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Aldosterone-to-Renin Ratio Changes in Patients With Renal Artery Stenosis and Aldosteronism

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ABSTRACT

We conducted a retrospective cohort study to investigate changes in the aldosterone-to-renin ratio (ARR) and other influencing factors in patients with renal artery stenosis (RAS) and primary aldosteronism (PA). Patients with RAS and PA admitted to our hospital between January 2016 and December 2021 were retrospectively selected. Based on the standardized PA screening results, the patients were divided into aldosterone-to-renin ratio-positive and -negative groups. The clinical features of the patients were compared. Binary logistic regression analysis was performed to identify the factors contributing to the comorbidity of RAS with false-negative PA. A total of 78 patients (mean age: 60.2 ± 10.2 years) were selected, among whom 46 (59%) were male. Overall, 69 patients had Stage 3 hypertension (88.5%) and 57 had hypokalemia (73.1%). Additionally, 42 (53.8%) and 36 (46.2%) patients were aldosterone-to-renin ratio-positive and -negative, respectively. The aldosterone-to-renin ratio-positive group showed significant differences in malignant hypertension (2.4% vs. 27.8%; $p = 0.002$), Stage 3 hypertension (81.0% vs. 97.2%; $p = 0.033$), and RAS degree (64.3 ± 16.4% vs. 71.8 ± 14.4%; $p = 0.032$). Malignant hypertension (odds ratio, 15.250; 95% confidence interval, 1.787–130.132; $p = 0.013$) and RAS degree (odds ratio, 1.034; 95% confidence interval, 1.002–1.068; $p = 0.036$) influenced the comorbidity of RAS with false-negative PA. Malignant hypertension and severe RAS can contribute to false-negative PA results. Therefore, PA screening test results should be carefully analyzed and rechecked following RAS treatment to confirm the presence of PA.

1 | Introduction

Renal artery stenosis (RAS) and primary aldosteronism (PA) are common causes of secondary hypertension. Both act on the renin–angiotensin–aldosterone system (RAAS) and trigger an increase in the aldosterone levels, resulting in similar clinical manifestations. However, reports pertaining to the regulation of plasma renin concentrations by RAS and PA are conflicting. The aldosterone-to-renin ratio (ARR) is a crucial index for PA screening. However, RAS may elevate renin concentration, leading to false-negative results in PA screening and an increase in the likelihood of misdiagnosis [1]. Therefore, when both conditions coexist, accurately interpreting the ARR screening results can be challenging.

In this study, we aimed to investigate the changes in the ARR in patients with RAS and PA. To our knowledge, this is the largest retrospective study to assess clinical data from patients with both

PA and RAS [2, 3]. By including many patients with PA and RAS, this study provides meaningful clinical insights that were previously unavailable.

2 | Materials and Methods

2.1 | Ethics Approval

All procedures involving human participants in this study adhered to the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. 2016-802). Written informed consent was obtained from all enrolled participants.

2.2 | Study Participants

During this retrospective study, data were continuously collected from patients diagnosed with RAS comorbid with PA following secondary hypertension screening procedures conducted from January 2016 to December 2021. The following patients were excluded: (1) those with other secondary factors triggering blood pressure elevation in addition to RAS and PA (mainly including sleep apnea syndrome, chronic kidney diseases, aortic coarctation, and other endocrine diseases); (2) those with RAS <50%; (3) those who could not undergo contrast-enhanced computed tomography (CT) examinations or contrast examinations of the renal arteries owing to severe renal dysfunction or an allergy to the contrast agent; (4) those who had been diagnosed with PA and treated regularly before admission; (5) those who had been diagnosed with RAS and had undergone renal artery intervention before admission; (6) those for whom the medication washout was not completed during the screening for PA; and (7) those with incomplete clinical data or no follow-up after diagnosis.

2.3 | Data Collection

All data were obtained from the electronic medical records at our hospital. Two researchers independently acquired the patients' demographic data, medical history, laboratory examination results, imaging examination results, and follow-up information.

2.4 | Definitions and Outcomes

2.4.1 | Screening and Diagnosis of PA

Preparation before standardized screening of PA included the following: (1) regulating blood potassium to the normal range; (2) maintaining normal sodium intake; (3) stopping the use of aldosterone receptor antagonists, diuretics, and licorice extract for at least 4 weeks; (4) stopping the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, central α_2 receptor antagonists, and non-steroid anti-inflammatory drugs for at least 2 weeks; and (5) using α-receptor antagonists and non-dihydropyridine calcium channel blockers for cases with uncontrolled blood pressure. The conditions during blood sample collection for PA screening were as follows: (1) maintaining a non-supine position (sitting or standing) for at least 2 h after waking up in the morning and collecting blood after sitting for 5–15 min; (2) avoiding hemolysis during blood sample collection; and (3) maintaining the blood samples at room temperature and sending them to the laboratory for detection and cryopreservation of the plasma following centrifugation. ARR represents the ratio of the plasma aldosterone concentration (PAC), measured in ng/dL, to the direct renin concentration (DRC), measured in mU/L. ARR is expressed as (ng/dL)/(mU/L). The PAC and DRC were determined using a chemiluminescence immunoassay. The threshold for a positive ARR was 3.7 (ng/dL)/(mU/L). The methods and criteria for the PA diagnosis were as follows: if an ARR ≥3.7 (ng/dL)/(mU/L) was detected, then a saline infusion test (SIT) and/or captopril challenge test (CCT) was conducted. The SIT involved continuous injection of 2000 mL of normal saline for 4 h, followed by PAC determination. A PAC level of <5 ng/dL was considered negative, whereas a PAC level of >10 ng/dL was considered positive. The PAC values between these two thresholds were suspected to be positive. During the CCT, patients were orally administered 50 mg captopril after 1 h of sitting or standing. The PAC, DRC, and cortisol concentrations were determined 1 and 2 h before and after administration of the medicine. A PAC inhibition rate of 30% was used as a threshold. In this study, adrenal imaging was assessed using CT and reported by two senior radiologists.

