Risk Factors of Large Artery Atherosclerotic Ischemic Stroke Based on Carotid Contrast-Enhanced Ultrasonography

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Research

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Abstract

Background

Ischemic stroke is a serious public health issue with a continuously increasing incidence worldwide. This study explores the risk factors of large artery atherosclerotic (LAA) ischemic stroke based on carotid contrast-enhanced ultrasonography (CEUS).

Methods

A total of 110 patients with LAA ischemic stroke and 34 patients without stroke were included. All participants underwent standard ultrasonography and CEUS, from which carotid artery plaque characteristics were obtained. The predicted performance of artery plaques was evaluated using the area under the receiver operating characteristics (ROC) curve and sensitivity and specificity at the optimal cut-off point.

Results

Subjects with LAA ischemic stroke were more likely to have a history of hypertension than the control group (P = 0.009). The area under the ROC curve (AUROC) for plaque echogenicity was 0.609 (95% CI, 0.524–0.689). With a cut-off value of ≤ class II (echolucent or predominantly hypoechogenic plaque), the sensitivity and specificity were 84.55% and 32.35%, respectively. The AUROC for plaque thickness was 0.676 (95% CI, 0.593–0.751). With a cut-off value of > 2.4 mm, the sensitivity and specificity were 41.82% and 88.24%, respectively. The AUROC for intraplaque neovascularization was 0.807 (95% CI, 0.733–0.868). With a cut-off value of > grade 2 (extensive appearance of bubbles within plaque), the sensitivity and specificity were 70.91% and 82.35%, respectively.

Conclusions

Hypertension, echolucent (or predominantly hypoechogenic) plaque, plaque thickness, and degree of intraplaque neovascularization are significantly relevant to LAA ischemic stroke in adults. These results may be helpful for clinical prediction of ischemic stroke risk.

1. Introduction

Stroke was the second most frequent cause of death worldwide between 2000 and 2015[1]. Known risk factors associated with ischemic stroke(IS) include age, gender, systolic blood pressure, diabetes, cardiovascular history, smoking history, atrial fibrillation, and carotid artery stenosis.[2-4] Moreover, the prevalence of extracranial internal carotid artery atherosclerosis in Asian countries has been increasing.[5, 6] Proximal internal carotid artery atherosclerosis is the second most common cause of strokes

associated with large artery disease.[7] Vulnerable atherosclerotic plaques in carotid arteries are closely related to the development of ischemic stroke.[8, 9] The most accepted features of vulnerability include thin cap fibroatheromas, large lipid cores, spotty calcification, positive remodeling, and intraplaque neovascularization (IPNV).[10] Therefore, the ability to assess the vulnerability of carotid artery plaques using imaging techniques is crucial.

Conventional ultrasonography is an easy and noninvasive technique used to examine carotid arteries. It can demonstrate carotid intima-media thickness (IMT), plaque morphology, plaque fiber cap integrity, plaque echogenicity, and uniformity. Contrast-enhanced ultrasonography (CEUS) has emerged as a reliable imaging modality that complements and enhances conventional vascular ultrasonography in clinical and scientific settings.[11] Contrast enhancement of the carotid plaque with sonographic agents is related to histologic density of neovessels and plaque echolucence. It is a well-accepted marker of high-risk lesions, but not the degree of stenosis.[12]

The purpose of the current study was to combine clinical characteristics and CEUS parameters for carotid artery to predict the risk of large artery atherosclerotic (LAA) ischemic stroke for patients with carotid atherosclerotic plaques. Using highly accurate and sensitive indicators, clinicians will be able to precisely develop a specific treatment strategy for each patient.

2. Materials And Methods

2.1. Patients and control participants

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College. Informed consent was obtained from participants before an examination was performed. Between December 2017 and May 2019, a total of 144 patients with clinical symptoms and carotid atherosclerotic plaques were enrolled. According to the American Heart Association/American Stroke Association[13] and the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system[14], participants were divided into LAA ischemic stroke group (study group) and no stroke group (control group). A total of 110 patients were enrolled into the study group. The inclusion criteria included the presence of focal neurological deficit symptoms (aphasia, neglect, and restricted motor involvement) persisting for >24 h, cortical or cerebellar lesion, brain stem or subcortical hemispheric infarction >1.5 cm in diameter on computed tomography or magnetic resonance imaging, and mild or moderate to severe stenosis of the carotid lumen[13]. A total of 34 patients underwent brain computed tomography or magnetic resonance imaging to exclude stroke and were enrolled in the control group. The exclusion criteria included hypersensitivity to sulfur hexafluoride lipid microsphere components, blood, blood products, or albumin[15], cerebral and subarachnoid hemorrhage, severe hypertension, possible pregnancy, previous carotid surgery or angioplasty, immune system disease, and cancer. Individuals with cardioembolic and lacunar strokes, as well as those with cerebral infarction caused by brain tumors or trauma, cerebrum surgery, recent infectious disease, cancer, peripheral vascular occlusive disease, liver or kidney dysfunction, acute myocardial infarction, or atrial fibrillation, were excluded.

