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A comprehensive clinical diagnostic score system for prediction of coronary artery spasm in patients with acute chest pain

Yaowang Lin [a], Haiyan Qin [b], Ruimian Chen [a], Qiyun Liu [a], Huadong Liu [a], Shaohong Dong [a,*]

[a] Department of Cardiology, Shenzhen People's Hospital, 2nd Clinical Medical College of Jinan University, first affiliated Hospital of South University of Science and Technology, No. 1017, Dongmen Northern Road, 518020 Shenzhen, Guangdong, PR China
[b] Department of Neurology, Longgang District People's Hospital of Shenzhen, No. 53, Love road, Longgang District, 518020 Shenzhen, Guangdong, PR China

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ABSTRACT

Background: Currently, there is no validated multivariate model to predict probability of coronary artery spasm (CAS) in patients with acute chest pain.
Methods: A total of 976 consecutive patients with acute chest pain were enrolled. Patients were divided into two groups based on the presence of significant CAS. To adjust potential confounders, a multivariable analysis was performed and a clinical diagnostic score system for CAS was utilized for score derivation.
Results: Multivariable analysis model selected 6 predictors for CAS. The integer score was assigned to each predictors: angina at rest alone (10 points), positive of hyperventilation test (8 points), allergies (3 points), asthma, ST-segment elevation and myocardial bridge (2 points each). We showed that the clinical diagnostic score system had accuracy in predicting CAS, as measured by the area under the curve (AUC), which was 0.952–0.966. The cut-off baseline value for the clinical diagnostic score system was set to 11–12 points with specificity of 91.0–93.3% and sensitivity of 90.7–92.9%, respectively.
Conclusion: A clinical diagnostic score system was derived and validated as an accurate tool for estimating the pretest probability of CAS in patients with acute chest pain.

1. Introduction

Coronary artery spasm (CAS) is known to be a risk factor of acute coronary syndrome (ACS) characterized by transient total or subtotal vessel occlusion [1–3]. Smoking, age, physical and/or mental stress, and myocardial bridge are significant risk factors for CAS [4–7]. Previous Asian studies of patients have showed that the prevalence of CAS is around 40–50% in patients with angina and 57% in patients with ACS [8–10]. In non-obstructive coronary arteries (MINOCA) patients, the positive of provocative test is about 46% [11]. Transient myocardial ischemia caused by CAS can be complicated by myocardial infarction, unstable angina, heart failure and malignant arrhythmia, which can result in sudden death [12]. Accordingly, a prompt diagnosis of provocative test usually is required to establish a definitive diagnosis of CAS. However, intravenous provocative test is invasive and can lead to severe complications [13,14]. Thus few doctors are willing to do the provocative test, leading to few diagnosis of CAS. Yusuke Takagi and colleagues have developed a novel scoring system, which provide the comprehensive risk assessment and prognostic stratification for CAS patients [15]. However, no clinical diagnostic score for CAS was studied.

In the present study, we thus aimed to develop a comprehensive clinical diagnostic scoring system for CAS patients. The major hypothesis of this trial was that the clinical diagnostic scoring system would help us easily diagnose CAS.

2. Methods

2.1. Patients

The present study was conducted as an investigator initiated observational clinical research. From 2010 to 2016 in Department of Cardiology, a total 1700 patients were consecutively enrolled with acute chest pain. All the patients received coronary angiography. 1123 (60.06%) patients showed no significant coronary stenosis (stenosis <50%) and continuously received ergonovine provocation test. The diagnosis of CAS was made based on the spasm provocation test defined by the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society [16]. The positive diagnosis of the provocation test was defined as a total or subtotal (>90%) coronary

* Corresponding author at: Department of Cardiology, Shenzhen People's Hospital, 2nd Clinical Medical College of Jinan University, first affiliated Hospital of South University of Science and Technology, No. 1017, Dongmen Northern Road, 518020 Shenzhen, Guangdong, PR China.
E-mail address: xnkdsh@yeah.net (S. Dong).

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artery narrowing induced by ergonovine during coronary angiography, accompanied by chest pain and/or ischemic electrocardiography (ECG) changes.