The criteria for adrenal enlargement were as follows: Diffuse enlargement (maintaining a normal shape and outline, with the length of the inner and outer branches greater than 5 cm and a thickness exceeding 10 mm); focal nodules or masses within a single adrenal gland; Multiple nodules in the adrenal gland; Smaller nodules within a nodular lesion.

Adrenal nodules were defined as round or oval masses on one or both sides of the adrenal glands. The masses are typically presented as various types of lesions, with adrenal adenomas being the most common. These usually appear as well-defined, uniformly dense, soft, round, or oval tissue masses on CT, usually located between the inner and outer branches of the adrenal gland. The mass may have an equal or near-water density. On contrast-enhanced scans, the mass may show homogeneous or heterogeneous transient enhancement. In the case of functional cortical adenomas, the contralateral adrenal gland tends to be atrophic, while in non-functional adenomas, the contralateral adrenal gland remains normal.

Adrenal hyperplasia was defined as the absence of abnormal changes in 50% of the cases. When abnormalities were present, CT typically showed bilateral adrenal enlargement. These enlargements could be diffuse or thickened, but the adrenal shape and outline generally remained normal. Alternatively, the enlargement may be accompanied by localized nodular protrusions in one or both adrenal glands, with the nodules being of equal or slightly lower density, depending on the fat density. Enhancement was usually mild, with a few cases showing moderate enhancement.

Malignant hypertension is defined as a rapid and severe increase in blood pressure, primarily characterized by an elevated diastolic pressure (≥120 mm Hg), and is accompanied by severe target organ damage. The primary organs affected are the eyes, kidneys, heart, and brain.

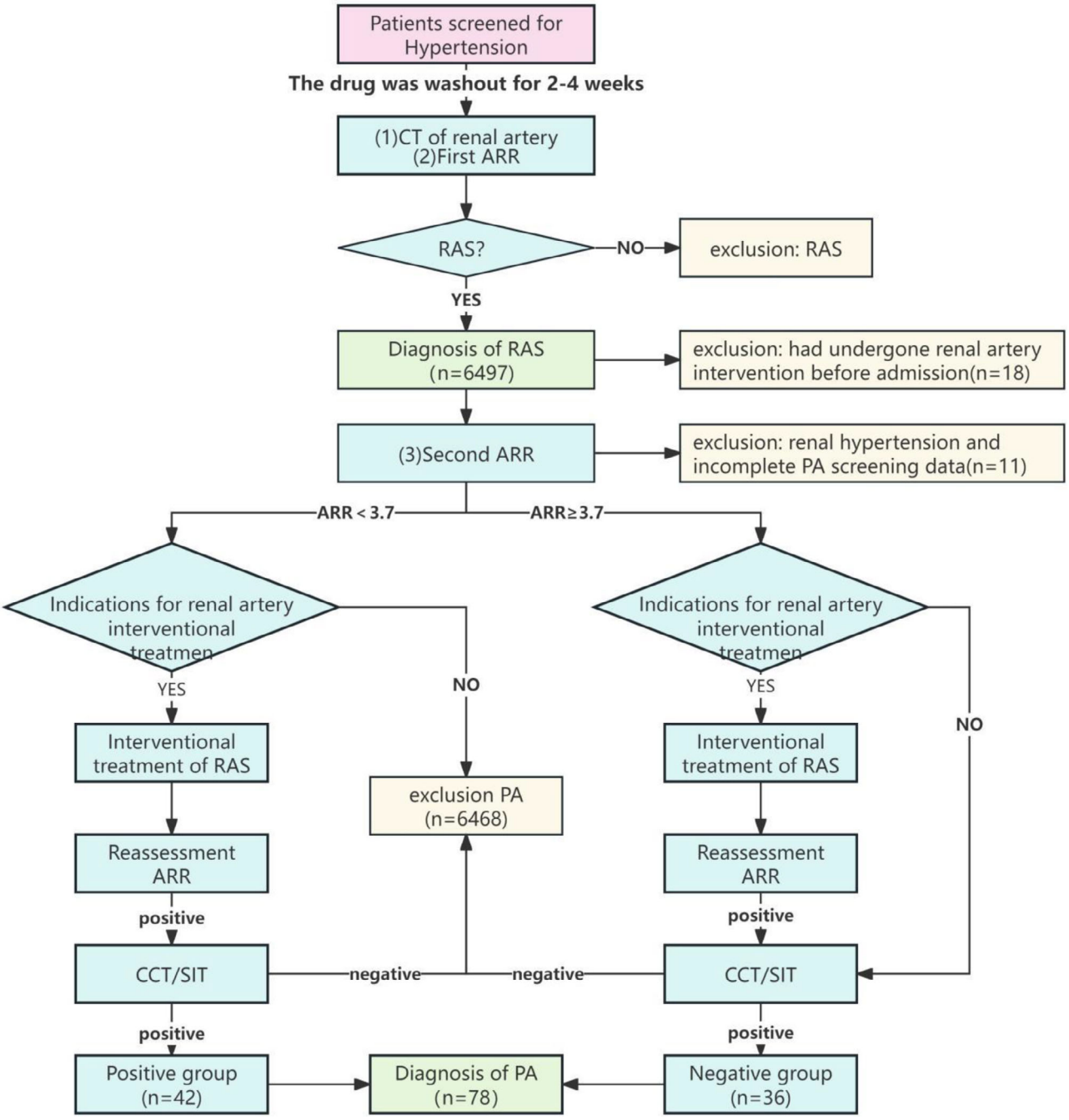

FIGURE 1 | Hypertension screening flowchart. ARR, aldosterone-to-renin ratio; CCT, captopril challenge test; PA, primary aldosteronism; RAS, renal artery stenosis; SIT, saline infusion test.

