Original Article

Combining ultrasound with bio-indicators reveals progression of carotid stenosis

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Background: Carotid artery stenosis (CAS) is one of the leading causes of ischemic stroke. However, knowledge of the changes in the plaque itself is lacking. Information about the ultrasound and clinical features of CAS will help elucidate the changes in prognostic and risk factors.

Methods: We evaluated 736 patients with carotid stenosis for an average 18-month follow-up. According to their degree of CAS stenosis, patients were allocated to one of three groups: regression (n=125), stable (n=443), or progression (n=168). An ordinal regression analysis was used to determine the risk factors for atherosclerosis progression. A logistic regression was subsequently applied to investigate the effects of CAS stenosis on cerebrovascular events after adjusting for various factors.

Results: The progression group had more male patients (P=0.02), hypoechoic plaque (P<0.01), high-risk high sensitivity C-reactive protein (hs-CRP) (P=0.02), ulcerative plaque (P=0.05), and hyperlipidemia (P=0.05) than the other two groups. There were no significant differences in residual ultrasound and clinical features among the three groups, including age, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), intima-media thickness (IMT), body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), coronary heart disease (CHD), statin use, ulcerative plaque. The ordinal regression analysis identified hypoechoic plaque (OR, 1.53; 95% CI: 1.14–2.05; P<0.01) and high-risk hs-CRP (OR, 1.75; 95% CI: 1.17–2.61; P<0.01) as independent risk factors for CAS progression. Logistic regression analysis revealed that the stroke/transient ischemic attack adjusted odds ratio was 1.80 (95% CI: 1.03–3.13) in the progression group.

Conclusions: High-risk hs-CRP and hypoechoic plaque are independently associated with CAS progression. The progression of carotid stenosis is associated with a high risk of cerebrovascular events.

Keywords: High-sensitivity C-reactive protein (hs-CRP); carotid stenosis; plaque progression; ultrasound; stroke

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Introduction

Stroke is the number one cause of disease burden in China, with the highest disability and mortality rates (1), and carotid artery plaque (CAP) is one of the primary causes of stroke. As the degree of carotid artery stenosis (CAS) increases, the risk of ipsilateral ischemic events increases (2). CAS is the leading cause and risk factor for ischemic cerebrovascular disease. The most common location of CAS is the carotid bifurcation, followed by the common carotid artery, internal carotid siphon, middle cerebral artery, and cerebral artery (3). Previous studies have shown that >60% of strokes are caused by carotid stenosis, and these events may lead to disability or even death (4). The Society of Vascular Surgery recommends that carotid endarterectomy should be performed to reduce the risk of stroke for patients with symptomatic CAS if noninvasive imaging determines that stenosis is >70% (Grade I/A) or if angiography determines that stenosis is >50% (Grade I/B) (5). Therefore, accurate assessment of the extent of CAS is essential to prevent stroke (6), and the elucidation of the mechanisms underlying CAS progression is urgently needed.

Digital subtraction angiography (DSA) is generally considered the gold standard for CAS diagnosis. However, the rate of stroke caused by invasive DSA surgery is 0.5–1% (7-9). With the development of noninvasive magnetic resonance and other imaging technology, the diagnostic value of magnetic resonance angiography (MRA), carotid double ultrasound (CDU), and computed tomography angiography (CTA) in CAS has become a highly debated topic. In the diagnosis of CAS, the results of these noninvasive methods have been consistent with those of DSA; therefore, MRA and CDU, as noninvasive screening methods, may be a suitable alternative to DSA. Compared to MRA, CTA, and DSA, CDU is a noninvasive, portable, reliable, low-cost method for examining plaques. Of these noninvasive tests, CDU is a more portable, reliable, and low-cost plaque detection method than MRA or CTA. But accuracy is the biggest limitation of CDU, which is related to the doctor's experience. CDU can not only detect the degree of carotid stenosis and the plaque area but can also detect the nature of CAP and has become the preferred method for the noninvasive longitudinal evaluation of CAS (10). A preliminary judgment of the nature of the plaque can provide recommendations for subsequent treatment.

