Research Square

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Risk Factors for Early Neurological Deterioration in Acute Isolated Pontine Infarction Without Any Causative Artery Stenosis

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Research Article

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Abstract

Background

This study aimed to investigate the risk predictors for early neurological deterioration (END) in isolated acute pontine infarction (API) without any causative artery stenosis.

Methods

In this retrospective study, patients with isolated API within 72 h of symptom onset were enrolled between October 2017 and December 2021. END was defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) score ≥ 2 points within the first week postadmission. Patients were divided into the END and the non-END groups. Multiple logistic regression analysis was used to evaluate independent predictors of END in patients with isolated API.

Results

A total of 153 patients were included in the final study (62 females; mean age, 67.27 ± 11.35 years), of whom 28.7% (47 of 153) experienced END. Multiple logistic regression analyses showed that infarct volume (adjusted odds ratio [aOR], 1.003; 95% CI, 1.001–1.005; P = 0.002) and basilar artery branch disease (BABD) (aOR, 3.388; 95% CI, 1.102–10.417; P = 0.033) were associated with END. The combined ROC analysis of the infarct volume and BABD for predicting END showed that the sensitivity and specificity were 80.9% and 72.6%, respectively.

Conclusion

BABD and infarct volume were associated with END in acute isolated pontine infarction and may be useful prognostic factors for neurological progression.

1 Background

Early neurological deterioration (END) is relatively common in isolated acute pontine infarction (API), which is caused by small vessel disease or steno-occlusion of the orifice of a perforator at the parent artery. Based on previous studies, END in isolated API has a high incidence of 25%~29% and is related to severe disability and poor outcome [1–3]. However, the mechanism of END is currently unclear and may be related to hemodynamic factors, thrombus expansion, excitotoxicity and inflammation [4–6].

In previous studies [3, 7], END was reported to be related to topographic location in pontine infarction. However, another study showed that END was independent of location and was not correlated with the size of the infarct [8]. Recently, a study showed that infarct size rather than topographic location in

pontine infarction might be a possible predictor of END [9]. In the same way, these studies indicated that END was not related to severe stenosis of the basilar artery [3, 9, 10]. Therefore, the purpose of this study was to investigate the risk predictors for END in acute isolated pontine infarction without any causative artery stenosis.

2 Methods

This retrospective study was approved by the Medical and Health Research Ethics Committee of the Second People's Hospital of Chengdu (Chengdu, China) and adhered to the Declaration of Helsinki. Because it was a retrospective study, informed consent was not needed, and all included patient information was anonymous.

2.1 Patient Selection

We retrospectively collected 153 patients with isolated API at Chengdu Second People's Hospital from October 2017 to December 2021. The inclusion criteria were as follows: (1) patients presenting within 72 h of onset; (2) diffusion-weighted imaging [DWI] within 48 h of admission showing isolated pontine infarction; and (3) patients with a modified Rankin scale (mRS) score ≤ 1 before admission. The exclusion criteria included (1) patients with pontine infarction with anterior circulation infarction or other vertebrobasilar infarction; (2) patients with vascular assessment (magnetic resonance angiography or computed tomography angiography) suggesting stenosis of the basilar artery (BA) (≥ 50%); (3) patients with cardiogenic embolism; (4) patients with severe cardiopulmonary, liver, or kidney insufficiency combined with malignant tumors; (5) patients with incomplete magnetic resonance imaging or poor imaging quality; and (6) patients with incomplete clinical data.