2.4.2 | Diagnosis and Treatment of RAS

All the patients were diagnosed with RAS using contrast-enhanced CT or renal arteriography, and patients with RAS ≥ 50% were included in the study. The clinical indications for RAS intervention included severe hypertension (sustained hypertension stages 2–3), malignant hypertension, refractory hypertension, worsening of hypertension or drug treatment intolerance, monofunctional kidney or bilateral RAS with renal insufficiency, monofunctional kidney or bilateral RAS with renal function deterioration, transient pulmonary edema, and unstable angina. Anatomical indications for intervention included (1) RAS exceeding 70% and (2) RAS ranging from 50% to 70%, accompanied by definitive hemodynamic evidence such as a systolic pressure gradient >20 mm Hg or mean pressure gradient >10 mm Hg. At least one clinical and anatomical indication was required for RAS intervention.

2.5 | Diagnosis and Treatment Process

Standardized medication washout was performed 2–4 weeks before admission (Figure 1). After admission, complete PA screening and enhanced renal artery CT were performed. Based on the

CT results, the patient was diagnosed with RAS. For patients with RAS, the following steps in diagnosis and treatment were carried out based on the ARR results. *Standardized status*: If the ARR value from the PA screening was ≥3.7, interventional treatment was performed based on the presence or absence of indications for renal artery intervention. If indications for intervention were present, the intervention was performed, and the ARR value was retested. After renal artery intervention, if the ARR remained ≥3.7, a diagnostic CCT/SIT was performed. If no intervention indications were present, a diagnostic CCT/SIT was performed directly. Similarly, in the standardized status, if the ARR value from the PA screening was <3.7, interventional treatment was performed based on the presence or absence of indications for renal artery intervention. For patients with indications for intervention, the intervention was performed, and the ARR was retested. After renal artery intervention, if the ARR was ≥3.7, a diagnostic CCT/SIT test was performed. If the ARR was <3.7 after the intervention, PA was excluded. Additionally, if the ARR was <3.7 and renal artery intervention due to stenosis was not indicated, PA was directly eliminated. The time for retesting the ARR after renal artery intervention is defined as 1-month post-procedure.

2.6 | Statistical Analysis

SPSS version 28.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Measurement data are expressed as the mean ± standard deviation or median with interquartile range, and comparisons were conducted using Student's *t*-tests or Mann–Whitney *U* tests. Enumeration data are expressed as a constituent ratio, and the χ^2 test was used for comparisons between the groups. Factors contributing to RAS comorbidity with false-negative PA results were identified using binary logistic regression analysis. A two-tailed test was used, and $p < 0.05$ was considered significant.

3 | Results

3.1 | Baseline Information

A retrospective analysis of 89 patients diagnosed with RAS comorbid with PA upon discharge from the hospital was performed using a medical record retrieval system. Among them, two patients with renal hypertension and nine with incomplete PA screening data were excluded. Ultimately, 78 patients who completed the PA screening and diagnostic procedure were diagnosed with RAS comorbid with PA. Baseline patient data are presented in Table 1. Among the included patients with a mean age of 60.2 ± 10.2 years and an average disease course of 17.1 ± 10.1 years, 46 were males (59%). Before admission, all the patients met the criteria for Stages 2–3 hypertension (mean systolic blood pressure, 158.3 ± 20.0 mm Hg; mean diastolic blood pressure, 92.4 ± 11.4 mm Hg). There were 69 cases of Stage 3 hypertension (88.5%), 45 cases of refractory hypertension (57.7%), 11 cases of malignant hypertension (14.1%), and 57 cases of hypokalemia (73.1%; serum potassium level, 3.16 ± 0.56 mmol/L; creatinine, 93.11 ± 38.54 μmol/L). The pathogenesis of RAS was associated with atherosclerosis (Figure 2A). Among them, 58 patients (74.4%) had abnormal adrenal gland morphology

TABLE 1 | Baseline information of the study participants.

Item	*n* = 78
Basic information	
Age, X ± *s* (years)	60.2 ± 10.2
Course of disease, X ± *s* (years)	17.1 ± 10.1
Male, *n* (%)	46 (59)
Body mass index, X ± *s* (kg/m^2)	26.63 ± 3.84
Blood pressure	
Mean systolic blood pressure, X ± *s* (mm Hg)	158.3 ± 20.0
Mean diastolic blood pressure, X ± *s* (mm Hg)	92.4 ± 11.4
Stage 3 hypertension, *n* (%)	69 (88.5)
Stage 2 hypertension, *n* (%)	9 (11.5)
Refractory hypertension, *n* (%)	45 (57.7)
Malignant hypertension, *n* (%)	11 (14.1)
Biochemical indices	
Serum creatinine, X ± *s* (μmol/L)	93.11 ± 38.54
Hypokalemia, *n* (%)	57 (73.1)
Serum potassium, X ± *s* (mmol/L)	3.16 ± 0.56
Serum sodium, X ± *s* (mmol/L)	141.91 ± 2.97
24-h urinary sodium, X ± *s* (mmol/24 h)	120.69 ± 102.81
24-h urinary potassium, X ± *s* (mmol/24 h)	37.66 ± 28.94
24-h urinary aldosterone, X ± *s* (μg/24 h)	7.41 ± 5.66
Medical treatment (before the washout)	
Types of antihypertensive drugs, X ± *s* (types)	3.4 ± 1.0
Two antihypertensive drugs, *n* (%)	18 (23.1)
Three antihypertensive drugs, *n* (%)	28 (35.9)
≥4 antihypertensive drugs, *n* (%)	32 (41.0)
Imaging of RAS features	
Bilateral RAS, *n* (%)	20 (25.6)
Unilateral RAS, *n* (%)	58 (74.4)
RAS degree, X ± *s* (%)	67.8 ± 15.9
RAS etiology, atherosclerosis, *n* (%)	100 (100)
Imaging features of adrenal gland structural abnormalities	
Structural abnormality of the adrenal gland, *n* (%)	58 (74.4)
Adrenal adenoma, *n* (%)	19 (24.4)
Adrenal nodules, *n* (%)	20 (25.6)
Adrenal hyperplasia, *n* (%)	7 (9.0)
Adrenal gland enlargement, n, (%)	15 (19.2)

