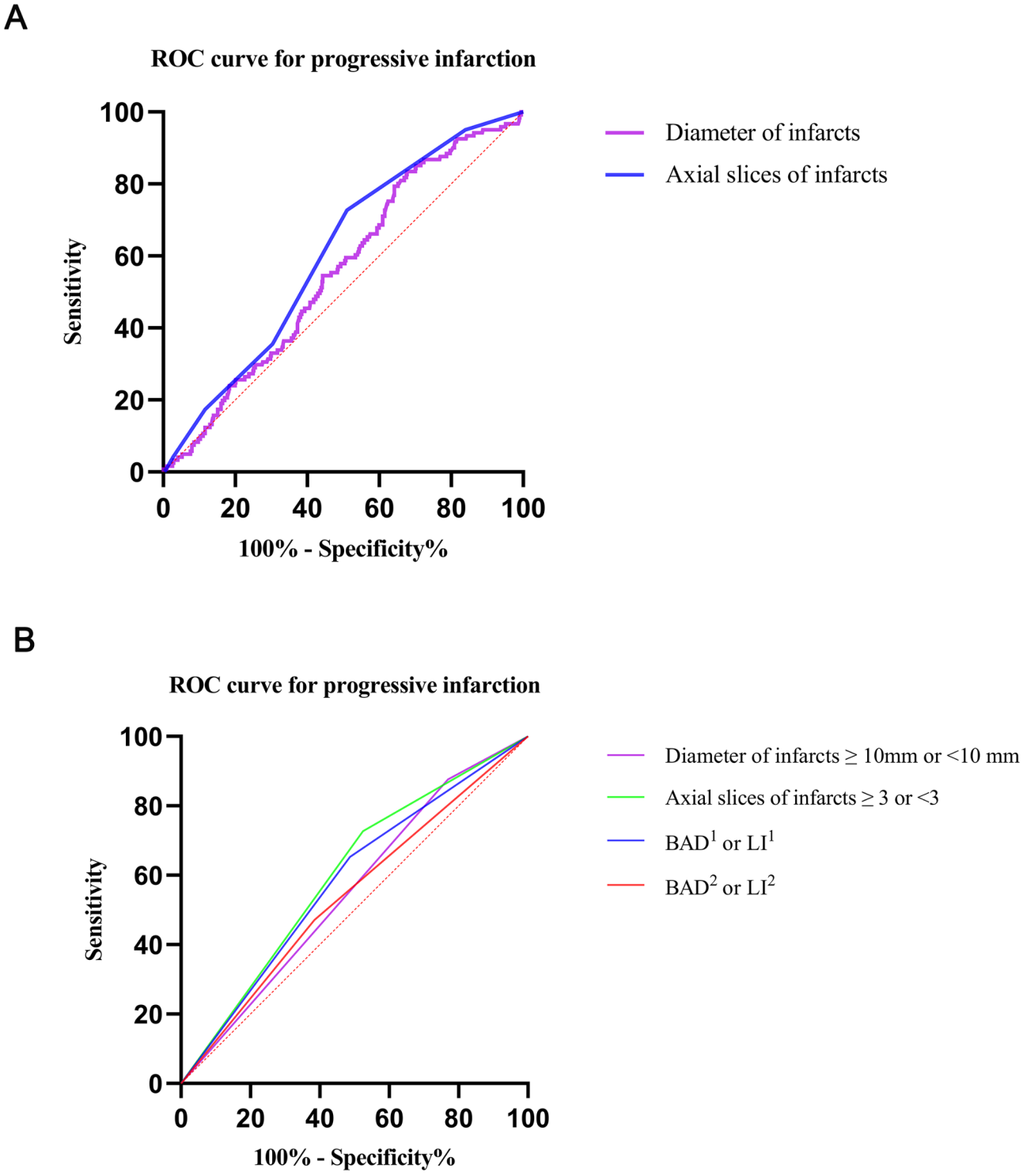

Fig. 1 Receiver operating characteristic curves to predict progressive infarction outcome. (**A**) Receiver operating characteristic curve for quantitative variables (diameter and axial slices of infarcts) to predict progressive infarction outcome. (**B**) Receiver operating characteristic curves for categorical variables (diameter of infarcts ≥ 10 mm or < 10 mm, axial slices of infarcts ≥ 3 or < 3, BAD [1] or LI [1], and BAD [2] or LI [2]) to predict progressive infarction outcome. BAD: Branch Atheromatous Disease. LI: Lacunar Infarction