2.2 Data Collection

2.1.1 Demographic Features and Conventional Risk Factors

Two clinicians reviewed the electronic medical record system at Chengdu Second People's Hospital to collect information, and a data extraction form was designed to record the patient information. Basic information included age, sex, hypertension, diabetes, smoking, drinking, and history of stroke, and the clinical data included time from onset to arrival, blood pressure at admission, baseline blood glucose level, National Institutes of Health Stroke Scale (NIHSS) score at admission, presence of END, NIHSS score at discharge, infarct site, treatment and hospital days. These risk factors were evaluated as follows: 1) hypertension: repeated blood pressure readings of ≥ 140/90 mmHg, a history of previous hypertension or use of antihypertensive drugs; 2) diabetes: a history of diabetes or the use of diabetes medications, or more than two measurements of fasting plasma glucose > 7.0 mmol/L or random plasma glucose > 11.1 mmol/L; 3) smoking: ≥10 cigarettes per day; and 4) drinking: alcohol use > 2 U/d [11]. Baseline examinations included routine laboratory tests, such as creatinine, alanine aminotransferase (ALT),

aspartate aminotransferase (AST), triglycerides, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), brain MRI, and computed tomography angiography (CTA)/magnetic resonance angiography (MRA) of the head.

2.3 Brain MRI Protocol and Analysis

MRI was performed within 48 h of admission using a Siemens 1.5T/3.0 T MRI scanner (Siemens AG, Munich, Germany). We recorded the location of the pontine infarct lesion, the volume, the diameter and width of the largest slice, and the distance of the lesion from the midline of the pons. The pons was divided into 3 sections based on the rostrocaudal location of the lesion by diffusion-weighted imaging (DWI; upper, middle, or lower pons) [3, 7]. The upper pons is characterized by a relatively round shape with a small, round-shaped aqueduct (Fig. 1A); the middle pons is characterized by its square-shaped fourth ventricle, large middle cerebellar peduncles, and silhouettes of trigeminal nerves (Fig. 1B); and the lower pons is characterized by a shape similar to that of the middle pons but with images of facial/acoustic nerves and grooves rather than trigeminal nerves (Fig. 1C). If more than one adjacent lesion was involved, the primary affected lesion was considered for grouping purposes. The diameter and width of the largest slice of each infarction were measured on DWI scans. We chose the diameter multiplied by the width of the largest infarction slice multiplied by the number of infarct slices multiplied by the slice thickness and then divided by two as the infarct volume (Fig. 1D). MRI scans were obtained at a 5-mm slice thickness.

2.4 Stroke Subtypes and END Definition

This retrospective study included 2 types of stroke: (1) basilar artery branch disease (BABD) characterized by an infarct that reached or approached the pontine surface without BA stenosis [12–14] and small artery disease (SAD) indicated by a deeper infarct without involvement of the ventral surface in the absence of BA stenosis [15]. END was defined as an NIHSS score increase $\geq$ 2 points within the first week after admission [13, 16].

2.5 Statistical Analysis

We used SPSS version 25.0 software (IBM Corp, Armonk, NY, USA) for statistical analysis. Continuous variables are expressed as the mean ± standard deviation (SD) or as the median and interquartile range (IQR). Differences between groups were compared using a t test or the rank-sum test. Categorical data are presented as frequencies (percentages), and the differences between groups were compared using the chi-squared test or Fisher's exact test. Variables in univariate analyses ($P < 0.10$) were included in multivariate analysis. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic value of our parameters for predicting END. Statistical significance was set at $P < 0.05$.

3 Results

3.1 Baseline Characteristics

A total of 202 patients with acute pontine infarctions were admitted to our neurology department from October 2017 to December 2021; 41 patients met the exclusion criteria, and eight patients had missing information. Finally, 153 patients with acute isolated pontine infarctions were included in the final study (91 males and 62 females; mean age, 67.27 ± 11.35 years)(Fig. 2). END occurred in 28.7% (47 of 153) of them after admission. The NIHSS score at discharge ($P < 0.001$) and number of hospital days ($P = 0.007$) were significantly higher in the END group than in the non-END group (Table 1).

There were no significant differences in sex, age, hypertension, diabetes, drinking, smoking, baseline blood glucose level, history of ischemic stroke, blood pressure at admission, laboratory results, initial NIHSS score, or treatment after admission between the 2 groups ($P > 0.05$; Table 1).

Table 1
Clinical characteristics of patients with and without END in acute isolated pontine infarction.