Abbreviations: RAS, renal artery stenosis; X ± *s*, mean ± standard deviation.

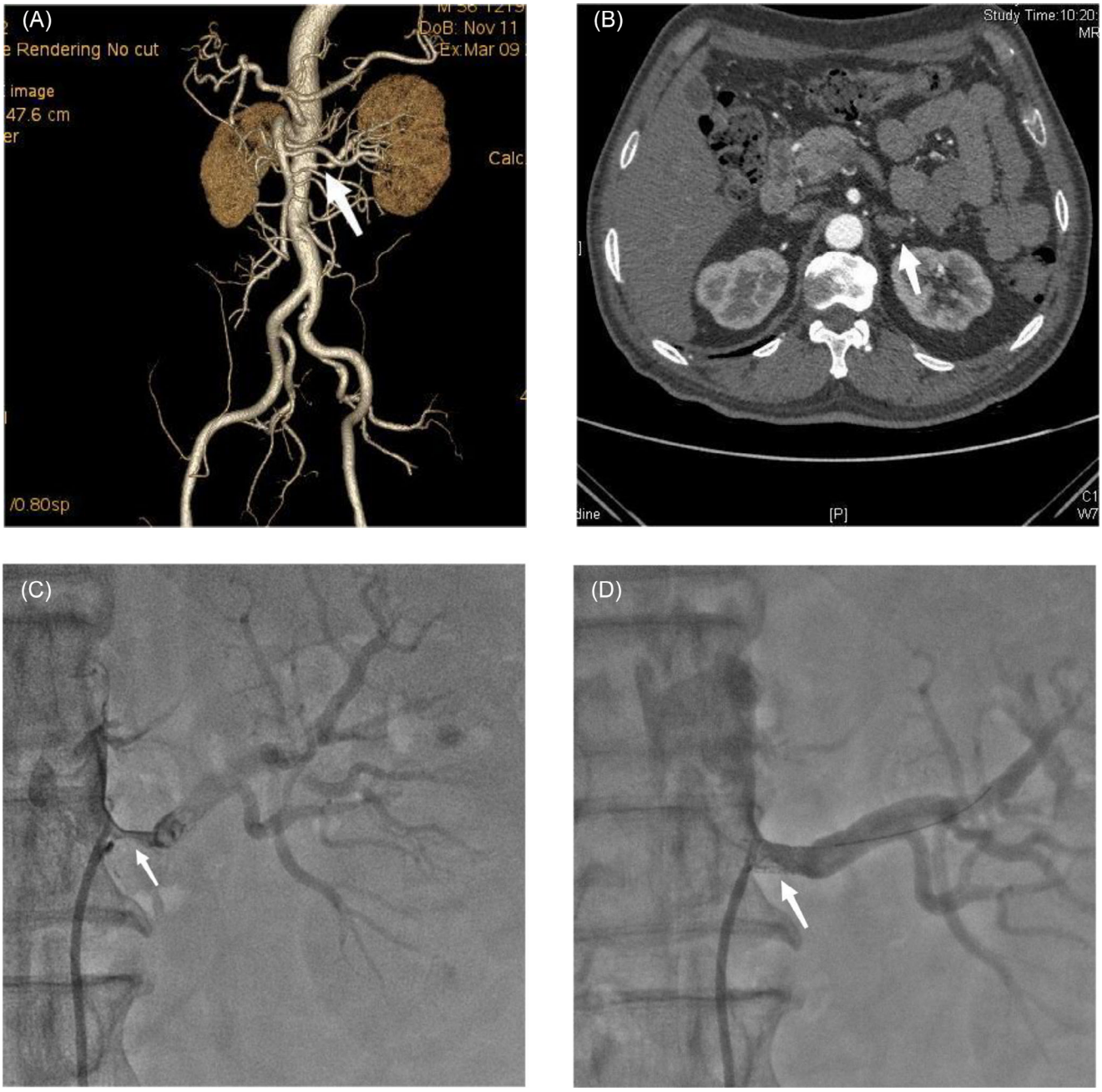

FIGURE 2 | Imaging Manifestations of Renal Artery Stenosis Combined with Primary Aldosteronism. (A) Computed tomography (CT) of the renal artery showing 90% stenosis of the left renal artery (B) CT of the renal artery showing a left adrenal nodule of approximately 13 mm in size. (C) Renal angiography revealed 90% stenosis of the left renal artery. (D) Dynamic 6 ×15 mm renal stent implanted into the left renal artery.