High-sensitivity C-reactive protein (hs-CRP) is known as an acute non-specific biomarker of inflammation (11), widely accepted as a predictive factor for risk of cardiovascular diseases (12). Most studies have focused on plaque formation or the severity of plaques and stenosis (13,14) because these factors are associated with cardiovascular and cerebrovascular events. It has been reported that the enhancement degree on is associated with hs-CRP levels. Here, we set out from another perspective to reveal the relationship between hs-CRP level and progression of CAS (15). In the present study, we aimed to retrospectively analyze and determine the predictive ultrasound features and hs-CRP and other clinical factors associated with CAS progression in a cohort study and investigate the relationship between CAS progression and cerebrovascular events. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2666).

Methods

Patients

This retrospective study was approved by the institutional review committee of Ruijin Hospital of Shanghai Jiaotong University School of Medicine (Ruijin LL-14-2006). We reviewed the Ruijin Hospital database records from 2009 to 2019 and identified a total of 1,338 patients (a collection of inpatients and outpatients) who had undergone two or more CDUs (*Figure 1*). Patients with missing data, severe infection, or hs-CRP ≥10 mg/L were excluded from the study, resulting in a final number of 736 patients included in the study. The classification of plaque stenosis was as follows: grade 1: 0–50% (including 50%), grade 2: 50–70%, and grade 3: >70% (including 70%), or patients who had received carotid stent surgery. We divided the population into three categories: the progression group, the stability group, and the regression group (*Figure 2*), defined as follows: for the progression group, the stenosis grade of the carotid artery assessed by the most recent CDU was greater than that assessed in the previous one; for the stable group, the stenosis grade was maintained at the same level in two or more CDU assessments; and for the regression group, the most recent stenosis grade was lower than the previous stenosis grade assessment of the carotid artery. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). As a retrospective study, it did not involve patients' privacy, and the written consent of

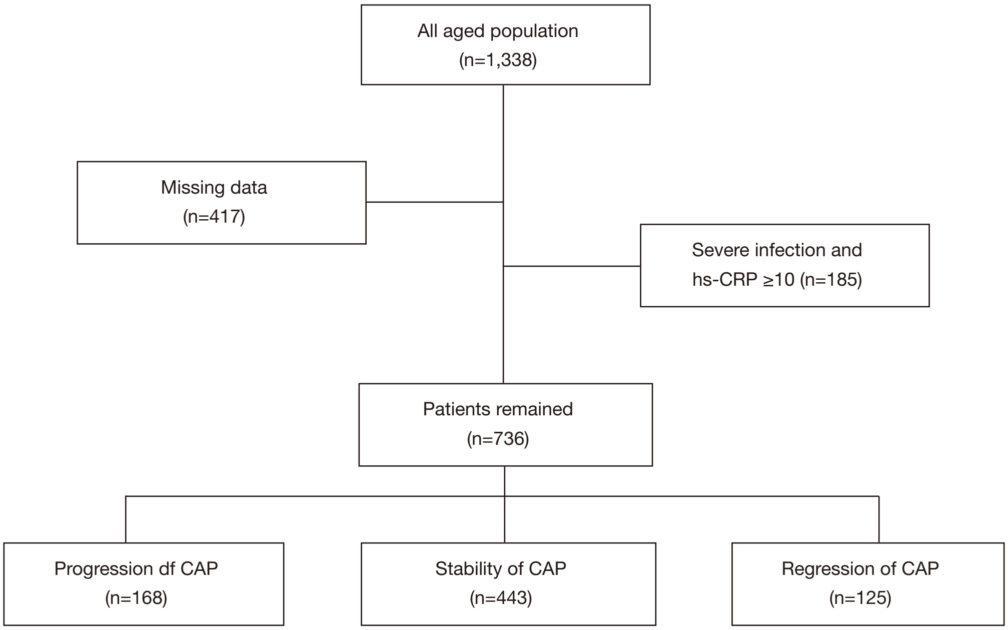

Figure 1 Sample recruitment. hs-CRP, high sensitivity C-reactive protein; CAP, carotid artery plaque.

patients was waived by Ruijin Ethical Committee.