	END (n = 47)	Non-END (n = 106)	P
Age, mean ± SD, year	65.3 ± 11.9	68.1 ± 11.0	0.158
Female, sex, n(%)	18(38.3)	44(41.5)	0.709
Hypertension, n(%)	38(80.9)	78(73.6)	0.333
Diabetes, n(%)	22(46.8)	36(34.0)	0.131
Smoking, n(%)	12(25.5)	20(18.9)	0.350
Drinking, n(%)	5(10.6)	17(16.0)	0.380
History of ischemic stroke, n (%)	0(0.0)	2(1.9)	0.343
Blood pressure at admission			
SBP, mean ± SD, mmHg	151.5 ± 19.9	152.2 ± 24.3	0.87
DBP, mean ± SD, mmHg	82.7 ± 12.3	85.5 ± 13.9	0.234
Baseline blood glucose level, median (IQR), mmol/L	7.2(6.2,11.2)	6.7(5.5,11.2)	0.260
Arrival time, median (IQR), hours	20.0(7.0, 24.0)	24.0(10.0.48.0)	0.085
NIHSS score at admission, median, mean ± SD	3.9 ± 2.1	3.9 ± 2.6	0.992
NIHSS score at discharge, median (IQR)	4.9 ± 2.5	2.4 ± 2.0	0.000
Number of hospital days	13.2 ± 3.1	11.8 ± 3.0	0.007
Laboratory tests			
Total cholesterol, mmol/l, mean±SD	4.7 ± 1.4	4.7 ± 1.3	0.958
Triglycerides, mmol/l, median (IQR)	1,47(1.05,2.12)	1.60(1.05, 2.31)	0.826
HDL, mmol/l, median (IQR)	1.11(0.93,1.26)	1.18(1.01,1.36)	0.062
LDL, mmol/l, mean±SD	2.9 ± 1.2	2.7 ± 1.0	0.490
Creatinine, mmol/l, mean±SD	66.6 ± 15.7	72.3 ± 23.3	0.08
AST, mmol/l, median (IQR)	19.0(15.0,24.0)	19.0(15.0,25.0)	0.960
ALT, mmol/l, median (IQR)	22.0(17.0,31.0)	20.0(16.0,27.2)	0.197
Treatment, n (%)			0.168

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, aminotransferase; IVT, intravenous thrombolytic therapy; DAPT, dual antiplatelet therapy.

	END (n = 47)	Non-END (n = 106)	P
IVT + DAPT	7(14.9)	6(5.7)	
DAPT	32(68.1)	80(75.5)	
Anticoagulation	8(17.0)	20(18.9)	

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, aminotransferase; IVT, intravenous thrombolytic therapy; DAPT, dual antiplatelet therapy.

Of the 153 patients, 86 patients (56.2%) had BABD, and 67 patients (43.8%) had SAD. The proportion of patients with END within one week after admission was 80.9% (38 of 86) in the BABD group and 19.1% (9 of 67) in the SVD group ($P < 0.001$) (Table 2).

DWI indicated that upper pontine infarcts were significantly less common in the patients with END (4.3%, 2 of 47) than in the patients without END (24.5%, 26 of 106) ($P = 0.003$). Lower pontine infarcts were significantly more common with END than without END (63.8% vs. 42.5%, $P = 0.015$). Middle pontine infarctions were not significantly different between the two groups ($P = 0.0659$). Patients in the END group had a greater infarct diameter ($P < 0.001$) and width ($P < 0.001$) than those in the non-END group. The infarct volume was higher in patients with END than in patients without END ($P < 0.001$). There were no significant differences in the distance of the lesion from the midline of the pons in the two groups ($p > 0.05$) (Table 2).

Table 2
Stroke subtypes and imaging parameters with and without END in acute isolated pontine infarction.

	END (n = 47)	Non-END (n = 106)	P
Stroke subtypes			<0.0001
BABD	38(80.9)	48(45.3)	
SAD	9(19.1)	58(54.7)	
Topographic locations			
Upper	2(4.3)	26(24.5)	0.003
Middle	15(31.9)	39(36.8)	0.659
Lower	30(63.8)	45(42.5)	0.015
The maximum diameter,mm	13.6(12.2,17.8)	11.5(8.4,15.35)	<0.001
The maximum width,mm	8.5(7.4,9.4)	6.6(4.7,7.7)	<0.001
Infarct volume,mL	351.5(259.6,551.3)	217.4(126.7,338.5)	<0.001
Lesion distance from midline,mm	2.1(1.5,3.6)	3.4(1.9, 4.8)	0.013
BABD,basilar artery branch disease;SAD, small artery disease.			

