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Atherosclerotic renal artery stenosis, mediating biomarkers, and risk of cardiac among individuals with hypertension: A real-world study

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ABSTRACT

Background: Atherosclerotic renal artery stenosis (ARAS) is commonly associated with cardiovascular diseases (CVD). Patients with ARAS typically present with cardiac structural and functional abnormalities, and the differences in cardiac structure and function compared to hypertensive patients without ARAS remain to be explored.

Methods: A total of 499 hypertensive patients were included, of whom 134 had ARAS and 365 had no renal artery stenosis (RAS). Parameters about cardiac function and structure detected by echocardiography and other clinical data are collected. Univariate and multivariate binary logistic regression and mediation analysis were performed on the collected data.

Results: Compared to hypertensive patients without ARAS, those with ARAS had significantly increased left ventricular (LV) internal diameter (LVIDd), posterior wall thickness (PWTd), LV geometric abnormalities, diastolic dysfunction, and a higher prevalence of LV hypertrophy (LVH). After adjustment, ARAS was significantly associated with LV diastolic dysfunction (LVDF) (OR = 1.12, 95 %CI = 1.03–1.3), LVIDd (OR = 1.07, 95 %CI = 1.02–1.13), LV geometry (OR = 1.24, 95 %CI = 1.12–1.36), PWTd (OR = 1.2, 95 %CI = 1.09–1.31), and LV mass index (OR = 1.31, 95 %CI = 1.18–1.47). Mediation analysis identified hypersensitive C-reactive protein (Hs-CRP) and serum creatinine (Scr) as significant mediators, accounting for 10.80 % to 59.54 % of the ARAS impact on LV abnormalities.

Conclusion: ARAS appears to be an independent risk factor for abnormalities in cardiac function and structure, potentially mediated by Hs-CRP and Scr. Hypertensive patients with ARAS demonstrate a higher prevalence of left ventricular hypertrophy (LVH) and diastolic dysfunction, underscoring the importance of vigilant monitoring in this population.

1. Introduction

Hypertension (HTN) is a leading contributor to morbidity and mortality associated with CVD, stroke, and renal disease [1]. Renal artery stenosis (RAS), an important comorbidity in hypertensive patients, is present in 1 % to 6 % of all hypertensive individuals and up to 30 % of those with known atherosclerotic disease [2]. ARAS is the most common type of renal artery stenosis (RAS), accounting for about 90 % of cases [3]. In hypertensive patients over 50, ARAS prevalence is estimated at 10–15 %, and this rises to 50–60 % among those with coexisting coronary atherosclerosis, peripheral arterial disease, or renal insufficiency [4,5]. Given the prevalence of ARAS in hypertensive populations, it likely contributes significantly to the CVD burden in these patients.

Several studies have proposed a link between ARAS and changes in

Abbreviations: ARAS, Atherosclerotic renal artery stenosis; CVD, cardiovascular diseases; RAS, renal artery stenosis; LV, left ventricular; Hs-CRP, hypersensitive c-reactive protein; Scr, Serum creatinine; LVDF, left ventricular diastolic function; LVg, left ventricular geometry; LVIDd, left ventricular internal dimension; PWTd, posterior wall thickness; LVH, Left ventricular hypertrophy.

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left ventricular (LV) structure and function [6], likely mediated by chronic activation of the renin-angiotensin-aldosterone system (RAAS) [7]. While certain studies suggest a strong association between ARAS and LVH [2,6,8–14], other studies, particularly smaller cohort studies, have reported no significant structural differences between RAS patients and those with primary hypertension [9]. This inconsistency highlights the need for larger, more definitive studies focusing specifically on ARAS, the most common RAS subtype, to determine its impact on cardiac morphology and function.

In addition to LVH, patients with ARAS frequently exhibit diastolic dysfunction, increasing the risk of heart failure with preserved ejection fraction (HFpEF) [15]. Diastolic dysfunction, characterized by impaired LV relaxation and elevated myocardial stiffness, is associated with structural cardiac abnormalities and a high annual mortality rate of 8 % [16]. Notably, some studies have found that adverse cardiovascular events in patients with renal hypertension are not exclusively attributable to hypertension or renal impairment [17]. However, previous studies didn't pay enough attention to ARAS. There isn't clear evidence about the relationship between ARAS and cardiac structural and functional abnormality. Besides, the mechanisms by which ARAS affects cardiac structure and function are unknown and require further study [6,18].

Given the high CVD burden in hypertensive ARAS patients and the conflicting findings in the current literature, further investigation is needed. This study aims to clarify the relationship between ARAS and cardiac structural and functional changes in hypertensive patients. Specifically, this study aims to assess left ventricular geometry and function in hypertensive patients with ARAS, exploring biomarkers as potential mediators of cardiac effects.

2. Methods

2.1. Study population

We included 5984 hypertensive patients who underwent Enhanced CT of the renal arteries or ultrasound from January 1, 2018, to September 30, 2023, in the First Hospital of Chongqing Medical University. We screened and identified 134 patients with ARAS combined with hypertension and 365 hypertensive patients without renal artery stenosis. The specific process is shown in Fig. 1. **Inclusion Criteria:** (1) Diagnosed primary hypertension. (2) Anatomical screening of renal arteries via enhanced CT or digital subtraction angiography (DSA). (3) Renal artery stenosis attributable specifically to atherosclerosis. **Exclusion Criteria:** (1) Secondary hypertension. (2) Renal artery stenosis due