(Figure 2B). A total of 19, 7, 20, and 15 cases revealed adrenal adenoma, adrenal hyperplasia, adrenal nodules, and adrenal gland enlargement, respectively.

3.2 | Diagnosis and Treatment

The secondary hypertension screening process used in the present study involved several steps. Initially, standardized PA screening was conducted, and the renal artery and adrenal gland conditions were simultaneously clarified using contrast-enhanced CT examination of the renal artery. Renal artery intervention was conducted as indicated in Figure 2C,D, followed by standardized PA screening again following the intervention. If interventional treatment was not required for RAS and ARR ≥ 3.7, SIT or CCT was performed to establish a definitive diagnosis of PA. Standardized PA screening identified 42 patients (53.8%) with positive ARRs. Among these cases, renal artery intervention was performed in nine (21.4%). Following the intervention, the ARR of these nine cases remained positive, and the patients were diagnosed with PA based on the SIT or CCT results. Furthermore, the ARR of 36 patients (46.2%) after standardized PA screening was negative. Renal artery intervention was performed in all the patients (100%); however, Stage 3 hypertension persisted after

the intervention. Twenty-eight cases (77.8%) revealed abnormal adrenal gland morphology, and 27 (75.0%) had unexplained hypokalemia. After the renal artery intervention, the ARRs of all 36 patients changed from negative to positive. These patients were diagnosed with PA based on the SIT or CCT findings. The PA screening results before and after intervention in these 78 patients were as follows: PAC (20.00 [14.53, 29.88] vs. 24.00 [18.70, 31.20] ng/dL, $p = 0.207$); DRC (3.35 [1.48, 8.68] vs. 2.70 [1.30, 4.80] mU/L, $p = 0.008$); and ARR (5.19 [2.50, 15.27] vs. 6.93 [4.53, 19.83](ng/dL)/(mU/L), $p = 0.018$) (Figure 3). At the time of standardized PA screening, the patients were divided into ARR-positive and ARR-negative groups. The PA screening results before and after intervention in these ARR-positive group were as follows: PAC (19.50 [14.15, 29.88] vs. 24.35 [15.90, 37.73] ng/dL, $p = 0.056$); DRC (1.85 [0.90, 3.33] vs. 2.05 [0.70, 3.50] mU/L, $p = 0.609$); and ARR (9.80 [5.57, 28.55] vs. 9.05 [5.91, 29.63] (ng/dL)/(mU/L), $p = 0.696$) (Figure 3). The PA screening results before and after intervention in these ARR-negative group were as follows: PAC (20.75 [16.18, 30.20] vs. 24.00 [19.20, 25.80] ng/dL, $p = 0.566$); DRC (10.65 [8.13, 18.43] vs. 4.00 [2.60, 5.80] mU/L, $p < 0.001$); and ARR (2.11 [1.44, 2.90] vs. 5.08 [4.08, 9.42] (ng/dL)/(mU/L), $p < 0.001$) (Figure 3). These two groups demonstrated significant differences in the proportion of malignant hypertension (2.4% vs. 27.8%; $p = 0.002$), proportion of Stage 3 hypertension (81.0% vs. 97.2%; $p = 0.033$), and RAS degree (64.3 ± 16.4% vs. 71.8 ± 14.4%; $p = 0.032$; Table 2). According to the binary logistic regression analysis results, malignant hypertension (odds ratio [OR] = 15.250; 95% confidence interval [CI]: 1.787–130.132; $p = 0.013$) and the degree of RAS (OR = 1.034; 95% CI: 1.002–1.068; $p = 0.036$) were considered factors influencing RAS comorbidity with false-negative PA (Table 3).

Renal artery interventions were performed in 45 patients. A subgroup analysis of 45 patients who underwent renal artery intervention was performed (Table 4). The degree of RAS (73.9 ± 14.0% vs. 59.4 ± 14.6%, $p < 0.001$) was significantly higher in the group treated with renal artery intervention compared to the group without intervention. The results of standardized PA screening performed before renal artery intervention and those of standardized PA screening performed after renal artery intervention were as follows: PAC (21.30 [15.30, 30.70] vs. 23.00 [18.88, 27.20] ng/dL, $p = 0.975$); DRC (8.60 [3.55, 16.10] vs. 3.55 [2.35, 5.75] mU/L, $p = 0.001$); and ARR (2.51 [1.78, 3.84] vs. 5.46 [4.12, 10.17] (ng/dL)/(mU/L), $p = 0.002$) (Figure 3). Following renal artery intervention and standardized drug therapy, the DRC decreased significantly, whereas the PAC did not. The rate of positive PA screening results increased from 53.8% to 100.0% with an increase in the ARR.

4 | Discussion

Both RAS and PA are common causes of secondary hypertension with prevalence rates of 1%–10% and 5%–20%, respectively [4, 5–7]. No large-scale epidemiological reports on the prevalence of RAS comorbid with PA have been published, and most of the current literature is limited to case reports [1, 8]. A previous study found that approximately 33% of patients preliminarily diagnosed with RAS had refractory hypertension following renal arterial revascularization with an increased ARR; moreover, 27% were diagnosed with PA [9].

Hyperaldosteronism may cause atherosclerosis by activating the inflammatory response, leading to endothelial cell dysfunction and vascular remodeling [10–13]. Moreover, these changes are not solely affected by blood pressure changes. All RAS cases in this study were attributed to atherosclerotic lesions. Although the RAS and PA sequences in these patients could not be confirmed through observational studies, this phenomenon was consistent with the aforementioned reasoning. It has been hypothesized that an increase in the renin activity triggered by RAS causes secondary hyperaldosteronism. Prolonged exposure to the elevated renin levels could potentially induce the adrenal gland to develop functionally autonomous hyperplasia or adenomas capable of independently producing excessive aldosterone. However, this hypothesis has not been confirmed by previous studies [14, 15]. In summary, when the RAS coexists with PA, it impacts the RAAS in various ways. Consequently, the changes in the PAC and DRC vary from those observed in the presence of RAS or PA alone, potentially influencing the ARR. When one factor is regulated, changes in the levels of the other hormones are observed, thereby revealing the original disease state.