To systematically test the model and evaluate the accuracy of the model, we randomly divided the data into 80% (781 cases including 335 in CAS group and 446 in non-CAS group) as the multivariate model training dataset and 20% (195 cases including 84 in CAS group and 111 in non-CAS group) as the testing dataset by the envelope of a random process.

2.2. The hyperventilation test

The hyperventilation test was performed in the early morning for provocation of the angina1 attack (6:30 AM to 8:30 AM). After a control 12-lead ECG and echocardiogram were recorded, the patients hyperventilated vigorously for 3 to 8 min. Nitroglycerin administration was stopped 2 h before the study. The hyperventilation test positive was defined as transient abnormalities of regional wall motion of left ventricle (LV) by echocardiographically monitoring during hyperventilation, or chest pain with ischemic ECG changes, especially transient ST-segment elevation during hyperventilation [17,18].

2.3. Histamine bronchial provocation test

The history of allergies and asthma were collected from a standardized validated questionnaire from each patient. Histamine bronchial provocation test was performed to confirm asthma.

2.4. Exclusive criteria

Patients were excluded if they had coronary stenosis >50%. Other exclusion criteria included pericarditis, pulmonary embolism, aortic dissection or pneumonia.

2.5. Statistical analysis

Statistical analysis was performed using the SPSS 22.0 and MedCalc® 15.2.2 statistical software. Data are presented as mean ± standard deviation (SD). Between-group differences with respect to continuous variables were assessed using the Student's test or Kruskal–Wallis test, while those with respect to categorical variables were assessed using Chi-squared test or Fisher Exact test (as appropriate). Univariable and multivariable Analysis model were applied to select the baseline characteristics that correlated with CAS. The variables showing statistical significance (OR > 1 and $p < 0.05$) in univariable model were subjected to multivariable analysis with a forced-entry method. The significant variables selected from multivariable model were assigned integer score proportional to their adjusted odds ratio (OR) for CAS.

The cut-off points were analyzed by a receiver operating characteristic curve (ROC) analysis to determine the area under the curve (AUC), sensitivity and specificity values for the clinical diagnostic score system in predicting CAS. The same way was performed in testing dataset to conform the accurate of the clinical diagnostic score system. A p value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of patients in the training dataset

The enrollment profiles are summarized in Table 1. 781 patients were screened including 335 (42.89%) in CAS group and 446 (57.11%) in non-CAS group. The mean (±SD) age of the patients in CAS group and non-CAS group was 52.06 ± 10.63 vs 59.84 ± 11.32 years ($p < 0.001$). There was significant difference between the two groups with respect to allergies (40, 11.93% vs 24, 5.46%; $p < 0.001$), asthma (30, 9.07% vs 16, 3.58%, $p < 0.001$), clinical situation of angina attack (rest: 255, 76.13% vs 55, 12.29%, $p < 0.001$; effort: 65, 19.33% vs 388, 87.03%, $p < 0.001$), ST-segment elevation during angina attack (172, 51.31% vs 138, 31.05%, $p < 0.001$), myocardial bridge (43, 12.89% vs 26, 5.97%, p < 0.001) and hyperventilation test (157, 46.78% vs 62, 13.99%, p < 0.001) in CAS group and non-CAS group. There was no significant difference between the two groups with respect to admission SBP, admission heart rate, life-threatening arrhythmia and LDL-C (Fig. 1).

Table 1
Characteristics of the patients at baseline.

Characteristics	The CAS group	The non-CAS group	*P*
Total	$N = 335$	$N = 446$	–
Age (year)	52.06 ± 10.63	59.84 ± 11.32	*<0.001*
Males, n (%)	177(52.74)	244(54.60)	0.234
SBP (mm Hg)	129.52 ± 14.57	128.81 ± 22.14	0.608
HR (bpm)	76.24 ± 12.17	76.38 ± 39.29	0.950
Allergies, n (%)[a]	40(11.93)	24(5.46)	*<0.001*
Asthma, n (%)[a]	30(9.07)	16(3.58)	*<0.001*
Coronary risk factor			
Hypertension, n (%)	76(23.15)	119(26.62)	0.672
Calcium antagonists, n (%)	74(22.09)	92(20.63)	0.720
Diabetes mellitus, n (%)	34(10.02)	56(12.63)	0.632
Smoking, n (%)	93(27.68)	103(23.04)	0.093
Clinical situation of angina attack			
Rest, n (%)	255(76.13)	55(12.29)	*<0.001*
Effort, n (%)	65(19.33)	388(87.03)	*<0.001*
Rest and effort, n (%)	26(7.64)	38(8.53)	0.084
ST-segment change during angina attack			
ST-segment elevation, n (%)	172(51.31)	138(31.05)	*<0.001*
ST-segment depression, n (%)	106(31.74)	193(43.34)	0.053
Life-threatening arrhythmias			
VT/VF, n (%)	34(10.26)	51(11.43)	0.558
AV block, n (%)	38(11.46)	50(11.26)	0.924
OHCA, n (%)	38(11.22)	59(13.31)	0.321
Myocardial bridge, n (%)	43(12.89)	26(5.97)	*<0.001*
LDL-C (mmol/L)	3.10 ± 0.51	3.05 ± 0.48	0.431
Hyperventilation test, n (%)	157(46.78)	62(13.99)	*<0.001*