When the factors associated with END in univariate analyses (P < 0.10) were entered into multivariate logistic regression analysis (adjusted for arrival time, HDL, creatinine, stroke subtype, topographic location, infarct volume, and the distance of the lesion from the midline of the pons), the results showed that infarct volume (aOR, 1.003; 95% CI, 1.001–1.005; P = 0.002) and BABD (aOR, 3.388; 95% CI, 1.102–10.417; P = 0.033) were associated with END (Table 3).

Table 3
Multivariate logistic regression analysis of predictors of END in acute isolated pontine infarction.

Risk factor	OR	95% CI	P
Arrival time	0.983	0.965–1.001	0.065
HDL	0.416	0.114–1.520	0.185
Creatinine	0.985	0.963–1.008	0.195
BABD	3.388	1.102–10.417	**0.033**
Upper lesion	0.201	0.034–1.168	0.074
Lower lesion	1.851	0.769–4.457	0.170
Infarct volume,mL	1.003	1.001–1.005	**0.002**
Lesion distance from midline,mm	0.084	1.088–0.837	0.529
HDL, high-density lipoprotein;BABD, basilar artery branch disease.			

END symptoms mainly include alterations in facial movements (4.2%, 2 of 47), motor function (arm) (76.6%, 36 of 47), motor function (leg) (87.2%, 41of 47), sensations (2.1%,1of 47), and language ability (19.1%, 9 of 47) (Table 4).

Table 4
The symptoms of Neurological deterioration and number of patients in END group.

	END group
Consciousness, n(%)	0(0)
Gaze, n(%)	0(0)
Visual fields, n(%)	0(0)
Facial movement, n(%)	2(4.2)
Motor function(arm), n(%)	36(76.6)
Motor function(leg), n(%)	41(87.2)
Limb ataxia, n(%)	0(0)
Sensory, n(%)	1(2.1)
Language, n(%)	9(19.1)
Articulation, n(%)	0(0)
Extinction or inattention, n(%)	0(0)

The combined diagnostic value of the infarct volume and BABD was a sensitivity of 80.9%, a specificity of 72.6%, and an AUC of 0.774 (95% CI, 0.698–0.850, $P < 0.05$) (Fig. 3).

4 Discussion

In our study, markers predicting END in patients with acute isolated pontine infarction were evaluated, and infarct volume and subtype-BABD were found to be strongly associated with END in API patients but not related to infarct location. Our study suggested that infarct volume may be a sensitive predictor in patients with isolated pontine infarction, especially BABD patients.

It has been reported that penetrating arterial infarction, especially pontine infarction, tends to progress to END, in contrast to cerebral deep penetrating artery infarction [1, 17]. Our study showed that 28.7% of the patients with isolated pontine infarction experienced END after admission, consistent with previous research findings, which reported an incidence of 27%~29% of END in API [1, 18]. In 1989, Caplan initially put forward the concept of BAD and proposed BA branch disease (BABD), which was defined as lesions extending to the ventral pontine surface in the blood supply region of the paramedian pontine artery with neither evidence of large arterial stenosis (> 50%) or occlusion nor evidence of cardiogenic embolism [19, 20]. In our study, BABD was responsible for 80.9% of END cases, and SVD accounted for only 19.1% ($P < 0.001$), indicating that the BABD subtype was associated with END in API, which was consistent with Gokcal's et al. [10] study. A large retrospective study showed that BABD was the most common cause of

API [15], accounting for 56.2% (86 of 153) of the APIs included in our study, and Yamamoto et al showed a relative frequency of approximately 40% [21]. Our study did not compare long-term outcomes between BABD and SVD. However, Erro et al. [22] indicated that BABD patients have a worse prognosis than patients with lacunar pontine infarctions.