Assessment of CAP

As part of the assessment process, stenosis, intima-media thickness (IMT), ulcer plaque, and echo characteristics were recorded at an average of 18 months of follow-up. The IMT of the carotid arteries was examined bilaterally using a Doppler ultrasound (HD11EX Ultrasound; Philips Medical Systems, Andover, MA, USA). IMT was measured on both the left and right carotid artery starting ~1.5 cm proximal to the carotid artery bulb. We took three recordings and calculated the mean value for each side. The affected side was taken as the standard. The degree of plaque stenosis was graded according to three levels: grade 1: 0–50% (including 50%), grade 2: 50–70%, and grade 3: >70% (including 70%), or patients who had received carotid stent surgery. The echo characteristics of the lesion detected by two-dimensional ultrasound were classified into five types: (I) uniformly echolucent, (II) predominantly echolucent, (III) predominantly echogenic, (IV) uniformly echogenic, and (V) consisted of plaques that could not be classified due to heavy calcification and acoustic shadows. In addition, the degree of CAS was diagnosed according to the widely accepted criteria published in 2003 by the expert panel of the Society of Radiologists in Ultrasound.

Measurement of biochemical parameters

After the subjects were fasted for 6 hours, a venous blood sample was taken in the morning and infused into a vacuum tube containing ethylenediaminetetraacetic acid. The serum concentrations of high sensitivity C-reactive protein (hs-CRP) were determined by particle-enhanced immunonephelometry using N high-sensitivity CRP reagent (Dade Behring Inc., Marburg, Germany). The lower limit of detection was 0.01 mg/L. All participants were further divided into two groups according to the hs-CRP baseline: low risk (<3.0 mg/L) and high risk (≥3.0 mg/L) (16). This article only discusses the effects of high-risk hs-CRP on the disease. High-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured by enzyme-linked immunosorbent assays on a Hitachi 912 analyzer (Roche Diagnostics, Germany).

Measurement of height, weight, and blood pressure

Weight and height were measured at baseline, and body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Subjects had their blood pressure measured twice with an automatic sphygmomanometer over a period of 10 minutes. The average value of the two measurements was recorded for further analysis.

