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Original Article

Clinical and Renal Cortical Blood Perfusion Characteristics in Patients with Severe Atherosclerotic Renal Artery Stenosis Who Underwent Stent Implantation: A Single-center Retrospective Cohort Study

Yan Li[1], Youjing Sun[1], Siyu Wang[1], Na Ma[1], Mengpu Li[1], Junhong Ren[1,*], Yongjun Li[2], Hu Ai[3], Hui Zhu[4], Yang Wang[5] and Fajin Guo[1]

Abstract

Objective This study aimed to observe the clinical imaging features of patients with severe atherosclerotic renal artery stenosis (ARAS) receiving stent implantation, and to evaluate the associations between baseline clinical and imaging factors and renal-function deterioration at a 1-year follow-up.

Methods This study was a single-center retrospective cohort study. A total of 159 patients with unilateral severe ARAS who underwent stent implantation at Beijing Hospital between July 2017 and December 2020 were consecutively enrolled. According to the renal glomerular filtration rate (GFR), detected by radionuclide renal imaging at 1-year follow-up, all patients were divided into a poor-prognosis group (with a ≥30% decrease in renal GFR; n=32 cases) and a control group (127 cases). Clinical imaging data, including the renal cortical blood perfusion pre- and post-sent implantation, were analyzed. Univariate and multivariate logistic regression analysis was used to evaluate the associations between clinical and imaging factors and renal-function deterioration.

Results Of the 159 patients enrolled, 83 (52.2%) were men, with an average age of (57.2±14.7) years. The patient age, rate of diabetes, and systolic blood and diastolic blood pressure in the poor-prognosis group were significantly higher than those in the control group (all $P<0.05$). Before stent treatment, patients in the poor-prognosis group, compared with the control group, had a significantly smaller area under the ascending curve (AUC1), area under the descending curve (AUC2), and peak intensity (PI), and a longer time to peak intensity (TTP) and mean transit time (MTT) (all $P<0.05$). After stent treatment, patients in the poor-prognosis group, compared with the control group, showed significantly smaller AUC1, AUC2, and PI, and longer MTT (all $P<0.05$). Multivariate logistic regression analysis indicated that age ($OR=1.251$, 95%*CI*: 1.113–1.406, $P=0.0002$), diabetes ($OR=1.472$, 95%*CI*: 1.110–1.952, $P=0.007$), systolic blood pressure ($OR=1.339$, 95%*CI*: 1.082–1.657, $P=0.007$), renal GFR ($OR=2.025$, 95%*CI*: 1.217–3.369, $P=0.006$), and AUC1 post-stent ($OR=2.173$, 95%*CI*: 1.148–4.113, $P=0.017$) were the factors associated with renal deterioration at the 1-year follow-up.

Conclusions Patients with severe RAS with renal-function deterioration after stent implantation were older, and often had diabetes, hypertension, and impaired renal cortical perfusion. Age, diabetes, systolic blood pressure, renal GFR, and AUC1 after stent implantation were independent factors associated with short-term renal deterioration.

Keywords

Prognosis, related factor, renal cortical blood perfusion, severe atherosclerotic renal artery stenosis, stent implantation.

[1]Department of Sonography, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China

[2]Department of Vascular Surgery, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China

[3]Department of Cardiology, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China

[4]Department of Nuclear Medicine, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China

[5]Department of Medical Research & Biometrics Center, National Center for Cardiovascular Diseases and Fuwai Hospital, CAMS and PUMC, Beijing 100037, China

*Correspondence to: Junhong Ren, E-mail: renjunhong2002@hotmail.com

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Background

Renal artery stenosis (RAS) refers primarily to the stenosis of the main or branch of the renal artery, thus leading to renal ischemia. The activity of the renin-angiotensin system significantly increases, thus leading to hypertension and impaired renal function. RAS is common in older people, with a prevalence of approximately 7% in people ≥65 years of age, and of up to 20% in people with diabetes and secondary hypertension [1, 2]. Studies have shown that RAS causes abnormal renal artery hemodynamics, thus leading to changes in renal function, such as renal blood perfusion. Therefore, some patients with mild RAS may have markedly impaired renal blood perfusion [3]. Revascularization is an important method used to treat severe RAS. However, large-scale randomized controlled clinical studies, such as ASTRAL and CORAL, have demonstrated that stent placement does not improve the prognosis of patients with severe RAS [4, 5]. In 2014, the American Society of Cardiovascular Angiography and Intervention released the Expert Consensus on Renal Artery Stenting, recommending revascularization treatment for patients with severe RAS. However, owing to the lack of prospective randomized controlled clinical trials, the current recommendations are based on only expert consensus (level of evidence, IIIA) [6]. Therefore, further evaluation of the factors affecting the prognosis of patients with severe RAS with stent implantation is necessary.