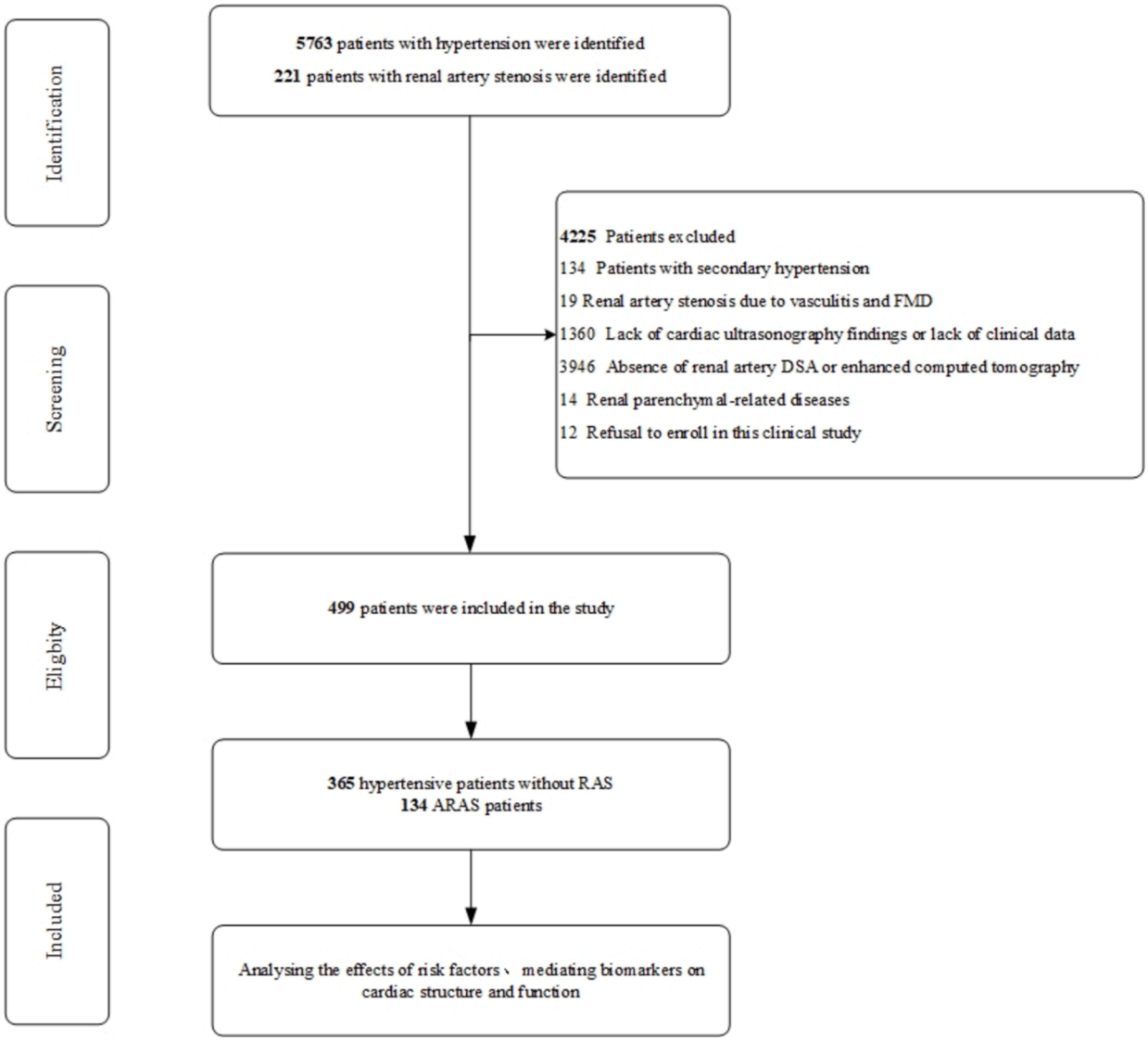

Fig. 1. Study flow diagram.

to vasculitis or fibromuscular dysplasia (FMD). (3) Incomplete echocardiographic or clinical data. (4) Absence of renal artery DSA or enhanced CT imaging. (5) Presence of renal parenchymal disease. (6) Refusal to participate in the study. The standardized selection was performed using guideline recommendations similar to the (CORAL) study to determine the presence of atherosclerotic renal artery stenosis [19–21].

2.2. Standard protocol approval, registration, and patient consent

All research procedures and protocols involving human subjects complied with the ethical standards of the 1964 Declaration of Helsinki, and the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University approved this study (Ethics No. 2023-354). Written informed consent was obtained from all individual participants or their legal representatives before participation.

2.3. Clinical data and echocardiographic parameters collection

Clinical and echocardiographic data were recorded by trained clinicians using the hospital's electronic medical record system. Collected demographic and clinical information including height, weight, age, sex, smoking history, alcohol use, history of diabetes mellitus, history of hypertension, and medication usage. Laboratory parameters included Hs-CRP, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and Scr.

Cardiac ultrasound data collected included:

1) PWTd.
2) Interventricular septum thickness in diastole (IVSTd).
3) Left ventricular internal diameter in diastole (LVIDd) and systole (LVesd).
4) Left ventricular geometry (LVg), LVDF, and ejection fraction (LVEF).

Echocardiograms were conducted by a senior cardiac technician following 10 min of rest in the semi-supine position. A blinded physician, unaware of the patient's clinical background, reviewed and reported all echocardiographic measurements.

2.4. Definition of abnormal cardiac function and structure

LV mass (LVM) was estimated using the Devereux formula [22] and indexed to body surface area [23]. LVH is defined as a left ventricular mass index (LVMI) of $>$ 115 g/m2 in men and $>$ 95 g/m2 in women. Other structural parameters included:

1) LVIDd (normal: $<$55 mm in men, $<$50 mm in women).
2) PWTd (normal: $<$11 mm).
3) IVSTd (normal: $<$11 mm).

LV configuration was categorized as either normal or abnormal, with abnormalities defined as thickening, hypertrophy, or enlargement. Based on the clinical echocardiographic diagnosis, LVDF was classified as normal or decompensated.

2.5. Statistical analyses

Statistical analysis was conducted using R software (version 4.1.2, The R Foundation, http://www.R-project.org). Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are presented as percentages. Initial comparisons between groups (No-RAS vs. ARAS) were made using two-sample t-tests for continuous variables and chi-square tests for categorical variables. To identify independent risk factors for cardiac structural and functional abnormalities, we performed:(1). Univariate binary logistic regression to identify associations between individual factors and LV abnormalities. (2). Multivariate binary logistic regression including all variables with $p < 0.05$ from univariate analysis to determine independent predictors of LV abnormalities, such as LVIDd, PWTd, LVMI, LVH, and LVDF. Differences were deemed significant if the P value was < 0.05. To evaluate the indirect effects of ARAS on left ventricular (LV) abnormalities, mediation analysis was conducted using the **Mediation** macro in R. We performed a mediation analysis according to the method suggested by Professor VanderWeele [24] to examine how mediator variables affect the relationship between ARAS(independent variable) and LV abnormalities (outcome variable). This analysis examined the roles of Hs-CRP and Scr as mediators in the relationship between ARAS and LV abnormalities, including LVIDd, PWTd, LVg, and LVDF. In addition, receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability in hypertensive patients with ARAS of LVH and LVDF. The area under the ROC curve (AUC) and the Jordon's index were calculated for each model to demonstrate its assessment capabilities [25,26].