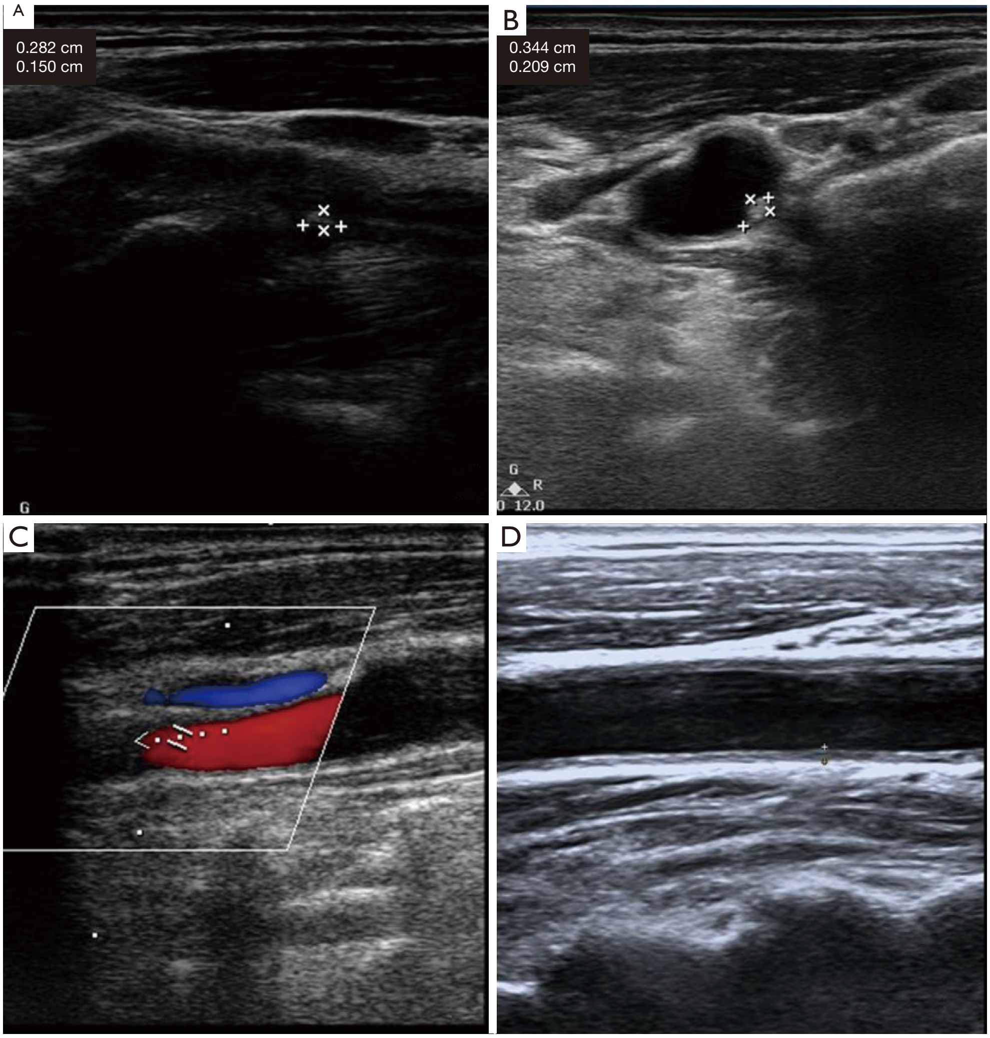

Figure 2 Ultrasound image of CAS during patients follow-up. (A,B) An example of CAS progression; (C,D) an example of CAS regression. CAS, carotid artery stenosis.

Statistical analysis

Based on an average 18-month follow-up, the patients were allocated to the following groups: progression, stability, and regression. The demographic factors (sex, age), atherosclerosis-affecting factors [high-risk hs-CRP, coronary artery disease, diabetes, hypertension, statin use and hyperlipidemia (HPL)], plaque characteristics (hypoechoic plaque and ulcerative plaque), and stroke/transient ischemic attacks (TIA) were compared by a chi-square test for categorical variables among the three groups. Comparisons of IMT, HDL-C, LDL-C, and BMI from baseline to follow-up in the three groups of patients were performed by repeated-measures analysis of variance (ANOVA). Following univariate analysis, variables (including sex, high-risk hs-CRP, hypoechoic plaque, hyperlipidemia, and ulcerative plaque) with a P value <0.05 were included in the ordinal regression model to determine the independent predictors of stenosis progression. A P value <0.05 was considered statistically significant. In this study, we used a binary logistic regression model to study the cross-sectional correlation between carotid plaque build-up and stroke/TIA in the group samples. We adjusted for potential confounders in different models: model 1, adjusted for sex; model 2, adjusted for sex, high-risk hs-CRP, hypoechoic plaque, hyperlipidemia, and ulcerative plaque. $P<0.05$ was considered statistically significant. Statistical analysis was conducted by SPSS Version 22.0 (IBM Corporation, USA).

Table 1 Clinical-demographic characteristics of patients

Parameters	All patients (n=736)	Regression (n=125)	Stable (n=443)	Progression (n=168)	P
Age, years	65.0±7.0	65.0±1.0	64.6±4.8	66.4±6.8	0.07
Male	542 (73%)	94 (75%)	317 (72%)	131 (78%)	0.04
LDL-C, mmol/L	2.4±0.9	2.4±1.0	2.4±0.9	2.5±0.9	0.95
HDL-C, mmol/L	1.1±0.3	1.1±0.3	1.1±0.3	1.1±0.3	0.56
IMT, mm	0.8±0.1	0.8±0.1	0.8±0.1	0.8±0.2	0.09
BMI, kg/m^2	25±3.1	25±3.3	25±2.9	25±3.5	0.68
High risk hs-CRP	111 (15.0%)	12 (9.6%)	64 (14.4%)	35 (20.8%)	<0.01
DM	314 (42.6%)	55 (44.0%)	188 (42.4%)	71 (42.3%)	0.94
HTN	632 (85.8%)	109 (87.2%)	373 (84.2%)	150 (89.3%)	0.50
CHD	637 (86.5%)	113 (90.4%)	376 (84.9%)	148 (88.1%)	0.06
HLP	269 (36.5%)	45 (36.3%)	162 (36.6%)	62 (36.8%)	0.05
Statin use	715 (97.1%)	122 (97.6%)	430 (97.1%)	163 (97%)	0.86
Hypoechoic plaque	303 (41.1%)	40 (30.2%)	182 (41%)	81 (48.2%)	<0.01
Ulcerative plaque	115 (15.6%)	20 (16.0%)	59 (13.3%)	36 (21.4%)	0.02
Stroke/TIA	200 (27.1%)	26 (20.8%)	116 (26.1%)	58 (34.5%)	<0.01