Previous studies have indicated that renal parenchymal blood flow and the glomerular filtration rate (GFR) are significantly associated with the prognosis of stent therapy [7, 8]. Our previous study has shown that stent intervention for severe RAS has no effect on short-term renal function [9], and contrast-enhanced ultrasound (CEUS) can be used to quantitatively assess renal parenchymal blood perfusion in real time. The cortical blood perfusion significantly differs in patients with mild, moderate, or severe RAS. Cortical blood perfusion parameters are significantly associated with the renal GFR, as detected by radionuclide renal imaging, and may affect prognosis [10, 11]. Therefore, we enrolled 159 patients with unilateral severe ARAS who underwent stent therapy at Beijing Hospital between January 2017 and December 2020, and analyzed the clinical imaging data and the associations between baseline clinical and imaging factors and renal-function deterioration.

Participants and methods

Research participants

This study was a single-center retrospective cohort study. A total of 573 patients (18–75 years of age) with RAS admitted to our hospital between July 2017 and December 2020 were enrolled. A total of 394 participants were excluded on the basis of the inclusion and exclusion criteria. Finally, 159 patients with unilateral severe ARAS who underwent stent treatment between July 2017 and December 2020 were included (**Figure 1**). This study was registered with the Chinese Clinical Trial Registration Center (ChiCTR1800016252), met the medical-ethics requirements, and was approved by the ethics committee of our hospital (2018BJYYEC-043-02).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) clinically diagnosed RAS with severe stenosis (diagnosed by digital subtraction angiography, CT angiography, or CEUS, indicating a decrease in lumen diameter by 70% to 99%) [2]; (2) 18–75 years of age, any sex; 3) stent implantation treatment; (4) provision of informed consent to voluntarily participate in this study.

The exclusion criteria were as follows: (1) simple essential hypertension; (2) severe cardiopulmonary dysfunction; (3) hypersensitivity to sulfur hexafluoride, the contrast agent used in CEUS; (4) renal artery occlusion (100% decrease in lumen diameter) (5) unclear ultrasound and other imaging findings; (6) advanced tumors; (7) pregnancy or breastfeeding; (8) non-cooperation with treatment; (9) refusal to sign informed consent (**Figure 1**).

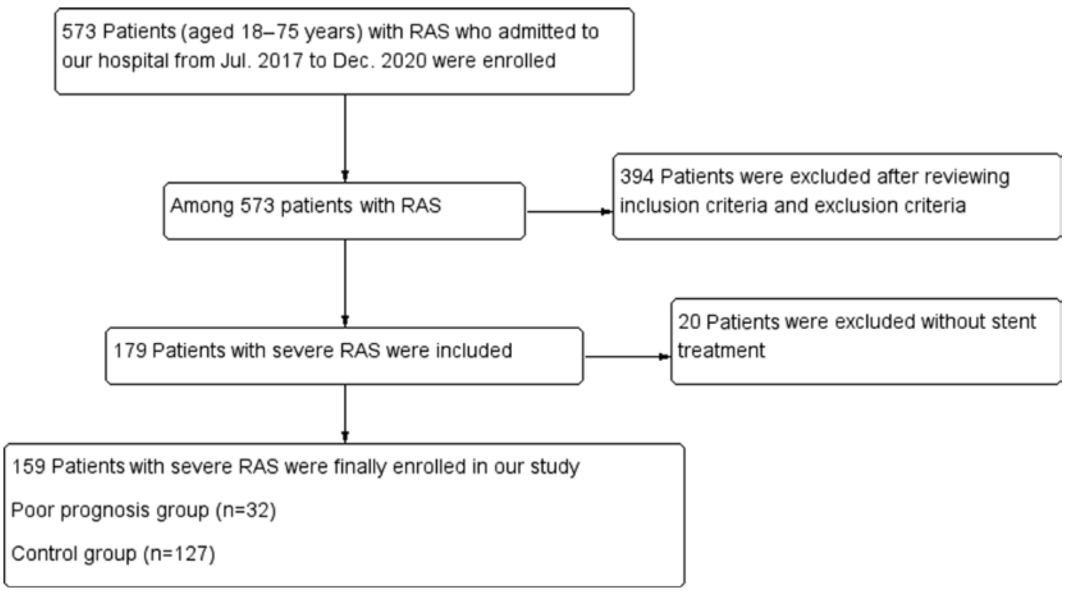

Figure 1 Flow chart.
RAS, renal artery stenosis.