3. Results

3.1. Basic demographic characteristics

After the filtration of our inclusion and exclusion criteria, a total of 499 (53.9 ± 17.9) were included in the study, comprising 365 No-RAS and 134 with ARAS. Key demographic and clinical characteristics are presented in Table 1. The ARAS group had a significantly higher mean age (67.5 ± 13.2 vs. 48.9 ± 16.7,) and greater prevalence of smoking (49.3 % vs. 31.2 %), alcohol use (38.8 % vs. 27.1 %), and CVD (29.9 % vs. 15.6 %). Additionally, ARAS patients exhibited significantly elevated levels of Hs-CRP (3.9 ± 3.2 vs. 2.4 ± 2.8) and Scr (118.6 ± 80.4 vs. 79.5 ± 43.9) compared to the No-RAS group. The selection process for study participants is summarized in the flowchart(Fig. 1).

3.2. Cardiac structure and function

Significant differences were observed between the two groups in terms of echocardiographic measurements. ARAS patients displayed larger LVIDd, increased LVesd, and PWTd. Furthermore, LVg was more prevalent in the ARAS group, as was LVDF. LVH was also significantly more common in the ARAS group. (Detailed in Table 1, Abbreviated article flow results can be found in **Graphical Abstracts**).

3.3. The influence of ARAS on cardiac structure and function

Univariate logistic regression (Table 2) identified ARAS, age, gender, smoking, alcohol consumption, blood pressure, and other factors as significant predictors of various left ventricular (LV) structural and functional abnormalities. In multivariate analysis (Table 3), our study found ARAS was associated with 1.12, 1.07, 1.24, 1.20, and 1.31 times higher odds for LVDF, LVIDd, LVg, PWTd, and LVMI, respectively($P < 0.05$).

Fig. 2 displays the odds ratios and 95 % confidence intervals for these associations, visually underscoring ARAS as a significant predictor across multiple cardiac dimensions. Additionally, the ROC curves in Fig. 3 demonstrate assessment capabilities for both LVH and LVDF, with AUC of 0.77 and 0.78(Youden index: 0.41 and 0.42), respectively.

3.4. Mediation analysis

Mediation analysis, as depicted in Fig. 4, identified Hs-CRP and Scr as partial mediators of the relationship between ARAS and specific cardiac abnormalities. Notable findings include(1). For LVIDd abnormalities, Scr mediated by 59.54 % and Hs-CRP mediated by 33.26 % of the ARAS effect. (2). Scr also mediated the association between ARAS and PWTd by 17.69 %, and LVg by 19.9 %.

These mediation effects highlight the substantial role of Hs-CRP and

Table 1
Clinical characteristics of patients with NoRAS or ARAS hypertension.

	Overall	No-RAS	ARAS	p-value
N(%)	499(100)	365 (73.1)	134 (26.9)	
age,y	53.9 ± 17.9	48.9 ± 16.7	67.5 ± 13.2	**<0.001**
sex,male(%)	293(58.7)	200 (54.8)	93(69.4)	**0.005**
BMI, kg/m2	25.5 ± 4.0	26.0 ± 3.9	24.2 ± 4.0	**<0.001**
smoking(%)	180(36.1)	114 (31.2)	66(49.3)	**<0.001**
alchohol(%)	151(30.3)	99(27.1)	52(38.8)	**0.016**
SBP,mmHg	157.2 ± 59.1	155.7 ± 25.7	161.5 ± 106.0	0.335
DBP,mmHg	92.6 ± 17.8	95.4 ± 17.6	85.0 ± 16.0	**<0.001**
PP,mmHg	64.7 ± 56.8	60.3 ± 17.5	76.4 ± 104.9	**0.079**
Comorbidities				
CAD,n(%)	97(19.4)	57(15.6)	40(29.9)	**0.001**
DM,n(%)	141(28.3)	118 (32.3)	23(17.2)	**0.001**
Cardiacstructureandfunction				
IVSTd,mm	11.5 ± 4.8	11.5 ± 5.5	11.4 ± 1.4	0.791
LVIDd,mm	48.1 ± 5.2	47.6 ± 5.0	49.4 ± 5.5	**0.001**
LVesd,mm	31.9 ± 4.7	31.5 ± 4.8	32.9 ± 4.3	**0.003**
LVg,n(%)	200(40.1)	132 (36.2)	68(50.7)	**0.004**
LVDF,n(%)	340(68.1)	222 (60.8)	118 (88.1)	**<0.001**
LVH,n(%)	272(54.5)	173 (47.4)	99(73.9)	<0.001
LVMI,g/m^2	118.4 ± 87.4	115.5 ± 100.9	126.3 ± 26.4	0.062
LVMI(male),g/m^2	127.11 ± 111.88	125 ± 134.3	131 ± 28.3	0.588
LVMI(female),g/m^2	106.04 ± 22.41	104 ± 22.9	116 ± 11.7	**<0.001**
PWTd, mm	11.0 ± 2.1	10.8 ± 1.6	11.4 ± 3.1	**0.009**
LVEF,%	62.6 ± 6.3	62.6 ± 6.4	62.6 ± 6.0	0.901
Antihypertensivedrug				
CCB,n(%)	364(72.9)	255 (69.9)	109 (81.3)	**0.014**
ACEI/ARBs,n(%)	278(55.7)	203 (55.6)	75(56.0)	1.000
Beta-blocker,n(%)	172(34.5)	126 (34.5)	46(34.3)	1.000
Diuretics,n(%)	97(19.4)	66(18.1)	31(23.1)	0.256
ARNI,n(%)	79(15.8)	73(20.0)	6(4.5)	**<0.001**
Alpha-blocker,n(%)	50(10.0)	38(10.4)	12(9.0)	0.755
Biochemicalindex				
Hs-CRP,mg/l	2.8 ± 3.0	2.4 ± 2.8	3.9 ± 3.2	**<0.001**
TC,mmol/l	4.5 ± 1.0	4.5 ± 1.1	4.4 ± 1.0	0.168
TG,mmol/l	2.0 ± 1.5	2.0 ± 1.7	1.8 ± 1.1	0.210
HDL-c,mmol/l	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.559
LDL-c,mmol/l	2.7 ± 0.9	2.7 ± 0.9	2.7 ± 0.7	0.480
Scr,umol/l	90.0 ± 58.6	79.5 ± 43.9	118.6 ± 80.4	**<0.001**