All participants with a diagnosis of carotid atherosclerotic plaque formation underwent standard ultrasonography and CEUS. In addition, collected clinical data included age, gender, levels of uric acid (UA), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL), and history of hypertension or diabetes mellitus (DM).

2.2. Standard ultrasonography study of the carotid artery

An Acuson S3000 ultrasound system (Siemens Medical Solutions, Erlangen, Germany) equipped with a L4-9 linear array probe was used for both standard and CEUS carotid examinations in this study. According to the Mannheim carotid IMT and plaque consensus[16], carotid artery plaque is defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5 mm, as measured from the media-adventitia interface to the intima-lumen interface. Extracranial carotid arteries are visualized in longitudinal and transverse sections when the patient is in a supine position with a slight rotation of the neck to the contralateral side and exerting minimal tension on the cervical muscles. The entire length of the carotid arteries and carotid bifurcations, including the internal carotid artery as far as was possible to observe, were examined for presence of atherosclerotic plaques. Carotid IMT and plaque measurements were acquired at the end of diastole. The location, size, and echogenicity of all plaques were recorded in detail. Lesion echogenicity was graded visually according to the G-W classification as follows[17]: uniformly echolucent (class I), predominantly hypoechogenic or anechoic with <50% echogenic areas (class II), predominantly hyperechogenic or echogenic with >50% echogenic areas (class III), or uniformly echogenic or extensively calcified (class IV).

2.3. Contrast-enhanced carotid ultrasonography

Carotid CEUS studies were performed with the same machine used for the standard studies with a low mechanical index of 0.14. SonoVue (Bracco Suisse SA, Geneva, Switzerland) was used as the ultrasound contrast agent in this study. A vial of SonoVue was diluted with 5 mL of saline and shaken to form a homogeneous microbubble suspension. After the standard ultrasonography examination, the real-time ultrasound contrast mode was switched on and image settings were adjusted to maximize contrast signal visualization. Then, an assistant injected a 2.0-mL bolus of contrast agent into a peripheral vein, immediately followed by a 5-mL saline flush. Participants were asked not to swallow during the procedure. All participants were observed for complications for 30 min before returning to the ward. The images were then stored for analysis.

The culprit lesion was determined using the following criteria in participants with more than one plaque: located at the distal portion of general carotid bifurcation or the origin of internal carotid artery; the largest lesion was selected from multiple lesions; no definite calcifications were present; and patient condition was consistent with an ipsilateral cerebral infarction. Assessment of intraplaque neovascularization following the classification of Stand et al.[18] was as follows: grade 1, no appearance

of bubbles within the plaque; grade 2, moderate amount of visible bubbles in the plaque at the adventitial side or plaque shoulder; and grade 3, extensive appearance of bubbles within the plaque (Figure 1).

2.4. Statistical analysis

All statistical analyses were performed using SPSS, v23.0 (IBM, Armonk, NY, USA) and MedCalc v12.3.0 (MedCalc, Mariakerke, Belgium). All quantitative variables (tested to have a normal distribution) were presented as mean ± SD. Pearson's chi-squared test or Fisher's exact test were used to compare categorical variables. Age, plaque thickness, TG, TC, HDL, LDL, and UA were analyzed using independent samples T test. Association between the degrees of intraplaque neovascularization and plaque echogenicity with clinical outcomes was evaluated using Spearman's rank correlation analysis. The optimal cut-off values were determined from the receiver operating characteristics (ROC) curves. The sensitivity, specificity, and area under the ROC curve (AUROC) were used as diagnostic performance indicators. The level of statistical significance was set at $P<0.05$.

3. Results

3.1 Comparison of clinical characteristics of all participants

The LAA ischemic stroke group included 110 participants (71 males; mean age 68.21 ± 10.51 years, range 35–89 years). The control group included 34 participants (23 males; mean age 64.85 ± 9.80 years, range 47–88 years). Subjects with LAA ischemic stroke were more likely to have a history of hypertension compared to the control group ($P = 0.009$, Table 1). However, there were no significant differences in gender, age, history of diabetes mellitus, TC, TG, HDL-C, and UA between the LAA ischemic stroke and control groups ($P > 0.05$, Table 1).