SBP: systolic blood pressure, HR: heart rate, VT/VF: ventricular tachycardia/ventricular fibrillation, AV block: atrioventricular block, OHCA: out-of-hospital cardiac arrest, LDL-C: low-density lipoprotein cholesterol.
[a] The history of allergies and asthma.

3.2. Correlated factors for CAS and assigned score

From univariable analysis for CAS, there was significant difference between the two groups with respect to age, allergies, asthma, coronary risk factor (hypertension and diabetes mellitus), angina at rest alone, ST-segment elevation during angina attack, myocardial bridge and hyperventilation test (Table 2). The variables showing statistical significance (OR > 1 and $p < 0.05$) in univariable model were subjected to multivariable analysis and selected 6 predictors for CAS. The integer score was assigned to each predictors: angina at rest alone (10 points), positive of hyperventilation test (8 points), allergies (3 points), asthma, ST-segment elevation and myocardial bridge (2 points each) ($p < 0.027$–0.001) (Table 3).

3.3. The AUC of the Diagnostic Score System for CAS in the training dataset

From Fig. 2-A, we showed that the clinical diagnostic score system had accuracy in predicting CAS, as measured by the AUC, which was 0.966 (95% confidence intervals (CI), 0.923 to 0.977). The cut-off baseline value was set to 11 points with specificity of 93.3% and sensitivity of 90.7%, respective.