P values ≤ 0.05 are given in bold. Data are presented as number (%), or mean ± SD, as appropriate.
Abbreviation: SBP systolic blood pressure; DBP diastolic blood pressure; PP, pulse pressure difference; DM, diabetes mellitus; BMI body mass index; BSA body surface area; CCB, calcium channel blockers; ACEI/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, ARNI, angiotensin receptor neprilysin inhibitor.

Scr in the pathway linking ARAS with LV structural and functional alterations. Full mediation results, including total, direct, and indirect effects, are provided in Table 4.

4. Discussion

ARAS, a sign of atherosclerosis, is strongly associated with cardiovascular disease, causing alterations in the structure and function of the heart. ARAS is a significant risk factor for CVD [27]. In this study, after adjusting for multiple covariates (including blood pressure, age, gender, smoking, alcohol consumption, medication use, and comorbidities), ARAS remained a risk factor for increased LVIDD and PWTd. LVMI, abnormal LVg, reduced LVDF, and LVH can influence through mediators such as Hs-CRP and Scr.

Previous studies have shown renal hypertension leads to poorer cardiac function and significant cardiac structural changes [6,28–31]. Hoshida S et al.'s study indicates that hypertensive patients with RAS have higher LVMI [2]. However, they used renal artery ultrasound to screen for renal artery stenosis, which lacks high accuracy. Additionally, the study included only 40 RAS patients and had numerous confounding factors. Khangura KK et al., in their study, illustrated that Renal vascular hypertension (RVHT) aggravates left ventricular hypertrophy and systolic and diastolic dysfunction [14]. In the real world, more often than not, ARAS is combined with primary hypertension, and most patients continue to have combined hypertension after relief of renal artery stenosis, making it challenging to prove renal hypertension [3]. Similarly, decades ago, Wright JR noted in his study that cardiac structure and function abnormalities are highly prevalent in patients with atherosclerotic renal vascular disease (ARVD). Still, the conclusions of this study are limited by the fact that the control group was comorbid with renal-related disease and was not explicitly examined in a population with comorbid hypertension [6]. Besides, previous clinical studies have not explored the possible underlying mechanisms. Therefore, our study included the ARAS population in hypertensive patients, and the control group was composed of patients with essential hypertension, avoiding the interference of renal disease, secondary hypertension, and renal artery stenosis due to non-ARAS causes. Compared to renal artery ultrasound [32], renal arteriography is the gold standard for diagnosis [33]. More importantly, our study found that Hs-CRP and Scr were investigated as essential mediators of cardiac effects through mediation analysis.

Patients with ARAS may experience left ventricular hypertrophy and impaired diastolic function, and the causes of these outcomes are multifaceted. Possible causes include higher blood pressure and increased volume load in ARAS patients, which affect the structure and function of the heart [3]. Left ventricular hypertrophy and dilation are adaptive mechanisms aimed at restoring reduced stroke volume in response to excessive hemodynamic burden [6]. However, in addition to hemodynamic overload, ARAS patients may also exhibit elevated levels of neurohumoral and growth regulatory factors [34]. Plasma renin activity is also higher in hypertensive patients with comorbid ARAS, implying that activation of regulatory targets of the systemic renin-angiotensin-aldosterone system is impaired by the amplifier [35–39]. In addition, the ARAS group in this study had a higher Hs-CRP (2.4 ± 2.8 vs 3.9 ± 3.2, $p < 0.001$), suggesting increased systemic inflammation in ARAS and inflammatory responses, oxidative stress, nitric oxide, endothelin release that arterial stenosis kidneys can induce, and that inflammation promotes myocardial fibrosis, which can lead to cardiac dysfunction [14,34,40,41]. This is consistent with previous studies that ARAS also produces inflammatory markers in the stenotested kidneys, including biomarkers such as tumor necrosis factor Tumor Necrosis Factor-α(TNF-α), interferon, and neutrophil gelatinase-associated lipocalin Neutrophil gelatinase-associated lipocalin (NGAL) [40,42].

Table 2
Univariate binary logistic regression models of the effects of different risk factors on LVDF, LVIDd, LVg, PWTd and LVMI.