Table 1
Comparison of participant clinical characteristics (n = 144).

Variable	Study group (n = 110)	Control group (n = 34)	P
Gender (F/M)	39/71	11/23	0.740
Age, mean (SD), years	68.21 (10.51)	64.85 (9.80)	0.101
History of diabetes mellitus, n (%)	46(41.82)	16(47.06)	0.590
History of hypertension, n (%)	84(76.36)	18(52.94)	0.009
Total cholesterol, mean (SD), mmol/L	4.86 (1.29)	4.97 (1.07)	0.647
Triglyceride, mean (SD), mmol/L	1.61 (1.30)	1.78 (1.12)	0.503
HDL cholesterol, mean (SD), mmol/L	1.07 (0.25)	1.14 (0.35)	0.324
LDL cholesterol, mean (SD), mmol/L	3.16 (1.00)	3.23 (0.75)	0.713
Uric acid, mean (SD), μmol/L	359.72 (104.17)	363.21 (97.10)	0.862
LDL = low-density lipoprotein, HDL = high-density lipoprotein.			

3.2 Carotid plaque features in ischemic stroke and control groups

The LAA ischemic stroke group had a significantly thicker carotid atherosclerotic plaque compared to the control group (2.42 ± 0.92 vs. 1.92 ± 0.60 mm; P = 0.000, Table 2). Spearman's rank correlation analysis demonstrated that the higher the level of intraplaque neovascularization, the more likely the occurrence of cerebral infarction, with a correlation coefficient of 0.51 (P = 0.000). In addition, the lower the grade of plaque echogenicity, the more prone the patient was to ischemic stroke, with a correlation coefficient of 0.176 (P = 0.035).

Table 2
Main features of carotid plaques measured using standard and contrast-enhanced ultrasonography.

Variable	Study group (n = 110)	Control group (n = 34)	P
Thickness of plaque, mean (SD), mm	2.42 (0.92)	1.92 (0.60)	0.000
Plaque echogenicity			0.035
Class I	62	14	
Class II	31	9	
Class III	13	5	
Class IV	4	6	
Degree of intraplaque neovascularization			0.000
Grade 1	12	20	
Grade 2	20	8	
Grade 3	78	6	

3.3 Correlation between carotid plaques and ischemic stroke

Table 3 shows the AUROC values for plaque echogenicity, plaque thickness, and IPNV for distinguishing ischemic stroke individuals and controls. The AUROC for plaque echogenicity was 0.609 (95% CI, 0.524–0.689). With a cut-off value of ≤ class II, the sensitivity and specificity were 84.55% (95% CI, 76.4–90.7%) and 32.35% (95% CI, 17.4–50.5%), respectively. The AUROC for plaque thickness was 0.676 (95% CI, 0.593–0.751). With a cut-off value of > 2.4 mm, the sensitivity and specificity were 41.82% (95% CI, 32.5–51.6%) and 88.24% (95% CI, 72.5–96.7%), respectively. The AUROC for IPNV was 0.807 (95% CI, 0.733–0.868). With a cut-off value of > grade 2, the sensitivity and specificity were 70.91% (95% CI, 61.5–79.2%) and 82.35% (95% CI, 65.5–93.2%), respectively (Fig. 2).

Table 3
Area under receiver operating characteristics curve (AUROC) with optimal cut-off value, sensitivity, and specificity for ultrasonography parameters.

Variable	AUROC	Cut-off value	Sensitivity	Specificity
Plaque echogenicity	0.609	≤class II	84.55%	32.35%
Plaque thickness	0.676	> 2.4 mm	41.82%	88.24%
Degree of IPNV	0.807	> grade 2	70.91%	82.35%
IPNV = intraplaque neovascularization.				

4. Discussion

Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.[13] It is a polyetiological disease with profound differences among subtypes.[19] Most of the previous studies attributed stroke to age, gender, hypertension, diabetes, hypercholesterolemia, smoking, coronary artery disease, arterial fibrillation, physical inactivity, and obesity.[20, 21] The present study explored the incidence of risk factors for LAA ischemic stroke based on carotid CEUS. It was concluded that the atherosclerotic ischemic stroke is associated with hypertension, plaque echogenicity, plaque thickness, and degree of intraplaque neovascularization in Chinese adults. Furthermore, the ROC curve for separating ischemic stroke patients from controls had a sensitivity of 70.91% (95% CI, 61.5–79.2%) and specificity of 82.35% (95% CI, 65.5–93.2%), with a cutoff value of IPNV > grade 2.