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Methods

The patients' baseline data were recorded, including demographic data, clinical data, and biochemical examination and imaging data. Renal cortex blood perfusion was detected before and after stent placement, and renal GFR was detected with radionuclide renal imaging at the 1-year follow-up.

Renal cortex blood perfusion

CEUS was performed on all patients with a Samsung ultrasound system to evaluate the renal cortex blood perfusion of the affected kidney. The starting imaging conditions were as follows: mechanical index 0.08, image depth 15 cm, and gain 56 dB. The patients received two bolus injections of contrast medium in each kidney, and the main renal artery (dose 1.0 ml/kidney) and renal cortex blood perfusion (dose 1.2 ml/kidney) were observed. The specific process was as follows. In patients lying on their sides, the long axis section of the kidney was fixed perpendicularly to the direction of the sound beam. The contrast mode was turned on, and the contrast agent was injected through the cubital veins. The renal cortex contrast agent perfusion storage image was dynamically observed for 3 minutes. Renal cortex blood perfusion parameters were analyzed, including the area under the ascending curve (AUC1), area under the descending curve (AUC2), peak intensity (PI), time to peak intensity (TTP), and mean transit time (MTT) (**Figure 2**) [12].

Renal GFR

All patients underwent radionuclide renal imaging to evaluate the GFR of the kidney, with Symbia E-type SPECT or Symbia T16-type SPECT/CT (Siemens, Germany) instruments under a low-energy high-resolution collimator. Images were collected through the GATES method, and the radioactivity counts of the full and empty needles were measured at 30 cm before the probe before and 6 s after injection. The patients were placed in supine position, and the probe field included both kidneys. After injection of 1.85×10^8 Bq 99mTc-DTPA (Atom High-Tech Co., Ltd.) through the cubital vein, the computer dynamic collection was started immediately. The acquisition matrix was 64×64, divided into two groups. For the first group, the blood perfusion phase, 30 frames were collected at 2 s/frame; for the second group, the intake and excretion phase, 20 frames were collected at 60 s/frame, for a total of 20 min. With ROI technology, the images were processed to construct the blood flow perfusion, uptake, and excretion curves of the bilateral kidneys. The GATES method was used to determine the total GFR and sub-renal GFR (ml/min).

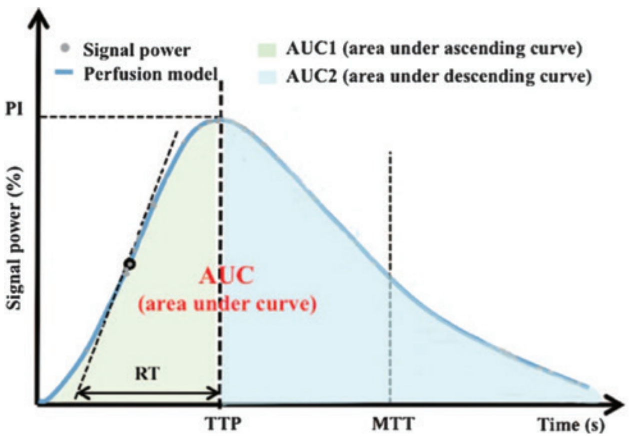

Figure 2 Time-dependent intensity curves (TIC) based on selected regions of interest.
AUC: area under the curve; MTT: mean transit time; PI: peak intensity; TTP: time to peak intensity; RT: rise time.

Deterioration of renal function

Deterioration of renal function refers to the estimated GFR, which was decreased by ≥30% after treatment and lasted for at least 60 days. Deterioration of renal function for other reasons was excluded [4, 5].