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; HTN, hypertension; CHD, coronary heart disease; HLP, hyperlipidemia; TIA, transient ischemic attack.

Results

Basic patient characteristics

Among the 1,338 eligible patients, we excluded 417 patients with missing data, and 185 patients with severe infection or hs-CRP ≥10 mg/L. We analyzed the data of the remaining 736 patients by groups. Their average follow-up period is 18 months. Based on the progression of carotid artery stenosis, we divided these 738 patients into three groups: regression, stable and progression (*Figure 1*). The average age of the 736 included patients was 64.91±9.66 years, and 73.2% of the patients were male. Except for high-risk hs-CRP (P<0.01) and hyperlipidemia (P=0.05), there were no significant differences in other carotid risk factors, such as hypertension, coronary heart disease (CHD), diabetes mellitus (DM), HDL-C, LDL-C, and BMI (*Table 1*).

The use of statin lipid-lowering drugs was almost 100% across the three groups, and thus, there was no difference in statin use. However, the degree of hypoechoic plaque (P<0.01) and ulcerative plaque (P=0.02) was significantly different in the progression group compared with the other two groups (*Table 1*).

During follow-up, 20 patients displayed increased carotid stenosis and subsequently received carotid stenting.

Independent Factors associated with plaque progression

In the ordinal logistic regression analysis, high-risk hs-CRP (OR, 1.75; 95% CI: 1.17–2.61; P<0.01) and hypoechoic plaque (OR, 1.53; 95% CI: 1.14–2.05; P<0.01) were found to be independent risk factors for CAS progression (*Table 2*). Other factors, such as ulcerative plaque (OR, 1.43; 95% CI: 0.96–2.12; P=0.08), hyperlipidemia (HLP) (OR, 1.01; 95% CI: 0.74–1.34; P=0.98), and sex (OR, 0.88; 95% CI: 0.64–1.23; P=0.46) were not independent risk factors for CAS progression (*Table 2*).

Relationship between carotid progression and stroke/TIA

The number of patients with a prior history of TIA or stroke was significantly different among the groups (P<0.01) (*Table 1*). We used a logistic regression model to analyze the cross-sectional relationship between the progression of carotid stenosis and stroke/TIA. After adjusting for several potential confounders, the stoke/TIA adjusted odds ratio was 1.80 (95% CI: 1.03–3.13) in the progression group (*Table 3*). This result proves that the progression of plaque itself is also an independent factor associated with stroke/TIA.

Discussion

It is well known that plate vulnerability is a risk factor for future ipsilateral ischemic stroke or TIA. Plaque echolucency is a potential biomarker of plaque vulnerability, and its ultrasound performance is equivalent to a necrotic nucleus (17-19). In this study, hypoechoic plaque proved to be an independent risk factor for progression of CAS, consistent with previous studies.

Hs-CRP is an inflammatory protein synthesized in the liver tissues, and high-risk hs-CRP is an independent predictive factor for cardiovascular disease (20). However, the relationship between hs-CRP and plaque changes has not been previously investigated. In this study, we used ordinal regression to prove that high-risk hs-CRP is closely related to plaque progression. This factor is not only a predictor of plaque production (14) but also a predictor of plaque progression.

Table 2 Risk factors of progression of carotid stenosis

Risk factor	B	OR	95% CI	P
Hypoechoic plaque	0.43	1.53	1.14–2.05	<0.01
High risk hs-CRP	0.56	1.75	1.17–2.61	<0.01
Ulcerative plaque	0.36	1.43	0.96–2.12	0.08
HLP	0.01	1.01	0.74–1.34	0.98
Sex	–0.12	0.88	0.64–1.23	0.46

Ordinal regression analysis is used for the statistics. hs-CRP, high-sensitivity C-reactive protein; HLP, hyperlipidemia; CI, confidence interval.