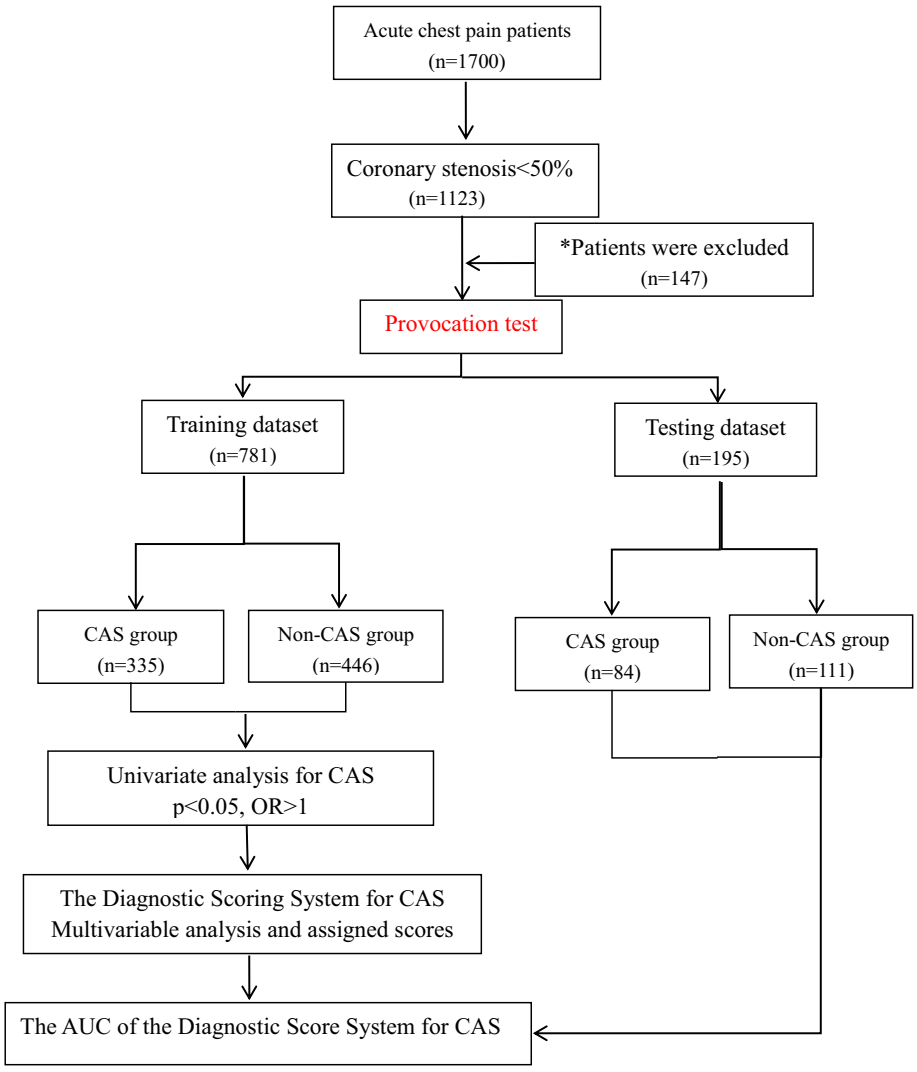

Fig. 1. Flowchart of the statistical analysis. *Patients were excluded including APE ($n = 34$), AoD ($n = 8$), pericarditis ($n = 12$), pneumonia ($n = 67$) and others ($n = 27$). APE: acute pulmonary embolism, AoD: acute arterial dissection, CAS: coronary artery spasm, OR: odds rate, AUC: area under the curve.

3.4. Validate the scoring system in the testing dataset

195 patients were screened including 84 in CAS group and 111 in non-CAS group in the testing dataset. We showed that the clinical diagnostic score system also had accuracy in predicting CAS, as measured by AUC, which was 0.952 (95% CI, 0.912 to 0.977). The cut-off baseline value was set to 12 points with specificity of 91.0% and sensitivity of 92.9%, respectively (Fig. 2-B).

4. Discussion

We performed an observational clinical research to develop a comprehensive clinical diagnostic score system for angina patients with CAS. The major finding of the present study was that the clinical diagnostic score system, in which 6 predictive factors derived from the multivariable analysis were integrated, showed a significant correlation with the diagnosis of CAS patients and an acceptable predictive capacity in the internal validation.

In our study, the clinical diagnostic score system demonstrated the AUC of 0.966 with specificity of 93.3% and sensitivity of 90.7% for CAS in the training dataset when the cut-off baseline value was set to 11 points. These values needed to be further tested and confirmed in real life practice. We validated the scoring system in the independent external dataset (testing dataset) and still represented an accurate tool with AUC of 0.952 for estimating the pretest probability of CAS in patients with acute chest pain. The important and unique characteristics of this study represents and suits in a real world practice or emergency room scenario that after the CAS patients are identified, they will be advised to seek specific treatment of calcium channel blockers that may improve symptoms and clinical outcomes in CAS patients without further delay. Montone and colleagues have found that CAS had significantly worse clinical outcomes—including all-cause mortality, cardiac death, readmission with acute myocardiac infarction (AMI), and frequency of angina episodes—compared with patients with non-CAS patients during a follow-up ranging from 12 to 60 months in MINOCA patients [11]. Because of being totally noninvasive and safe, the diagnostic score system may represent a useful tool to raise awareness as to the possible diagnosis of CAS in a given angina patient and improve prognosis of patient with CAS in routine daily practice.

A diagnosis of CAS cannot be directly established based on symptoms, standard 12-lead ECG results, Holter monitoring, or treadmill testing [19,20]. There was no significant difference regarding clinical characteristics when MINOCA patients with or without CAS were compared [11]. Coronary angiography with provocative test is the only certain method of diagnosing CAS [10]. Pharmacological provocation, with

Table 2
Univariable analysis for CAS.