Variable	LVDF		LVIDd		LVg		PWTd		LVMI	
	OR(95 %CI)	p-value	OR(95 %CI)	p-value	OR(95 %CI)	p-value	OR(95 %CI)	p-value	OR(95 %CI)	p-value
age,y	1.06(1.04,1.07)	<**0.001**	1.00(0.99,1.02)	0.596	1.00(0.99,1.01)	0.486	0.99(0.98,1.01)	0.337	1.02(1.01,1.03)	<**0.001**
sex, male	0.77(0.52,1.14)	0.196	1.29(0.68,2.55)	0.445	2.15(1.48,3.14)	<**0.001**	3.06(2.02,4.69)	<**0.001**	0.53(0.37,0.76)	<**0.001**
BMI, kg/m^2	0.99(0.94,1.04)	0.637	1.02(0.94,1.10)	0.632	1.07(1.02,1.12)	**0.006**	1.09(1.04,1.14)	<**0.001**	0.00(0.00,0.00)	**0.022**
smoking(%)	1.35(0.91,2.02)	0.142	1.37(0.71,2.58)	0.340	1.97(1.36,2.86)	<**0.001**	2.54(1.73,3.76)	<**0.001**	0.87(0.60,1.25)	0.441
alchohol(%)	1.26(0.83,1.92)	0.285	1.83(0.95,3.46)	0.066	1.98(1.34,2.92)	<**0.001**	2.34(1.57,3.49)	<**0.001**	0.95(0.65,1.40)	0.798
SBP,mmHg	1.00(1.00,1.01)	0.232	1.00(0.99,1.00)	0.890	1.02(1.01,1.03)	<**0.001**	1.02(1.02,1.03)	<**0.001**	1.02(1.01,1.03)	<**0.001**
DBP,mmHg	0.99(0.98,1.00)	0.102	1.00(0.99,1.02)	0.592	1.02(1.01,1.03)	<**0.001**	1.03(1.02,1.04)	<**0.001**	1.01(1.00,1.02)	0.074
ARAS	4.75(2.78,8.62)	<**0.001**	2.20(1.14,4.19)	**0.017**	1.82(1.22,2.72)	<**0.001**	1.70(1.12,2.57)	**0.011**	3.14(2.05,4.91)	<**0.001**
DM	2.47(1.56,4.01)	<**0.001**	0.48(0.19,1.05)	0.087	1.20(0.81,1.78)	0.363	1.07(0.7,1.61)	0.749	1.09(0.74,1.62)	0.669
CCB	0.95(0.62,1.45)	0.826	0.92(0.47,1.92)	0.817	1.36(0.90,2.06)	0.145	1.68(1.08,2.65)	**0.024**	1.61(1.08,2.39)	**0.020**
ACEI/ARBs	1.33(0.91,1.94)	0.143	0.57(0.30,1.07)	0.083	0.95(0.66,1.37)	0.794	0.90(0.62,1.32)	0.603	0.68(0.48,0.98)	<**0.001**
Betablocker	1.65(1.10,2.51)	**0.017**	1.82(0.96,3.45)	0.064	1.08(0.74,1.57)	0.692	1.02(0.69,1.51)	0.919	0.94(0.65,1.36)	0.740
Diuretics	1.64(1.00,2.79)	0.056	1.99(0.96,3.92)	0.052	3.03(1.93,4.83)	<**0.001**	2.94(1.87,4.65)	<**0.001**	1.62(1.03,2.5)	**0.039**
ARNI	1.25(0.75,2.17)	0.404	2.03(0.94,4.12)	0.059	1.77(1.09,2.88)	**0.021**	1.74(1.06,2.84)	**0.027**	1.64(1.00,2.73)	0.052
Alphablocker	0.74(0.41,1.37)	0.328	2.77(1.18,5.98)	**0.013**	3.28(1.79,6.19)	<**0.001**	4.41(2.42,8.28)	<<**0.001**	2.32(1.24,4.56)	**0.011**
TC,mmol/l	1.06(0.88,1.27)	0.561	1.20(0.89,1.59)	0.226	1.08(0.91,1.29)	0.366	1.04(0.87,1.24)	0.685	1.07(0.91,1.27)	0.419
TG,mmol/l	1.14(0.99,1.34)	0.099	1.12(0.93,1.29)	0.175	1.29(1.13,1.50)	<**0.001**	1.18(1.05,1.34)	<**0.001**	1.15(1.01,1.33)	**0.040**
HDL-c,mmol/l	1.21(0.65,2.30)	0.556	0.39(0.12,1.21)	0.121	0.37(0.19,0.70)	**0.003**	0.25(0.12,0.49)	<**0.001**	1.09(0.61,1.96)	0.776
LDL-c,mmol/l	0.97(0.78,1.21)	0.778	1.21(0.85,1.71)	0.274	0.97(0.79,1.19)	0.779	0.98(0.79,1.22)	0.871	0.97(0.79,1.19)	0.788

Abbreviation: OR, OR odds ratio; CI, confidence interval. P values ≤ 0.05 are given in bold.

Table 3
Multivariate binary logistic regression Models of the Effect of ARAS on LVDF, LVIDd, LVg, PWTd and LVMI.

Variable	OR	95 %CI	P value
LVDF	1.12	1.03–1.3	**0.008**
LVIDd	1.07	1.02–1.13	**0.008**
LVg	1.24	1.12–1.36	<**0.001**
PWTd	1.20	1.09–1.31	<**0.001**
LVMI	1.31	1.18–1.47	<**0.001**

P values ≤ 0.05 are given in bold.
Model for PWTd: Adjusted for smoking (yes, no), sex (male, female), alcohol (yes, no), BMI (continuous, kg/m$^{2)}$, SBP (continuous, mmHg), DBP (continuous, mmHg), CCB (yes, no), Diuretics (yes, no), ARNI (yes, no), Alphablocker (yes, no), TG (continuous, mmol/l), HDL-c (continuous, mmol/l).
Model for LVIDd: Adjusted for Alphablocker (yes, no).
Model for LVDF: Adjusted for age (consecutive years), DM (yes, no), Betablocker (yes, no). Mold for LVg: Adjusted for sex (male, female), alcohol (yes, no), BMI (continuous, kg/m$^{2)}$), smoking (yes, no), SBP (continuous, mmHg), DBP (continuous, mmHg), ARNI (yes, no), Alphablocker (yes, no), Diuretics (yes, no), TG (continuous, mmol/l), HDL-c (continuous, mmol/l).
Model for LVMI: Adjusted for age (consecutive years), sex (male, female), SBP (continuous, mmHg), DBP (continuous, mmHg), BMI (continuous, kg/m^2), Alphablocker (yes, no), ARNI (yes, no), Diuretics (yes, no), CCB (yes, no), ACEI/ARBs(yes, no), TG (continuous, mmol/l).