One of the most important clinical manifestations of RAS and PA is uncontrolled hypertension. In this study, 88.5% of the patients had Stage 3 hypertension, 57.7% had refractory hypertension, and 14.1% had malignant hypertension. Moreover, 76.9% of the patients used three or more antihypertensive drugs (average, 3.4 ± 1.0 drugs). When RAS was complicated by PA, hyperaldosteronism was diagnosed based on the laboratory examination findings, and the average standardized aldosterone level during this study was 20.00 (14.53, 29.88) ng/dL. Recently, many studies have demonstrated that PA may manifest as hypertension with normal serum potassium levels, accounting for 39%–50% of PA cases [16, 17]. Therefore, hypokalemia cannot be considered a definite criterion for the diagnosis of PA [18], nor can normal serum potassium levels be considered a sufficient criterion for excluding the possibility of PA. However, we found that the average serum potassium level of the included patients was 3.16 ± 0.56 mmol/L, which was significantly lower than the normal range, and the proportion of hypokalemia was 73.1%. This might be attributable to the dual effect of RAS comorbid with PA, thus making the low blood potassium level more obvious than that in patients with a single disease.

ARR is often influenced by many factors, among which RAS is important [19]. Additionally, the use of multiple antihypertensive drugs for refractory hypertension can influence the ARR. In this study, a detailed comparison of various influencing factors during PA screening of patients with RAS was performed. The comparison between the ARR-negative and -positive groups indicated significant differences in the proportion of patients with Stage 3 hypertension, the proportion of patients with malignant hypertension, and the degree of RAS. Binary logistic regression analysis indicated that malignant hypertension and RAS degree influenced false-negative ARRs in patients with RAS comorbid with PA. Malignant hypertension may excessively activate the RAAS, leading to a significant increase in the DRC accompanied by an increase in the PAC and angiotensin II. Owing to severe stenosis and excessive renin response, the negative feedback mechanism of the RAAS is disrupted, resulting in a vicious cycle causing a sharp increase in the blood pressure. The insufficient blood supply induced by RAS results in decreased blood pressure