Statistical methods

STATA 14.0 statistical software was used for data analyses. Normally distributed data are expressed as $\bar{x}\pm s$, and independent-sample *t* test was used for comparisons between groups; count data are expressed as percentages, and the comparison of rates between groups was assessed with χ^2 tests. Univariate logistic regression analysis was used to identify possible associations between baseline data and the risk of renal-function deterioration. Factors with a *P* value <0.1 in univariate logistic regression analysis were used to perform multivariate logistic regression analysis. A *P* value <0.05 was considered statistically significant.

Results

Baseline clinical imaging data

Among the 159 patients with severe RAS, 83 (52.2%) were men, and the average age was 57.2±14.7 years. According to the renal GFR, detected by radionuclide renal imaging at the 1-year follow-up, the patients were divided into a poor-prognosis group (with a renal GFR decrease ≥30%) [4, 5] (32 cases) and a control group (127 cases). Between groups, the age, rate of diabetes, systolic blood pressure, and diastolic blood pressure in the poor-prognosis group were significantly higher than those in the control group, whereas the GFR of the stenotic kidney was significantly lower in the poor-prognosis group than the control group (all $P<0.05$). However, no significant difference was observed in sex, duration of hypertension, previous history (hyperlipidemia, smoking, or coronary artery disease), creatinine level, and degree of RAS between groups (all $P>0.05$) (**Table 1**).

Table 1 Baseline Clinical-imaging Data

Data	Poor-prognosis Group (n=32)	Control Group (n=127)	t/χ^2 Value	*P* Value
Basic data				
Age (yr)	62.2±14.7	56.0±9.3	2.961	0.004
Male sex [n(%)]	17(53.1)	66(52.0)	0.014	0.907
HP duration (yr)	13.1±8.9	11.8±5.1	1.088	0.278
History [n(%)]				
Diabetes	24(75.0)	42(33.1)	18.508	<0.001
Hyperlipidemia	16(50.0)	48(37.8)	1.561	0.212
Smoking	19(59.4)	60(47.2)	1.511	0.219
Coronary artery disease	14(43.8)	39(30.7)	1.897	0.162
Blood pressure				
SBP (mmHg)	152.7±22.8	138.8±18.9	3.562	<0.001
DBP (mmHg)	94.7±18.3	86.8±9.2	3.450	<0.001
Chemical results				
Creatinine (μmol/L)	112.0±34.6	104.7±24.6	1.374	0.172
Imaging data				
Degree of RAS (%)	87.2±15.4	83.9±17.4	1.751	0.082
GFR of the stenotic kidney (ml/min)	21.4±6.2	25.3±4.7	3.919	0.0001

HP: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; RAS: renal artery stenosis; GFR: glomerular filtration rate.

Cortical blood perfusion in the two groups

Before treatment, patients in the poor-prognosis group, compared with the control group, had significantly smaller AUC1, AUC2, and PI, and longer TTP and MTT (all $P<0.05$). After treatment, compared with those in the control group, patients in the poor-prognosis group had significantly smaller AUC1, AUC2, and PI, and longer MTT (all $P<0.05$) (**Table 2**, **Figure 3**).

Routine ultrasound and CEUS (**Figure 3A**) and DSA (**Figure 3B**) showed 85% localized stenosis of the right renal artery with impaired renal cortical blood perfusion (**Figure 3C**), which significantly improved after stent implantation (**Figure 3D**).

Logistic regression analysis

Univariate logistic regression analysis indicated that age, diabetes, systolic blood pressure, diastolic blood pressure, RAS degree, renal GFR, AUC1, AUC2, PI, TTP, and MTT after stent implantation were factors associated with renal-function deterioration (all $P<0.1$). Multivariate logistic regression analysis revealed that age (*OR*=1.251, 95%*CI*: 1.113–1.406, *P*=0.0002), diabetes (*OR*=1.472, 95%*CI*: 1.110–1.952, *P*=0.007), systolic blood pressure (*OR*=1.339, 95%*CI*: 1.082–1.657, *P*=0.007), renal GFR (*OR*=2.025, 95%*CI*: 1.217–3.369, *P*=0.006), and AUC1 post-stent (*OR*=2.173, 95%*CI*: 1.148–4.113, *P*=0.017) were factors associated with renal-function deterioration after 1-year follow-up (**Table 3**).