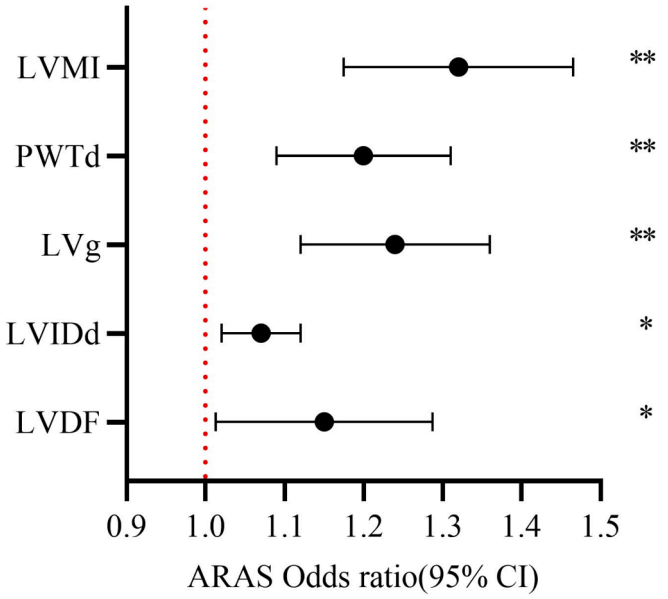

Fig. 2. Effect of ARAS on LVDF, LVIDd, LVg, PWTd and LVMI. **, P < 0.001; *, P < 0.05.

Sympathetic activation triggered by local production of hypoxia-related substances (e.g. adenosine) in the kidney may also play a role [42]. Similarly, a preliminary study by Yoshio Iwashima et al. suggests that autonomic (sympathetic and parasympathetic) changes may be one of the pathophysiological mechanisms in patients with renal artery stenosis [43]. Alternatively, it has been suggested that renal function is related to cardiac structure and modulates remote myocardial microvascular integrity. This result highlights a functionally important cardiorenal link mediated by renal injury signaling, which may induce cardiac remodeling and impair its function beyond the hemodynamic effects of hypertension [44]. This may be related to the present study's ARAS group having higher serum creatinine values (79.5 ± 43.9 vs 118.6 ± 80.4,p < 0.001).

We are the first paper to employ mediation analysis to investigate potential pathways of cardiac injury resulting from ARAS. This analysis enhances comprehension of the risk of ventricular remodeling and the changes in heart function that are linked to ARAS. Our data indicates that Hs-CRP and Scr play a crucial role in causing changes in heart structure and function. Out of the factors considered, accounted for 59.54 % of the influence of ARAS on LVIDd abnormalities, while Hs-CRP accounted for 33.26 %. This provides more evidence that ARAS triggers inflammatory reactions, resulting in deteriorated renal function and unmanageable hypertension, which subsequently lead to worsened cardiac structure and function and potentially unfavorable cardiovascular complications[6,27,45,46]. Victor H et al. also showed that selective improvement in renal function reduced renal and systemic oxidative stress and inflammation and preserved distal myocardial microvascular function and structure, which validates the important mediating role of Hs-CRP and Scr in mediating cardiac injury in this study [44].

The correlation between renal and cardiac failure is intricate and necessitates additional investigation. Ultimately, the modified shape of the ventricle and the reduced ability to relax during diastole in patients with ARAS are caused by a combination of many causes, leading to an increased occurrence of negative outcomes. During the initial phases,

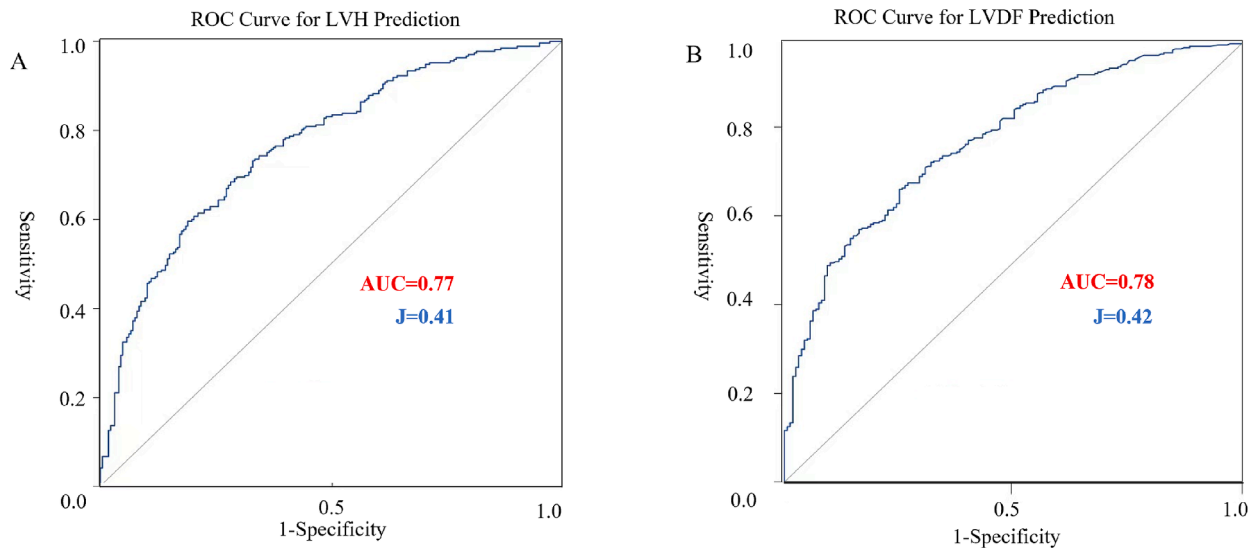

Fig. 3. Receiver operating characteristic curves of ARAS for predicting LVH (A), LVDF (B).J: Youden's index.