Our data show that the deterioration of symptoms was related to the maximum infarct volume (P = 0.002). Recently, a retrospective study that included 407 patients with API by Haiyan Li et al also found that infarct size might be a predictor for neurological progression with isolated acute pontine infarction (aOR 4.580, P < 0.0001), which was different from our study in which the infarct size was represented by the maximal data of the ventrodorsal length multiplied by rostrocaudal thickness. Interestingly, another study [8] suggested that END was not related to the size of either; however, its sample size was relatively small (n = 38), the expansion of ischemic lesions was not found to be correlated with END, and the actual lesion size was not measured.

Huang et al.'s [7] and Oh et al.'s [3] studies have shown that lower pons lesions may have a higher probability of progressive motor deficits in patients with isolated acute pontine infarction than those in the upper and middle pons. In Gokcal et al.'s [10] study, END was just numerically higher in patients with lower pontine infarction, but there was no statistically significant difference. Our multiple logistic regression data showed that the deterioration of symptoms was not related to lower pons lesions (P = 0.17), which was consistent with Li et al.'s [3] (P = 0.132) and Nakase et al.'s [8] conclusions. In addition, our study quantitatively analyzed the relationship between the distance between the lesion and the midline of the pons and END, and the results exceeded our expectations and were negative, which was consistent with Oh et al. [3], who qualitatively divided the patients into paramedian pontine infarcts and extended pontine infarcts according to axial lesion location.

In analyzing the relationship between END and infarct location and size in API from an anatomical point of view, the corticospinal tracts are loosely distributed along the corticospinal fibers in the upper pons, situated in the dorsolateral part of the pontine base at the level of the upper pons, and then converge into the anteromedial surface of the upper medulla to form compact bundles [23, 24]. Therefore, Huang et al. [7] and Oh et al. [3] thought that as a result of the corticospinal tracts in the lower pontine region being denser, typically in the paramedian ventral area, the damage to the corticospinal tracts is more serious. However, corticobulbar tracts are more widespread in the upper pons than in the lower areas of the pons [25]. Therefore, from an anatomical point of view, the index reflecting the damage degree of the corticospinal tracts to the greatest extent should be the volume of the lesion rather than the location of the infarct. Both our study and Haiyan Li's study showed that infarct volume was independently associated with END in API.

This study has the following limitations. First, it was a single-center retrospective study with a modest sample size. Second, repeat MRI was not performed after deterioration to determine whether there was infarct volume expansion in END patients and to identify the cause of the neurological deterioration. Third, our study did not compare the long-term functional outcomes of the two groups of patients.

5 Conclusion

Our results indicate that stroke subtype-BABD and infarct volume are associated with END in isolated API and may be useful prognostic factors for neurological progression. Therefore, when encountering a large infarct volume in isolated API, especially in patients with the BABD subtype, it is necessary to be aware of the risk of END.

List Of Abbreviations

API acute pontine infarction

END early neurological deterioration

NIHSS National Institutes of Health Stroke Scale

BABD basilar artery branch disease

ALT aminotransferase

AST aspartate aminotransferase

LDL low-density lipoprotein

HDL high-density lipoprotein

CTA computed tomography angiography

MRA magnetic resonance angiography

DWI diffusion-weighted imaging

SAD small artery disease

SD standard deviation

IQR interquartile range

ROC receiver operating characteristic

Declarations

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Y-LL was involved in the entire process of the study, including designing the study, collecting data, analyzing the data, and drafting the original manuscript. H-MP participated in data collection, data analysis and form making, and Y-X participated in data management and statistical analysis. L-YH and J-W revised the manuscript. F-X designed the study and revised the manuscript. All authors have read and approved the final manuscript.

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Data Availability Statement

All original data can be obtained via email correspondence to 694421243@qq.com, and all charts in this study are presented in the article/Supplementary Material.