	Univariable Analysis		
	OR	95% CI	*P*
Age	0.937	0.926–0.949	*<0.001*
Males	0.462	0.357–0.596	0.220
Allergies[a]	3.083	2.640–5.782	*<0.001*
Asthma[a]	2.394	2.057–5.375	*<0.001*
Coronary risk factor			
Hypertension	0.547	0.412–0.727	*<0.001*
Diabetes mellitus	0.474	0.313–0.718	*<0.001*
Smoking	1.279	0.959–1.705	0.094
Clinical situation of angina attack			
Rest	12.186	10.083–15.757	*<0.001*
Effort	0.001	0.001	0.992
Rest and effort	0.459	0.268–0.785	0.064
ST-segment change during angina			
ST-segment elevation	1.145	0.886–1.479	*<0.001*
ST-segment depression	1.01	1.000–1.172	0.063
Life-threatening arrhythmias			
VT/VF	0.886	0.591–1.329	0.558
AV block	1.019	0.687–1.513	0.924
OHCA	0.823	0.559–1.210	0.332
Myocardial bridge	1.947	1.601–3.990	*<0.001*
LDL-C	1.162	0.899–1.503	0.252
Hyperventilation test	7.144	6.551–10.979	*<0.001*

VT/VF: ventricular tachycardia/ventricular fibrillation, AV block: atrioventricular block, OHCA: out-of-hospital cardiac arrest, LDL-C: low-density lipoprotein cholesterol.
[a] The history of allergies and asthma.

Table 3
Multivariable analysis for CAS and assigned score.

	Multivariable analysis			Assigned score
	OR	95% CI	*P*	
Allergies*	2.693	2.449–5.549	*<0.001*	3
Asthma*	2.063	2.009–5.500	*<0.001*	2
Angina attack at rest	10.12	10.352–15.179	*<0.001*	10
ST-segment elevation	1.843	1.073–3.165	*0.027*	2
Myocardial bridge	2.142	1.122–4.890	*<0.001*	2
Hyperventilation test	8.038	6.208–10.086	*<0.001*	8

Allergies* and Asthma*: the history of allergies and asthma.

intracoronary acetylcholine or with intravenous or intracoronary ergonovine has been used to diagnose CAS for a long time. In 1986, Okumura and Yasue et al., have reported that the sensitivity and specificity of spasm provocation test in active variant angina were 90–99% [21,22]. However, in the Younger Patients (mostly age < 40 years), the sensitivity of the provocation test was only 40–75% [23]. Besides, false negative results may be obtained when the disease activity is low, or nitroglycerin administration is not stopped immediately, a negative test cannot always exclude CAS [24].

Ascribing to pharmacological spasm provocation test is invasive method, we always have the potential to encounter complications when performing the test. The overall serious major complications were 0.62% of patients including death (0.001%), coronary aorta bypass graft surgery and acute myocardial infarction (0.004%), ventricular tachycardia and ventricular fibrillation (0.53%), cardioversion (0.035%), Brady (0.11%), cardiogenic shock (0.035% and so on [25]. Furthermore, there are contraindications including pregnancy, severe hypertension, severe left ventricular dysfunction, moderate to severe aortic stenosis or outflow obstruction and high-grade left main coronary artery disease [10]. Finally, coronary spasm provocation test, undertaken either in the digital subtraction angiography (DSA) room or at bedside, is a potentially risky and challenging procedure, requiring a high degree of skill on the part of the operator.

In this study, we also found that the history of allergies and asthma was new predictive factory for CAS. Cardiovascular allergic and anaphylactic reactions to various allergens have been well established for many years. Kounis and Zavras described the “allergic angina syndrome” as coronary spasm progressed to allergic acute MI [26]. The main pathophysiological mechanism is vasospasm of coronary arteries due to increased inflammatory mediators that are released during a hypersensitivity reaction or asthmatic attack. Mast cell degranulation and anaphylaxis or anaphylactoid reactions can occur after drug exposure or asthmatic attack [27]. Coronary involvement in hypersensivity reactions is probably secondary to increased circulatory inflammatory mediators mainly histamine, interleukins (IL), endothelins (ET), proteases such as tryptase and chymase or products of arachidonic acid metabolism [28].