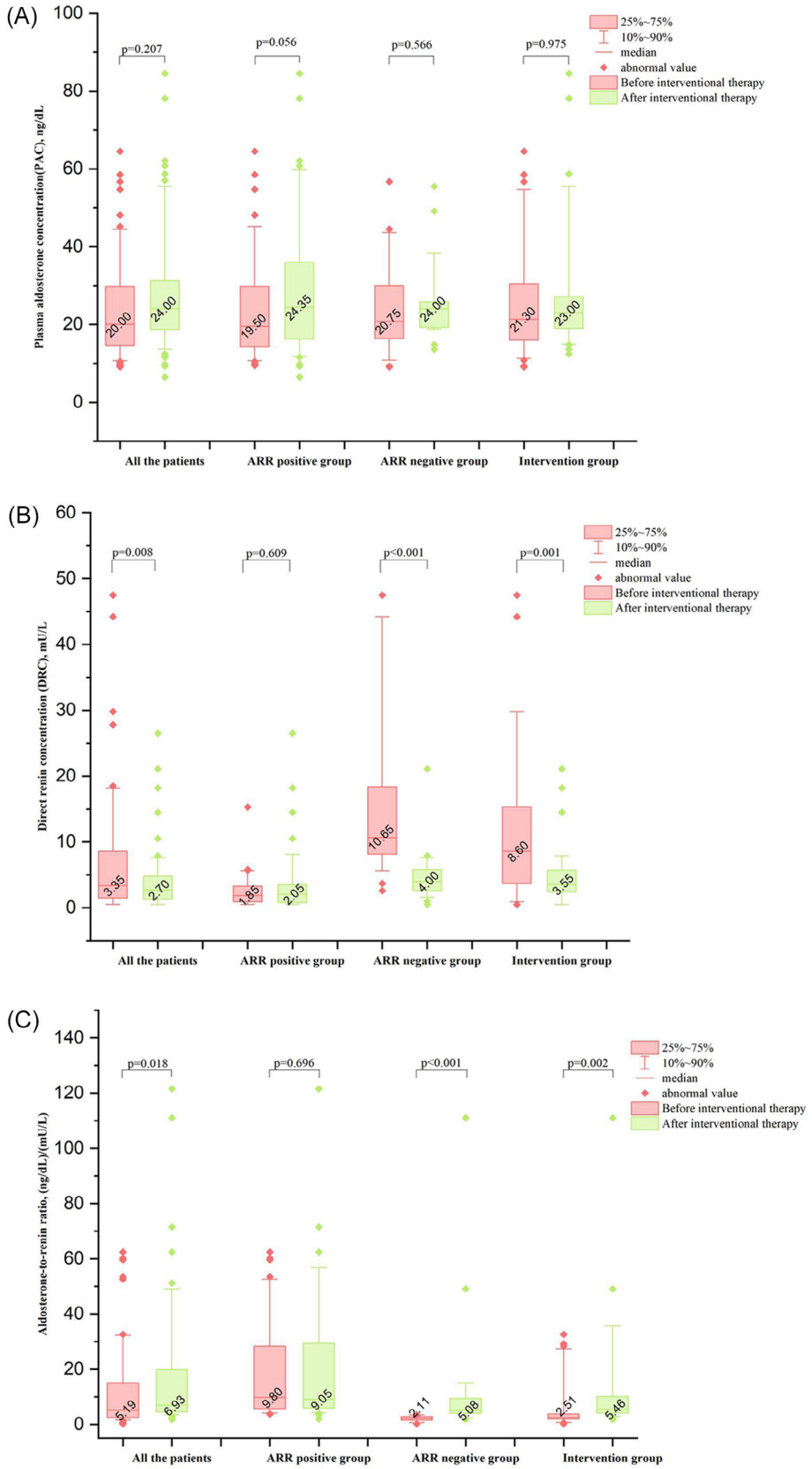

FIGURE 3 | The changes of plasma aldosterone concentration (PAC), direct renin concentration (DRC), and aldosterone-to-renin ratio(ARR). (A) The change of plasma aldosterone concentration (PAC), measured in ng/dL. (B) The change of direct renin concentration (DRC), measured in mU/L. (C) The change of aldosterone-to-renin ratio (ARR). ARR is expressed as (ng/dL)/(mU/L).

TABLE 2 | Comparison of groups with positive and negative standardized PA screening results.

Item	ARR-positive group, $n = 42$	ARR-negative group, $n = 36$	*P*-value
Basic information			
Age, X ± *s* (years)	61.3 ± 10.8	58.8 ± 9.6	0.428
Disease course, X ± *s* (years)	18.7 ± 10.6	15.3 ± 9.3	0.565
Male, *n* (%)	23 (54.8)	23 (63.9)	0.491
Body mass index, X ± *s* (kg/m^2)	26.51 ± 3.42	26.77 ± 4.34	0.238
Blood pressure			
Mean systolic blood pressure, X ± *s* (mm Hg)	159.4 ± 20.3	157.1 ± 19.9	0.528
Mean diastolic blood pressure, X ± *s* (mm Hg)	91.9 ± 10.2	93.0 ± 12.7	0.101
Stage 3 hypertension, *n* (%)	34 (81.0)	35 (97.2)	0.033*
Refractory hypertension, *n* (%)	25 (59.5)	20 (55.6)	0.819
Malignant hypertension, *n* (%)	1 (2.4)	10 (27.8)	0.002*
Biochemical indices			
Hypokalemia, *n* (%)	30 (71.4)	27 (75.0)	0.801
Serum potassium, X ± *s* (mmol/L)	3.13 ± 0.61	3.20 ± 0.49	0.174
Serum sodium, X ± *s* (mmol/L)	142.10 ± 3.04	141.70 ± 2.91	0.750
Serum creatinine, X ± *s* (μmol/L)	85.71 ± 25.05	101.75 ± 48.89	0.211
24-h urinary aldosterone, X ± *s* (mmol/L)	7.52 ± 6.60	7.27 ± 4.22	0.115
24-h urinary natrium, X ± *s* (mmol/24 h)	106.33 ± 59.04	137.66 ± 136.99	0.062
24-h urinary potassium, X ± *s* (mmol/24 h)	39.21 ± 32.85	35.82 ± 23.89	0.791
Before interventional therapy			
PAC, M [P25, P75] (ng/dL)	19.50 (14.15, 29.88)	20.75 (16.18, 30.20)	—
DRC, M [P25, P75] (mU/L)	1.85 (0.90, 3.33)	10.65 (8.13, 18.43)	—
ARR, M [P25, P75] (ng/dL)/(mU/L)	9.80 (5.57, 28.55)	2.11 (1.44, 2.90)	—
After interventional therapy			
PAC, M [P25, P75] (ng/dL)	24.35 (15.90, 37.73)	24.00 (19.20, 25.80)	—
DRC, M [P25, P75] (mU/L)	2.05 (0.70, 3.50)	4.00 (2.60, 5.80)	—
ARR, M [P25, P75] (ng/dL)/(mU/L)	9.05 (5.91, 29.63)	5.08 (4.08, 9.42)	—
Abnormal anatomy			
RAS degree, X ± *s* (%)	64.3 ± 16.4	71.8 ± 14.4	0.032*
Structural abnormality of the adrenal gland, *n* (%)	30 (71.4)	28 (77.8)	0.608
Medical treatment (Before the washout)			
Types of antihypertensive drugs, X ± *s* (types)	3.4 ± 1.0	3.3 ± 1.0	0.625
α-Receptor antagonist, *n* (%)	19 (45.2)	17 (47.2)	1.000
β-Receptor antagonist, *n* (%)	23 (54.8)	22 (61.1)	0.649
ACEI/ARB, *n* (%)	38 (90.5)	29 (80.6)	0.328
CCB, *n* (%)	42 (100.0)	34 (94.4)	0.210
Diuretics, *n* (%)	25 (59.5)	21 (58.3)	1.000

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotonin II receptor blocker; ARR, aldosterone-to-renin ratio; CCB, calcium channel blockers; DRC, direct renin concentration; M median; PA, primary aldosteronism; PAC plasma aldosterone concentration; P25, the first quartile; P75, the third quartile; RAS, renal artery stenosis; X ± *s*, mean ± standard deviation.

*$p < 0.05$.

TABLE 3 | Binary logistics regression analysis of standardized PA screening false-negative results.