Ethics Approval and Consent to Participate

We obtained ethical approval for this study from the Medical and Health Research Ethics Committee of the Second People's Hospital of Chengdu. Because it was a retrospective study, the Medical and Health Research Ethics Committee of the Second People's Hospital of Chengdu waived the need of informed consent and all included patient information was anonymous.

Consent for publication

Not applicable.

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Figures

Figure 1

(**A**): upper pons; (**B**): middle pons; (**C**): lower pons; (**D**): API volume measurement based on DWI: a multiplied by b and then multiplied by the number of layers divided by 2.

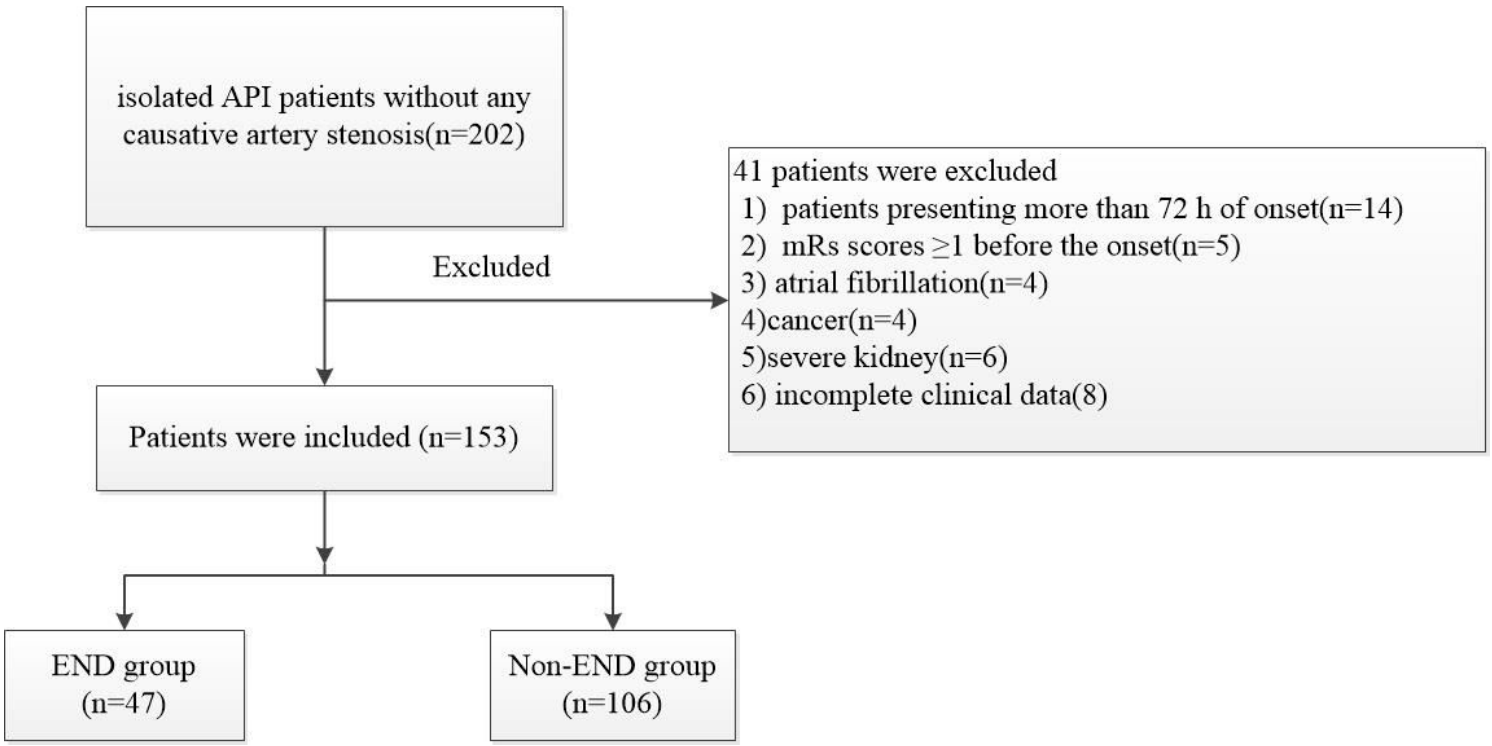
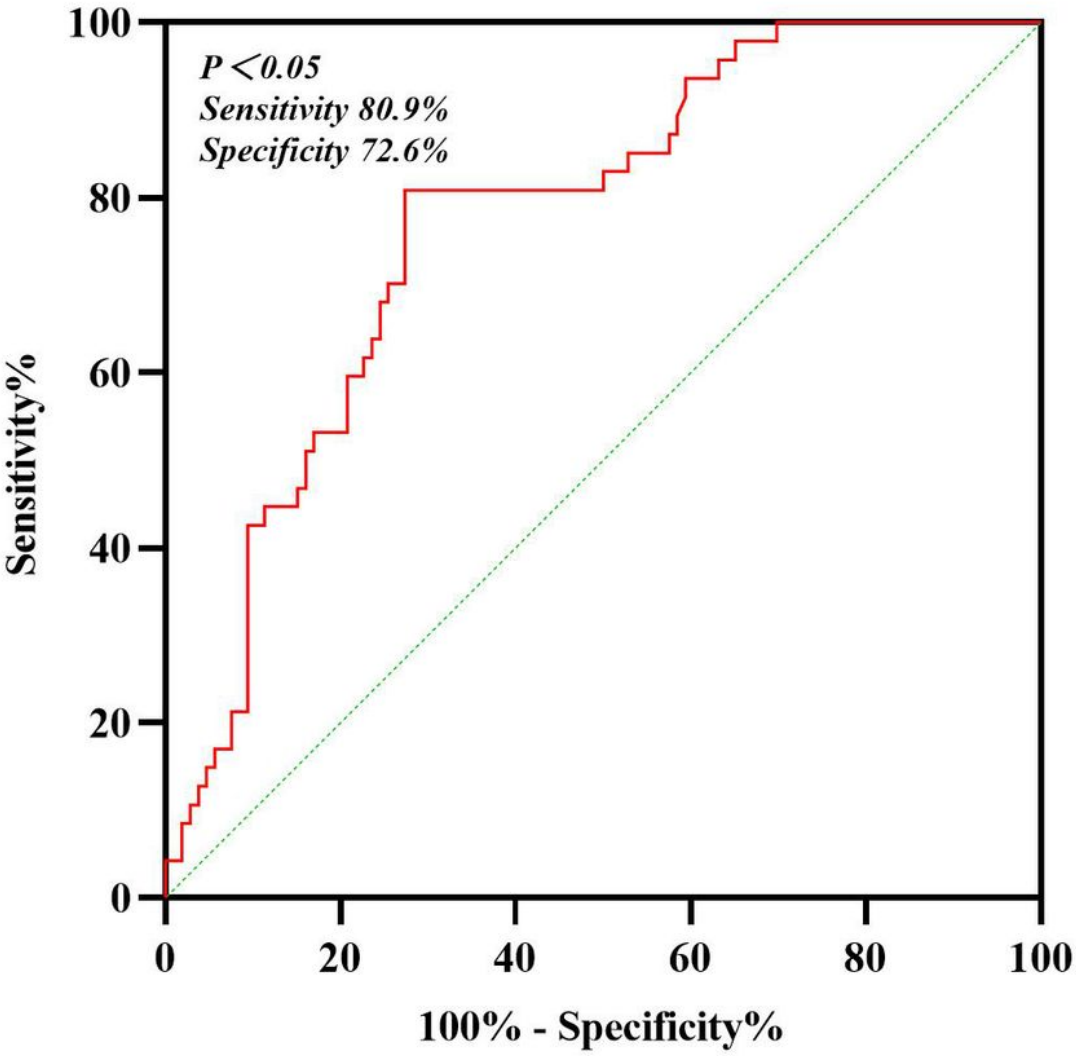


Figure 2

Flowchart of the selection of eligible subjects.



Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.774	.039	.000	.698	.850

The test result variable(s): Predicted

Figure 3

Combined ROC curve analysis of the infarct volume and BABD.