Statins are one of the primary drugs for carotid atherosclerosis treatment. In addition to their lipid-lowering effects, these drugs can also improve vascular endothelial function, inhibit inflammatory response, reduce endothelial cell lipid deposition, inhibit platelet aggregation, and stabilize plaques. Statins are an essential component of primary and secondary stroke prevention programs (21). More than 97% of patients in this study had been taking statins for an extended period of time, so the statin use may have reduced the extent of carotid stenosis (22-24). In addition to the statins mentioned, current interventions for CAS include 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, aggressive antihypertensive drugs to control blood pressure, strict blood glucose control in diabetics, smoking cessation, the use of antiplatelet drugs, or surgical treatment including carotid endarterectomy (CEA) and intracranial stenting (25).

In this longitudinal cohort study of CAS patients, we found that the difference in stroke and TIA between the groups was significant, and logistic regression demonstrated that plaque progression had a significant effect on stroke and TIA. Therefore, we concluded that CAS progression is also a predictor of cerebrovascular events, such as stroke and TIA (23,26,27).

Both high-risk hs-CRP and hypoechoic plaque were independent risk factors for the progression of carotid stenosis. Some studies have also shown that the concentration of hs-CRP is positively correlated with the formation of CAP (14); hypoechoic plaque is also an independent risk factor for the progression of carotid stenosis. An increase in the degree of carotid stenosis increases the occurrence of cerebrovascular events. Here, we hypothesized that the characteristics of the plaque itself have a higher impact on the disease than the biochemical indicators. Therefore, our main research direction in the future is to ascertain how to effectively convert hypoechoic

Table 3 Adjusted odds ratios and 95% CI for risk of stroke/TIA across different CAS groups in 726 Chinese adults

Model	Regression	Stable	Progression	P
All	125	443	168	–
Stoke/TIA	26	116	61	–
Model 1	Ref	1.32 (0.81–2.15)	1.86 (1.07–3.21)	0.03
Model 2	Ref	1.30 (0.79–2.13)	1.80 (1.03–3.13)	0.03

Model 1: adjusted for sex, age. Model 2: adjusted for sex, age, high risk hs-CRP, hyperlipidemia, ulcerative plaque, and hypoechoic plaque. TIA, transient ischemic attack; CAS, carotid artery stenosis.

plaques into hyperechoic plaques and convert unstable plaques into stable plaques. Studies have been performed from the perspective of platelets and macrophages, changing the chemokines and their receptors that cause interactions (28), thereby changing the composition of plaques or converting macrophage types from M1 to M2. These chemokines can also act on circulating smooth muscle progenitor cells (28,29) and have a beneficial effect on plaque stability. Endothelial progenitor cells (30,31) are important for plaque stabilization, whether they are progenitor cells themselves or exosomes secreted by cells. Studies have also shown that the main features of carotid plaques are highly heritable (32), and the problem of plaques may be solved from a genetic perspective in the future.

In our study, males were overrepresented (73% *vs.* 27%), which could be due to several reasons. First, in China, male smoking rates are much higher than those of females, which may explain the higher rate of extracranial stenosis in men (33). Second, the incidence of male stroke is significantly higher in all age groups in China than in females (34). Finally, Ruijin Hospital is a comprehensive tertiary medical center that accepts patients nationwide. Our analysis of patients' demographic profiles (both inpatient and outpatient service) from 2009 to 2019 revealed that more males than females were treated in our neurosurgery department, which may be due to referral patterns and local demographics.

There are some limitations to our study. First, this is essentially a retrospective cohort study and future prospective studies are needed to confirm our results. Second, during follow-up, we did not provide more detailed information on vascular risk factors (like hypertension, diabetes, or hyperlipidemia).

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2666

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-2666

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2666). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the institutional review committee of Ruijin Hospital of Shanghai Jiaotong University School of Medicine (Ruijin LL-14-2006). As a retrospective study, it did not involve patients' privacy, and the written consent of patients was waived by Ruijin Ethical Committee.

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