infarction across studies were different [2]. In our study, we compared the correlation between the two most common BAD definitions and PI, and found a higher frequency of BAD compared to LI in ACSSI patients with PI when BAD was defined as axial slices of infarcts ≥3 and the infarct diameter ≥10 mm. However, the percentage of BAD was comparable between the PI group and non-PI group while BAD was considered as axial slices of infarcts ≥3 and the infarct diameter ≥15 mm. In addition, the best cutoff value of infarct diameter was 11.1 mm, which was closer to 10 mm. Taken together, BAD, defined as axial slices of infarcts ≥ 3 and the infarct diameter ≥ 10 mm, may be more suitable for predicting PI.

There is currently controversy over the correlation between the diameter of infarct and PI [7–11]. Some scholars suggested a positive relationship between the infarct diameter and PI [9–11]. However, it was also reported no association between the size of the lesion and PI in the previous studies [7, 8]. Similarly, the findings regarding the correlation between the infarct slices and PI are not consistent [7–11]. The infarct with slice number≥3 was more frequent in the PI group according to previous studies [7, 9–11]. Nevertheless, a study revealed that infarct slice number was not associated with PI [8]. Therefore, based on the findings of our previous study, we enrolled the largest sample size so far to explore the correlation between imaging characteristics and PI, and demonstrated that a lesion visible ≥ 3 slices was associated with PI. In addition, the frequency of infarct diameter ≥ 10 mm tended to be higher in the PI group while it was not related to PI after adjusting significant variables. Furthermore, we compared the predictive abilities of these imaging features and suggested that a lesion visible ≥3 slices was superior to other imaging markers for predicting PI.

The present study has three limitations. First, this is a retrospectively single-center study although our sample size is enough. Based on our previous study [7], a total of 98 patients would be necessary ($\alpha = 0.05$, power = 90%). Finally, we recruited 638 patients in this study and the sample size was sufficient. Moreover, the detection of infarct slices using the same slice thickness in a stroke center resulted in better uniformity. Further research should recruit multiple stroke centers to confirm our findings. Second, although our findings revealed PI had a negative impact on short-term prognosis (discharge NIHSS), we did not investigate the role of PI or radiological features on long-term prognosis. A prospective study should be conducted to explore the relationship. Thirdly, dyslipidemia and statins therapy are closely associated with clinical outcomes in ischemic stroke patients [17, 18]. However, we did not focus on the effect of statins therapy on PI because this was a retrospective study. In the future, we would select patients who are prone to progression and conduct randomized controlled studies to reveal the effect of statins therapy on PI.

Conclusions

In conclusion, our study suggests a lesion visible ≥ 3 slices (slice thickness of 5 mm) is an independent predictor of PI in ACSSI patients. The slice number of infarcts in ASCCI is a better indicator to predict PI than other imaging markers. Intuitive screening of patients with a higher probability of experiencing PI based on imaging characteristics, and subsequent more powerful antiplatelet therapy such as tirofiban may prevent PI.

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Author contributions
JL, LD, QH and XM drafted the article, collected, and organized the database. JL and LD performed the statistical analysis. QH and XM interpreted the data. ZX, SL, KJ made critical revision of the manuscript. Supervision was performed by JT, and XL. All authors have approved the final draft of the article.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of First Affiliated Hospital of Nanchang University (Medical Research Ethic Fast Review No. 3–004). Written informed consent was obtained from all patients. The research was conducted in accordance with the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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