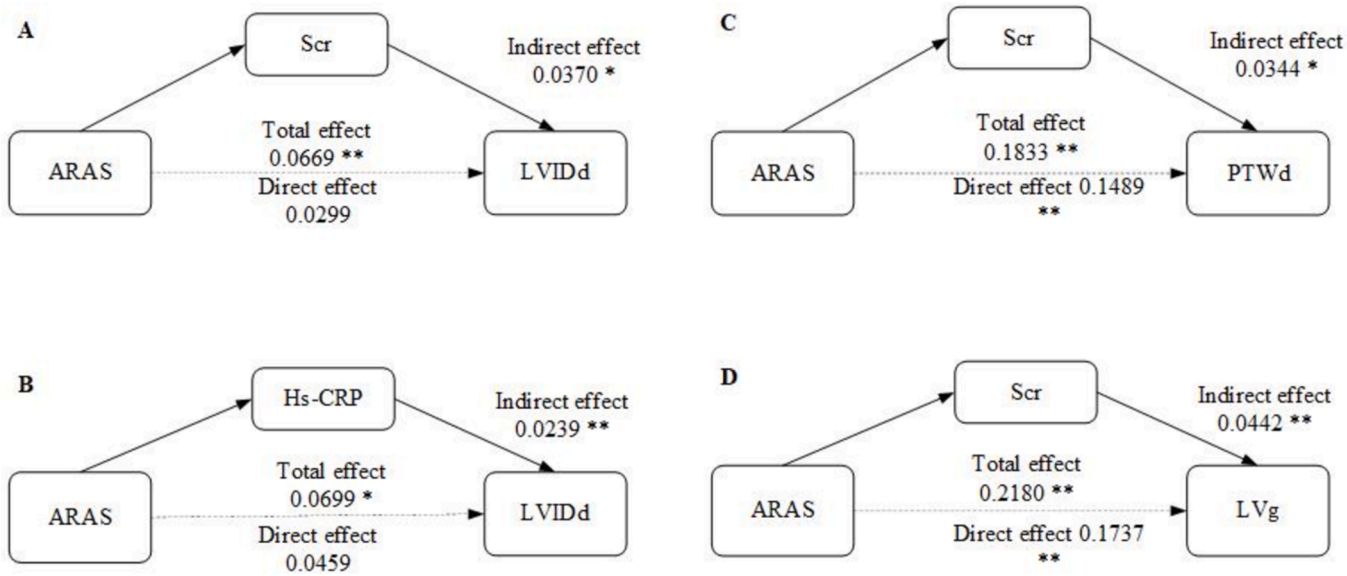

Fig. 4. Model for the mediating effect of ARAS on LVIDd、PTWd, or LVg via Scr and Hs-CRP. A: Effects of Scr-mediated ARAS on LVIDd. B: Effects of Hs-CRP-mediated ARAS on LVIDd. C: Effects of Scr-mediated ARAS on PTWd. D: Effects of Scr-mediated ARAS on LVg. **, $P < 0.001$; *, $P < 0.05$.

left ventricular hypertrophy and dilatation have the potential to be reversed [6]. Osami etal. [47] reported a case of a patient with complete occlusion of the right renal artery whose cardiac function improved after successful stent implantation. This provides new ideas for follow-up studies and reaffirms the existence of adverse effects of renal artery stenosis on the heart. ARAS patients are at risk of disease progression and loss of renal function [3]. Therefore, identifying patients who require aggressive renal artery revascularisation before it becomes irreversible is an important clinical matter [48–50].In the future, more accurate noninvasive means (e.g., contrast-enhanced ultrasound (CEUS)) will still be needed to screen patients for ARAS so that high-risk patients can be identified in a timely manner [51].

Our study, as a single-institution cross-sectional analysis, has limitations that may introduce potential biases. Conducting the study at a single center may limit the generalizability of our findings, as patient demographics and practices vary across regions, possibly leading to institutional bias. The retrospective design also limits causal inference, as associations may be influenced by unmeasured confounders. Additionally, selecting participants from specific procedural databases (echocardiography, renal artery-enhanced CT, or arteriography) may introduce selection bias by overrepresenting patients with more severe disease profiles, potentially impacting both the direction and magnitude of observed associations. Due to the retrospective nature, we could not perform repeated ultrasound measurements to assess inter- and intra-observer variability, which may affect the precision of our results, though standardized protocols were used to ensure data quality. Our sample's predominantly Chinese demographic further limits applicability to other ethnic groups, introducing potential ethnic bias as genetic and lifestyle factors vary by population. Furthermore, the absence of key biomarkers such as renin and aldosterone may lead to information bias, resulting in residual confounding and incomplete insights into the RAAS pathway's role in ARAS-related cardiac changes. Although these limitations may affect the interpretation of our findings, this study contributes valuable insights into the impact of ARAS on cardiac function. Future multicenter studies involving diverse populations and a more comprehensive biomarker profile are necessary to validate and expand

Table 4
Association of Atherosclerotic renal artery stenosis with left ventricular structure and function abnormality mediated by biomarkers.