Table 2 Changes in Cortical Blood Perfusion Pre- and Post-stent Implantation

Data	Poor-prognosis Group (n=32)	Control Group (n=127)	*t* Value	*P* Value
AUC1 (dB×s)				
Pre-stent	792.5±316.5	1146.2±273.2	6.335	<0.001
Post-stent	968.4±275.2[a]	1377.6±243.1[a]	8.283	<0.001
AUC2 (dB×s)				
Pre-stent	4022.5±1579.8	4816.4±1127.5	3.263	<0.001
Post-stent	4246.3.2±1772.2[a]	5305.2±1228.1[a]	3.957	<0.001
PI (dB)				
Pre-stent	108.4±22.8	117.1±27.2	1.667	0.098
Post-stent	120.5±20.7[a]	131.6±15.1[a]	2.309	0.022
TTP (s)				
Pre-stent	22.8±5.4	19.8±4.1	3.457	<0.001
Post-stent	19.7±5.2[a]	17.6±5.8	1.867	0.064
MTT (s)				
Pre-stent	58.1±13.3	48.6±11.5	4.044	<0.001
Post-stent	52.5±13.5[a]	45.4±10.3[a]	3.262	0.001

AUC1: area under the ascending curve; AUC2: area under the descending curve; PI: peak intensity; TTP: time to peak intensity; MTT: mean transit time. Compared with pre-sent: [a]$P<0.05$.

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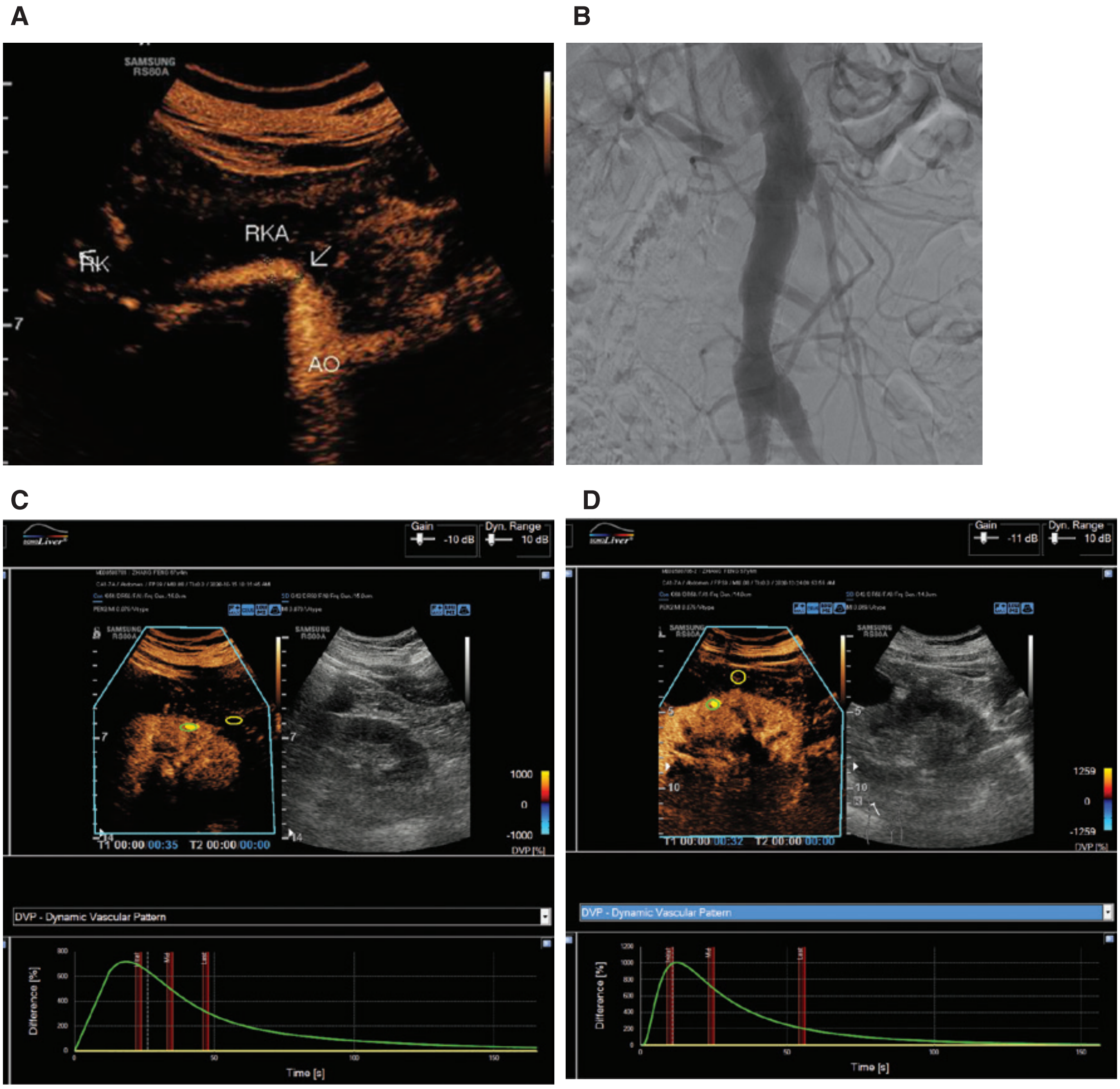