According to the TOAST classification system, large-artery atherosclerosis, cardioembolism, small artery occlusion (lacunar), stroke of other determined etiology, and stroke of undetermined etiology are primarily based on clinical features in addition to information obtained during brain imaging, echocardiography, neurosonography, and cerebral angiography.[14] The risk factors, clinical characteristics, and prognosis of ischemic stroke may vary greatly among subtypes. Previous studies have shown that the proportion of strokes due to LAA is greater than that due to small artery occlusion or cardioembolism.[19] Data from randomized controlled trials indicate that a 10-mm Hg reduction in systolic blood pressure was associated with a decrease in risk of stroke of approximately one third.[22] In a meta-analysis of individual participant data from 61 prospective observational studies on blood pressure and mortality, every 20-mm Hg decrease in systolic blood pressure or 10-mm Hg decrease in diastolic blood pressure was associated with a more than two-fold decrease in stroke mortality for blood pressure ≥ 115/75 mm Hg.[23] Consistent with previous research[24, 25], the present study found that hypertension is associated with an increased risk of atherosclerotic ischemic stroke. Elevated blood pressure led to premature aging and increased endothelial cell turnover, which progressed to endothelial dysfunction.[26] A recent report showed that hypertension driven by the sympathetic nervous system can influence mechanisms that regulate the hematopoietic system, contributing to atherosclerosis and cardiovascular events.[27] Li et al. demonstrated that very high blood pressure during the acute phase of ischemic stroke increased the risk of adverse clinical outcomes.[28]

Carotid plaques reflect the degree of atherosclerosis in the vascular system. Unstable atherosclerotic carotid plaques are particularly vulnerable to rupture, which is induced by the loss of thin fibrous cap integrity, strong intraplaque inflammatory reaction, and luminal blood communication with the thrombogenic core of the plaque.[29, 30] Thrombogenic material is diffused into circulation after plaque rupture, thereby occluding the intracranial cerebral arteries and resulting in ischemia of cortical and subcortical brain tissue. However, identification of vulnerable atherosclerotic plaques in patients poses a significant clinical challenge.

A Northern Manhattan Study demonstrated that plaque subjects with maximum carotid plaque thickness > 1.9 mm had a 2.8-fold increase in risk of combined vascular events and were associated with a 1.8-fold

increase in risk of ischemic stroke[31]. Consistent with this notion, carotid plaque thickness for the LAA stroke group was significantly greater than that for the non-cerebral infarction group (2.42 ± 0.92 vs. 1.92 ± 0.60 mm; P = 0.000). The specificity to predict the incidence of LAA stroke was 88.24% (95% CI, 72.5–96.7%), with a cut-off value of > 2.4 mm.

In a meta-analysis of individual patient data from seven studies with a total of 7557 subjects, Gupta et al. demonstrated a significant positive relationship between predominantly echolucent plaques (compared to predominantly echogenic) and the risk of future stroke across all degrees of stenosis.[32] Another study showed that juxtaluminal hypoechoic plaque area had a linear association with future stroke rate, stratified by a juxtaluminal black hypoechoic area size of 8 mm^2.[33] Consistently with previous research, echogenicity of plaques in the present study group was mainly class I (uniformly anechoic) or class II (predominantly hypoechogenic or anechoic with < 50% echogenic areas). Furthermore, with a cut-off value of ≤ class II, the sensitivity predicting the onset of LAA stroke was 84.55% (95% CI, 76.4–90.7%). A number of histopathologic studies suggest that the presence of hypoechoic or echolucent areas in any one component of the plaque was associated with a lipid-rich necrotic core and intraplaque hemorrhage, which are markers for plaque vulnerability[34, 35]. This explains why echolucent plaques have a higher relative risk of stroke compared to patients with echogenic plaques.