	Total effect				Natural Direct effect				Natural indirect effect				Proportion eliminated	
	Beta	Lower	Upper	p	Beta	Lower	Upper	p	Beta	Lower	Upper	p	%(95 %CI)	p
PWTd														
Scr,umol/l	0.1833	0.0708	0.2700	**<0.001**	0.1489	0.0386	0.2300	**<0.001**	0.0344	0.0059	0.0600	**0.020**	17.69(0.05,0.52)	**0.020**
Hs-CRP, mg/l	0.1764	0.0942	0.2700	**<0.001**	0.1556	0.0815	0.2600	**<0.001**	0.0209	0.0015	0.0500	**0.020**	10.80(0.01,0.27)	**0.020**
LDL-c, mmol/l	0.1876	0.0813	0.3000	**<0.001**	0.1888	0.0806	0.3000	**<0.001**	0.0012	0.0090	0.0000	0.820	0.00(0.06,0.02)	0.820
TC,mmol/l	0.1819	0.0939	0.2900	**<0.001**	0.1821	0.0958	0.2900	**<0.001**	0.0002	0.0076	0.0000	0.940	0.00(0.05,0.03)	0.940
LVg														
Scr,umol/l	0.2180	0.0859	0.3300	**<0.001**	0.1737	0.0518	0.2800	**<0.001**	0.0442	0.0212	0.0700	**<0.001**	19.90(0.09,0.45)	**<0.001**
Hs-CRP, mg/l	0.1867	0.0844	0.3000	**<0.001**	0.1463	0.0487	0.2600	**<0.001**	0.0405	0.0181	0.0700	**<0.001**	21.25(0.08,0.49)	**<0.001**
LDL-c, mmol/l	0.1821	0.0589	0.3200	**<0.001**	0.1819	0.0570	0.3200	**<0.001**	0.0002	0.0060	0.0000	0.860	0.11(0.04,0.04)	0.860
TC,mmol/l	0.1830	0.0591	0.3200	**<0.001**	0.1821	0.0594	0.3200	**<0.001**	0.0009	0.0081	0.0100	0.940	0.08(0.06,0.07)	0.940
LVIDd														
Scr,umol/l	0.0669	0.0138	0.1200	**<0.001**	0.0299	0.0263	0.0900	0.320	0.0370	0.0056	0.0700	**0.020**	59.54(0.10,2.44)	**0.020**
Hs-CRP, mg/l	0.0699	0.0043	0.1400	**0.020**	0.0459	0.0182	0.1100	0.200	0.0239	0.0074	0.0400	**<0.001**	33.26(0.092,3.05)	**0.020**
LDL-c, mmol/l	0.0712	0.0093	0.1400	**0.020**	0.0717	0.0095	0.1400	**0.020**	0.0005	0.0037	0.0000	0.660	0.56(0.17,0.06)	0.680
TC,mmol/l	0.0705	0.0124	0.1200	**0.020**	0.0726	0.0159	0.1200	**0.020**	0.0021	0.0090	0.0000	0.340	2.12(0.32,0.03)	0.360
LVDF														
Scr,umol/l	0.1249	0.0394	0.2200	**<0.001**	0.1462	0.0606	0.2500	**<0.001**	0.0213	0.0632	0.0000	0.080	14.65(1.20,0.01)	0.080
Hs-CRP	0.1233	0.0448	0.2200	**<0.001**	0.1323	0.0537	0.2200	**<0.001**	0.0089	0.0414	0.0200	0.520	0.08(0.36,0.15)	0.520
LDL-c, mmol/l	0.1323	0.0369	0.2400	**<0.001**	0.1332	0.0349	0.2400	**<0.001**	0.0008	0.0086	0.0100	0.780	0.21(0.09,0.06)	0.780
TC,mmol/l	0.1266	0.0519	0.2200	**<0.001**	0.1299	0.0580	0.2200	**<0.001**	0.0033	0.0120	0.0000	0.320	2.10(0.17,0.02)	0.320
LVMI														
Scr,umol/l	0.2923	0.2038	0.3900	**<0.001**	0.2692	0.1816	0.3600	**<0.001**	0.0231	0.0067	0.0400	**<0.001**	0.07(0.02,0.17)	**<0.001**
Hs-CRP	0.2698	0.1685	0.3600	**<0.001**	0.2598	0.1596	0.3600	**<0.001**	0.0100	0.0024	0.0300	0.180	0.03(0.01,0.10)	0.180
LDL-c, mmol/l	0.2948	0.1970	0.4200	**<0.001**	0.2971	0.1951	0.4200	**<0.001**	0.0022	0.0118	0.0100	0.540	0.00(0.04,0.02)	0.540
TC,mmol/l	0.2821	0.1927	0.3800	**<0.001**	0.2811	0.1906	0.3800	**<0.001**	0.0009	0.0084	0.0100	0.780	0.00(0.03,0.04)	0.780

Model for PWTd: Adjusted for smoking (yes, no), sex (male, female), alcohol (yes, no), BMI (continuous, kg/m^2), SBP (continuous, mmHg), DBP (continuous, mmHg), CCB (yes, no), Diuretics (yes, no), ARNI (yes, no), Alphablocker (yes, no), TG (continuous, mmol/l), HDL-c (continuous, mmol/l).
Model for LVIDd: Adjusted for Alphablocker (yes, no).
Mold for LVDF: Adjusted for age (consecutive, years), DM (yes, no), Betablocker (yes, no).
Model for LVg: Adjusted for sex (male, female), alcohol (yes, no), BMI (continuous, kg/$m^{2)}$), smoking (yes, no), SBP (continuous, mmHg), DBP (continuous, mmHg), ARNI (yes, no), Alphablocker (yes, no), Diuretics (yes, no), TG (continuous, mmol/l), HDL-c (continuous, mmol/l).
Model for LVMI: Adjusted for age (consecutive, years), sex (male, female), SBP (continuous, mmHg), DBP (continuous, mmHg), BMI (continuous, kg/m^2), Alphablocker (yes, no), ARNI (yes, no), Diuretics (yes, no), CCB (yes, no), ACEI/ARBs(yes, no), TG (continuous, mmol/l).

upon these results.

5. Conclusion

Our study indicates that LVIDd and PWTd measurements are elevated, with increased likelihoods of LVg abnormalities, LVDF decompensation, and LVH in patients with ARAS and concurrent hypertension. The findings suggest that ARAS may serve as an independent risk factor for abnormalities in cardiac function and structure. Mediation analysis reveals that Hs-CRP and Scr may significantly mediate these effects. These insights hold clinical value for identifying ARAS patients at elevated risk of cardiac geometric and functional alterations, underscoring the importance of continuous echocardiographic assessment to monitor therapeutic efficacy, and emphasizing that inflammatory markers and monitoring of renal function markers are of clinical importance in patients with ARAS. Understanding the independent impact of ARAS on cardiac function may also inform prevention and management strategies for this condition.

CRediT authorship contribution statement

Yanwei Li: Writing – original draft, Investigation, Data curation. **Zhulu Chen:** Writing – original draft, Software, Formal analysis, Data curation. **Rui Lan:** Writing – original draft, Methodology, Formal analysis, Data curation. **Tao Ran:** Investigation, Data curation. **Jingyi He:** Investigation, Data curation. **Jialian Li:** Investigation, Data curation. **Qiuyue Shi:** Writing – original draft, Investigation, Data curation. **Min Mao:** Writing – review & editing, Project administration, Conceptualization. **Zhong Zuo:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Y.L. and Z.C. designed the study. Y.L. and Z.C. developed the study methods, reviewed the literature, performed the analyses, and wrote the first draft of the manuscript. R.L., J.H., J.L., and Q.S. participated in the investigation and validated the data. R.L., M.M., and Z.Z. critically revised the manuscript. All authors contributed to the interpretation of data and the final approved version. Heart and human cartoon images used in Graphical Abstracts were obtained from Scidraw.io.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101556.

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