Figure 3 Cortical blood perfusion before and after stent implantation in a 62-year-old woman with 85% stenosis at the origin of the right renal artery. Routine ultrasound and CEUS (A) showed 85% stenosis at the origin of the right renal artery, which was confirmed by DSA (B). The affected right kidney's cortical blood perfusion was decreased before stenting (C) and partially increased after stenting (D).
CEUS: contrast-enhanced ultrasound; DSA: digital subtraction angiography.

Table 3 Logistic Regression Analysis of Factors Associated with Renal-function Deterioration

Risk factor	β	*SE*	Wald χ^2	*OR*	95%*CI*	*P*
Age	0.224	0.057	0.881	1.251	1.113–1.406	0.0002
Diabetes	0.388	0.144	1.038	1.472	1.110–1.952	0.007
SBP	0.292	0.109	0.782	1.339	1.082–1.657	0.007
GFR	0.706	0.260	1.913	2.025	1.217–3.369	0.006
AUC1 post-stent	0.776	0.326	0.848	2.173	1.148–4.113	0.017

SBP: systolic blood pressure; GFR: glomerular filtration rate; AUC1: area under the ascending curve.

Discussion

Stent placement does not improve the prognosis of all patients with severe RAS but is a common treatment for patients with severe RAS. However, multi-center randomized clinical trials, such as ASTRAL and CORAL, have indicated that stent placement in patients with severely stenotic RAS does not decrease the incidence of adverse cardio-renal vascular events [4, 5]. However, those studies had a substantial limitation of selection bias. In the CORAL study, patients with recent heart failure and severe RAS who might have benefitted from stent therapy were excluded, whereas in the ASTRAL study, patients with stenosis of 50%–70% were selected. A total of 50% to 70% of patients with RAS with stenosis did not show significant hemodynamic improvement, and tend not to benefit from stent placement. Subgroup analysis revealed that only 25% of patients with moderate to severe stenosis had improved renal function after surgery, and the basic renal function in these patients was acceptable. In contrast, the basic renal function of patients with poor prognosis was poor, and RAS did not reach significant blood flow improvement [13, 14]. Studies have confirmed that, for patients with RAS of 50%–70% in terms of diameter, arterial hemodynamics and pathophysiological changes must be evaluated simultaneously [15]. If the GFR or blood flow of the affected kidney decreases by more than 25% on the contralateral side, according to the causal relationships among vascular stenosis, hypertension, and renal damage, vascular reconstruction is feasible. For patients with severe RAS (>70%), most of the glomeruli in the affected kidney must survive (≥50%) without irreversible damage [2, 6, 15]. Therefore, we speculate that patients with severe RAS with no significant decline in basic renal function may benefit from revascularization therapy. In this study, 17.3% (13/75) of the patients had poor prognosis, and diabetes, hypertension, underlying renal dysfunction, and abnormal renal cortical blood perfusion were often observed.