Ultrasound contrast agents can serve as blood pool-enhancing agents to allow better visualization of vascular structures and flow as well as perfusion in the context of imaging vasa vasorum and atherosclerotic plaque neovascularization[15]. CEUS results indicated that hypoechoic plaques and IPNV among atherosclerotic ischemic stroke patients were more common than in control patients. In addition, IPNV was a very strong predictor of LAA ischemic stroke, with the area under the ROC curve of 0.807 at the cutoff point of IPNV > grade 2. Consistent with these findings, hypoechoic plaques tend to have more vulnerable pathologic features, abundant lipids, and hemorrhage and are associated with an increased risk of cerebrovascular events[32]. Varetto et al. reported a statistically significant correlation between increased vascularization of carotid atherosclerotic plaques evaluated by CEUS and cerebrovascular neurological events[30]. Similarly, Wu et al. concluded that strong contrast enhancement can reveal culprit lesions, likely suggesting greater neovascularization and/or inflammatory activity in atherosclerotic lesions[36].

Information on the degree of carotid stenosis was not included in this study. Recent atherosclerosis research has suggested that lumen narrowing may not be a reliable indicator of plaque severity because positive artery remodeling of the vessel wall is associated with the culprit lesions[36, 37]. Notably, vulnerable atherosclerotic plaque may suggest an increased risk of cerebrovascular events, even with low-grade carotid narrowing[38]. Plaque thickness was incorporated in the study, which can represent the degree of stenosis to some extent. Indeed, by combining standard carotid ultrasonography and CEUS, carotid atherosclerotic plaques with a high risk of rupture can be detected.

Several limitations should be considered in the present study. First, the data were based on one hospital-based cohort. The number of enrolled cases was low, with different numbers of cases between study and

control groups, which may imply some bias. Second, this study utilized a visual approach to semi-quantify IPNV using CEUS, rather than an objective quantitative method. Finally, the findings were not validated within the scope of this study and several years may be needed for other prospective studies to estimate the risk factor performance.

5. Conclusions

This study compared clinical characteristics and carotid plaque features among patients with and without LAA ischemic stroke based on CEUS. It was concluded that hypertension, echolucent (or predominantly hypoechogenic) plaque, plaque thickness, and degree of intraplaque neovascularization are significantly relevant to LAA ischemic stroke. IPNV can be used as a strong indicator to define the population with increased susceptibility to LAA ischemic stroke, allowing for better selection of prevention and treatment strategies aimed towards personalized medicine.

Abbreviations

IS: ischemic stroke; CEUS: contrast-enhanced ultrasonography; IPNV: intraplaque neovascularization; LAA: large artery atherosclerotic; ROC: receiver operating characteristics; AUROC: area under the receiver operating characteristics curve; IMT: intima-media thickness; UA: uric acid, TC: total cholesterol; TG: triglycerides; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; DM: diabetes mellitus.

Declarations

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Authors' contributions

CSQ and TXR were involved in the design of the study and interpretation of data. DXY and YZK were involved in the collection and analysis of data, and wrote the manuscript. CQZ was involved in the collection of data. All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

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Availability of data and materials

The data, analytic methods, and study materials during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College, which approved analysis of pre-existing data for research purposes.

Consent for publication

Not applicable (patient identifiers not included in manuscript).

Competing interests

All authors have no conflicts of interest to disclose.