Additionally, we found that the hyperventilation test was preferable to diagnose CAS. In our study, the positive of hyperventilation test was 13.99% vs 46.78% ($P < 0.001$) in non-CAS group and CAS group, which was agreed with Hiromi Fuji's study [29]. DeGregorio reported a case of a comatose patient with tracheostomy in whom hyperventilation, caused by excessive bronchial secretion resulting in partial obstruction of the tracheal cannula, was followed by ST segment elevation mimicking acute myocardial infarction [30]. The attack of coronary spasm is induced by hyperventilation causing respiratory alkalosis, which enhances Na—H and Na—Ca exchanger, resulting in an increased intracellular Ca concentration [31].

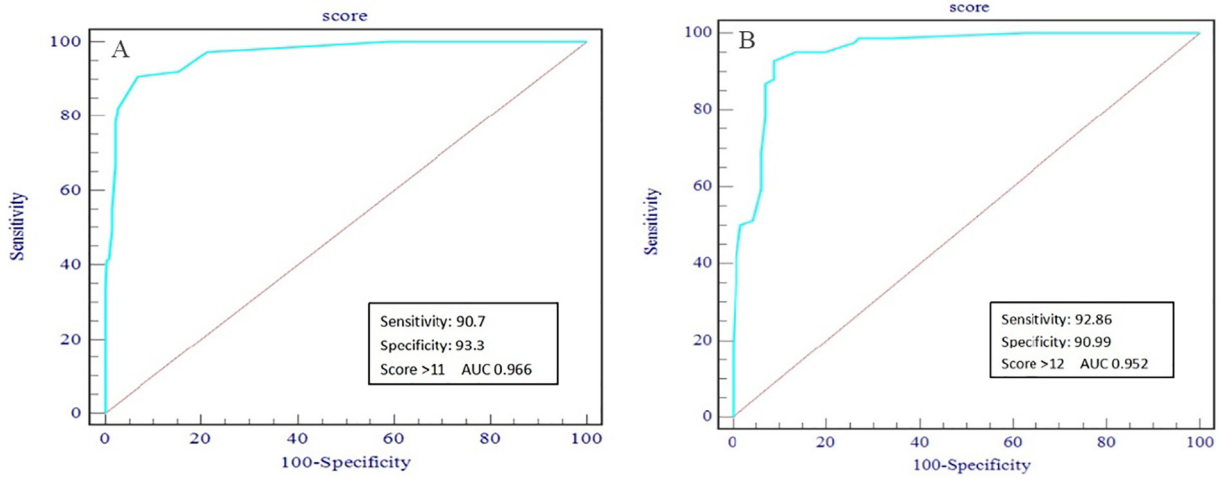

Fig. 2. The AUC of the Diagnostic Score System for CAS in the training dataset. The AUC was 0.966 (95% CI, 0.923 to 0.977). The cut-off baseline value was set to 11 points with specificity of 93.3% and sensitivity of 90.7%, respectively (Fig. 2-A). The AUC of the Diagnostic Score System for CAS in the testing dataset. The AUC was 0.952 (95% CI, 0.912 to 0.977). The cut-off baseline value was set to 11 points with specificity of 91.0% and sensitivity of 92.9%, respectively (Fig. 2-B).

We would like to acknowledge that our study does have several limitations. First, as a single centre study, the scoring system consisted of only clinical variables that we have searched from previous studies, some important predictors may possibly be missed. Second, 65% of the hypertensive patients were treated with calcium antagonists, which might suppress the spasm in the coronary arteries and mask the diagnosis of spasm. Third, ascribing to an investigator initiated observational clinical research, larger scale of clinical data is needed to examine its predictive accuracy and specificity. However, despite these limitations, the present clinical diagnostic score system should merit emphasis for better understanding and diagnosis of CAS.

5. Conclusion

In conclusion, we show that the clinical diagnostic score system is an accurate tool for estimating the pretest probability of CAS in patients with acute chest pain who have no organic stenosis angiographically. Further studies including the diagnostic score system and convolutional neural networks (CNNs)or machine learning algorithms are required to improve the diagnosis of CAS.

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Yaowang Lin collected, analyzed and wrote this manuscript. Haiyan Qin collected and analyzed the data. Ruimian Chen, Qiyun liu, Huadong Liu assisted in this study conduction. Shaohong Dong was the principal investigator.

Statement of ethics

All the included patients were informed and consented with regard to their participation in this study. The study protocol was approved by the institutional review board at Shenzhen People's Hospital.

Conflict of interest

The authors declare no conflict of interest.

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