Renal cortex blood perfusion is a sensitive indicator for evaluating hemodynamic disorders in patients with RAS. Cortical blood perfusion differs among patients with mild, moderate, or severe RAS. Paul et al. [16] have used CT perfusion imaging to assess the blood perfusion of the renal parenchyma, and divided the time-density curves of the bilateral kidneys into the following groups: (1) type I, bilateral symmetrical, with similar shapes of bilateral time-density curves; (2) type II, bilateral asymmetric, with a prolonged time to peak on the affected side but similar bilateral cortical perfusion; and (3) type III, with significantly decreased cortical perfusion on the affected side and peak value, and prolonged peak time. Studies have confirmed that mild RAS (stenosis <50%) does not cause hemodynamic changes, and the time-density curve shows type I symmetry. As the degree of stenosis increases, the time-density curve follows type II and type III. Our previous study has indicated that the AUC1, AUC2, and MTT in patients with mild RAS significantly differ from those in normal controls; and in patients with moderate or severe RAS, the TTP and MTT are significantly delayed, and the AUC1, AUC2, and PI are significantly smaller than those in normal controls (all $P<0.05$) [10, 11].

Renal cortex blood perfusion is significantly associated with the prognosis of patients with RAS and is an important indicator for evaluating renal function. Cui et al. [7] have used 99mTc-EC to determine the effective renal plasma flow and radionuclide renal imaging to determine GFR, then calculated the renal filtration fraction (normally 18%–22%), The authors have found that the renal filtration fraction increased significantly before stent treatment. Patients with high kidney filtration scores had good prognosis; kidneys with normal renal filtration scores before surgery showed partially improved renal function; and kidneys with lower kidney filtration scores before surgery had poor prognosis. Therefore, significantly elevated or normal RAS before surgery is an indication for renal artery stenting. Chrysochou et al. [8] have found that the renal parenchymal blood flow, measured by magnetic resonance, and the renal GFR ratio, measured by radionuclide imaging, can help identify "hibernating" kidneys with good prognosis (AUC=0.93). Renal function can significantly improve after treatment; therefore, patients with high renal GFR ratios are suitable for renal artery stent therapy. In this study, before treatment, patients in the poor-prognosis group, compared with the control group, had significantly smaller AUC1, AUC2, and PI, and longer TTP and MTT (all $P<0.05$). After treatment, patients in the poor-prognosis group, compared with the control group, had significantly smaller AUC1, AUC2, and PI, and longer MTT (all $P<0.05$).

Similarly to previous studies [17–18], our study indicated that several established related factors, such as age (OR=1.242, 95%CI: 1.081–1.427, $P=0.002$), diabetes (OR=1.242, 95%CI: 1.107–2.156, $P=0.011$), systolic blood pressure (OR=1.328, 95%CI: 1.056–1.670, $P=0.015$), and renal GFR (OR=2.374, 95%CI: 1.216–3.887, $P=0.009$) [19], were factors associated with renal-function deterioration. Furthermore, the AUC1 after stent implantation (OR=2.646, 95%CI: 1.553–6.369, $P=0.002$) was a related factor. Therefore, AUC1 after stent implantation is a new biomarker that may help clinicians evaluate the degree of renal ischemia and determine prognosis. Moreover, combined with established related factors (age, diabetes, systolic blood pressure, and GFR), renal cortical blood perfusion parameters may be useful for select patients who might clinically benefit from stent implantation [20].

Study limitations

This study has several limitations. (1) This study was a single-center cohort study with a small sample size. More studies with larger sample sizes should be conducted to verify the identified association. (2) Patients included in our study had atherosclerotic RAS, and those with non-atherosclerotic RAS, such as that due to Takayasu's arteritis, fibromuscular dysplasia, or embolism, might have different characteristics of renal cortical blood perfusion [21–23]. (3) The patients enrolled were often middle-aged or older (average age 59.5 years), and had several atherosclerosis-related factors. Therefore, those younger patients with fewer atherosclerosis-related factors might have different factors associated with short-term renal-function deterioration [24–27]. (4) All patients had unilateral severe ARAS. However, one-third to two-thirds of patients with severe ARAS have bilateral lesions, and findings for both kidneys are associated with prognosis [28–29]. (5) Patients were followed up for 1 year; however, longer follow-up periods are needed to evaluate the incidence of adverse cardio-renal vascular events.

Conclusions

Patients with severe RAS with poor prognosis after stent therapy often have diabetes, hypertension, and impaired renal cortical blood perfusion. Multivariate logistic regression analysis indicated that—in addition to several established related factors, including age, diabetes, systolic blood pressure, and renal

GFR—AUC1 after stent implantation was an independent factor associated with short-term renal deterioration. However, more large-scale studies are needed to confirm these findings.

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Conflicts of interest

The authors report no conflicts of interest.

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