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Figures

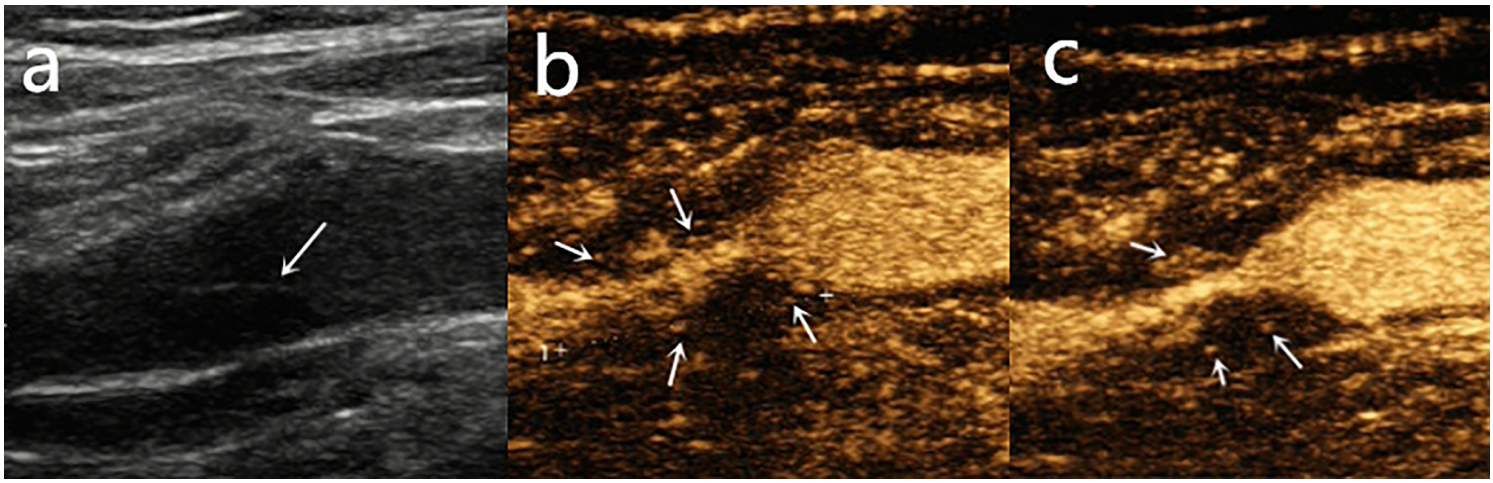

Figure 1

Standard ultrasonography (a) demonstrates a uniformly echolucent plaque (arrow; class I) in a carotid artery sinus. Contrast-enhanced ultrasonography (b, c) shows intraplaque neovascularization (arrows), which is detectable by microbubbles (arrows) moving within the plaque (grade III).

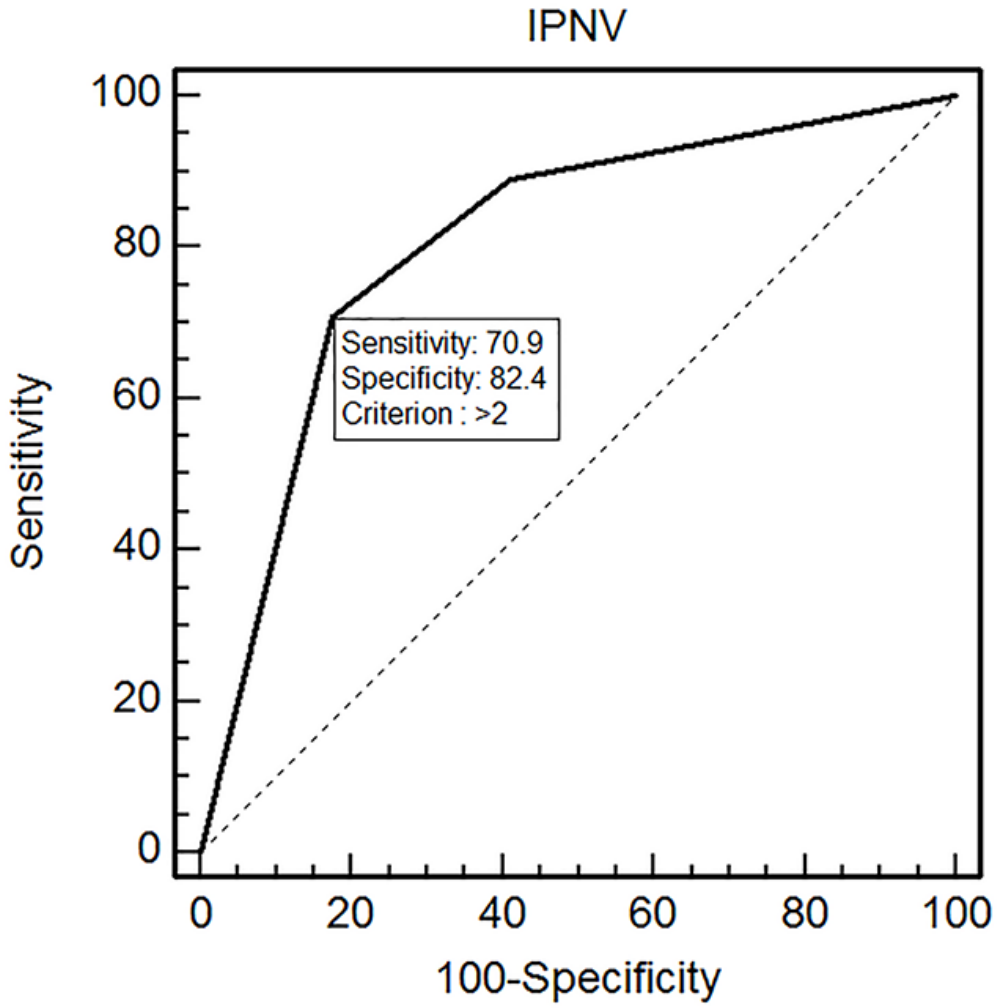

Figure 2

Receiver operating characteristics curve with sensitivity and specificity for IPNV.