	OR	95% CI	*p* value
Malignant hypertension	15.250	1.787–130.132	0.013*
RAS degree	1.034	1.002–1.068	0.036*
Stage 3 hypertension	5.371	0.612–47.131	0.129

Abbreviations: CI, confidence interval; OR, odds ratio; PA, primary aldosteronism; RAS, renal artery stenosis.
*$p < 0.05$.

and reduced flow in the renal afferent arterioles, which in turn stimulate the stretch receptors on the afferent arteriole wall and increase renin secretion from the juxtaglomerular cells. The glomerular filtration rate and amount of Na^+ flowing to the macula densa decrease, activating the macula densa receptors. The RAAS is then activated, altering the level of vasoactive substances, such as the DRC, angiotensin II, and PAC causing blood pressure elevation. Common features of malignant hypertension and RAS include decreased kidney perfusion and RAAS activation. However, the increase in the DRC is markedly higher than that in the PAC, which might influence false-negative ARRs.

We conducted a subgroup analysis of patients who underwent renal artery interventions. Following renal artery intervention, the DRC level decreased significantly ($p < 0.05$), the ARR increased, and the rate of positive PA screening results increased from 53.8% to 100.0%, when no obvious change was observed in the PAC. These results indicate that RAS may counteract the suppression of renin activity by stimulating renin secretion, thus causing a decrease in the ARR leading to false-negative results. These findings validate our hypothesis. After renal artery intervention, RAS interference was excluded, revealing the true manifestation of the disease, and positive ARRs were observed.

In 2016, the American Association of Clinical Endocrinologists [20] suggested that PA screening should be conducted in patients with refractory hypertension, severe hypertension, suspected familial hypertension, hypertension accompanied by hypokalemia, adrenal incidentaloma, and obstructive sleep apnea. The PA guidelines of the European Society of Hypertension 2020 have adjusted the PA screening recommendations for different categories of patients based on new evidence [21]. The screening population included patients with moderate-to-severe hypertension; patients with hypertension and spontaneous or diuretic-induced hypokalemia, adrenal incidentaloma, and atrial fibrillation without structural heart disease; patients with early onset hypertension or a family history of stroke at a young age (younger than 40 years); and patients with PA and relatives with Stage 1 hypertension. For specific cases of RAS comorbid with PA, the exclusion of PA based on negative ARRs resulted in a high rate of missed diagnoses. To prevent missed diagnoses of RAS coexisting with PA in patients with suspected secondary hypertension, patients with RAS and clinical manifestations of malignant hypertension or severe RAS should undergo retesting following renal artery interventional therapy according to the standard algorithm.

TABLE 4 | Compare the relevant information of the intervention group and the non-intervention group of renal artery stenosis.

Factor	*n* = 45	*n* = 33
Basic information		
Age, X ± *s* (years)	60.0 ± 9.9	60.5 ± 10.9
Disease course, X ± *s* (years)	17.1 ± 10.4	17.2 ± 9.9
Male, *n* (%)	27 (60.0)	19 (57.6)
Body mass index, X ± *s* (kg/m^2)	26.99 ± 4.56	26.45 ± 3.53
Blood pressure		
Mean systolic blood pressure, X ± *s* (mm Hg)	157.2 ± 17.2	160.6 ± 12.1
Mean diastolic blood pressure, X ± *s* (mm Hg)	92.4 ± 11.7	92.5 ± 10.2
Stage 3 hypertension, *n* (%)	43 (95.6)	26 (78.8)
Stage 2 hypertension, *n* (%)	2 (4.4)	7 (21.2)
Refractory hypertension, *n* (%)	25 (55.6)	20 (60.6)
Malignant hypertension, *n* (%)	10 (22.2)	1 (3.0)
Biochemical indices		
Serum creatinine, X ± *s* (μmol/L)	100.67 ± 45.73	82.80 ± 22.58
Hypokalemia, *n* (%)	34 (75.6)	23 (69.7)
Serum potassium, X ± *s* (mmol/L)	3.17 ± 0.52	3.15 ± 0.62
Serum sodium, X ± *s* (mmol/L)	141.74 ± 2.62	141.97 ± 3.35
24-h urinary sodium, X ± *s* (mmol/24 h)	139.38 ± 173.48	104.99 ± 57.82
24-h urinary potassium, X ± *s* (mmol/24 h)	33.10 ± 15.73	41.00 ± 36.22
24-h urinary aldosterone 24, X ± *s* (μg/24 h)	7.46 ± 5.53	7.35 ± 5.94
Standardized ARR screening of PA		
Positive, *n* (%)	9 (20.0)	33 (100.0)
Negative, *n* (%)	36 (80.0)	0 (0)

Abbreviations: ARR, aldosterone-to-renin ratio; DRC, direct renin concentration; PA, primary aldosteronism; PAC, plasma aldosterone concentration; X ± *s*, mean ± standard deviation.
*$p < 0.05$.

In conclusion, for patients with RAS comorbid with PA, standardized ARR screening demonstrated a false-negative rate of approximately 50%. However, this study suggests that malignant hypertension and RAS are important influencing factors that contribute to false-negative PA screening results. Therefore, the results of standardized ARR screening should be interpreted with

caution in patients with RAS comorbid with PA, and patients with suspected secondary hypertension should be retested following RAS treatment to avoid misdiagnosis. Future prospective studies with larger sample sizes are warranted to achieve a uniform and standardized diagnostic process that can be used in clinical practice.

Author Contributions

Qian Wang, Hui Dong, Hongwu Li, and Yujie Zuo: investigation, extracted the data, formal analysis, writing, and editing original draft. Qian Wang, Yubao Zou, and Xiongjing Jiang: design of the study. Qian Wang, Yubao Zou, and Xiongjing Jiang: conceptualization, writing, review, and editing. All authors reviewed and approved the manuscript.

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Ethics Statement

This study was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. 2016-802).

Consent

Written informed consent was obtained from all enrolled participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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