Int J Clin Exp Med 2020;13(11):8765-8773
www.ijcem.com /ISSN:1940-5901/IJCEM0118448

Original Article

A study on early clinical screening and intervention scheme for primary hyperaldosteronism

Yuwei Xing, Xuejiao Chai, Yongqiang Ma

Department of Endocrinology, The Second Hospital of Shijiazhuang, Shijiazhuang, Hebei Province, China

Received July 19, 2020; Accepted August 15, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: To explore the early clinical screening and intervention scheme for primary aldosteronism (PA). Methods: 70 patients with PA and 90 patients with essential hypertension (EH) were selected as the observation group and control group respectively for the retrospective study. The clinical data of the two groups were compared, and the association between aldosterone-to-renin ratio (ARR), cardiac echocardiographic parameters, and cervical vascular ultrasound parameters with PA was analyzed using univariate and multivariate analysis. The ROC curve was drawn to explore the diagnostic efficacy of the meaningful indicators in multivariate analysis for PA. Besides, patients with PA were divided into group A and group B according to different treatment methods. Group B received conventional therapy, while group A adopted additional irbesartan based on conventional therapy. The efficacy and safety of these two methods were then compared. Results: Multivariate logistics regression analysis showed that ARR (OR=3.149; P=0.015; 95% CI: 2.359-3.911), LVEDD (OR=2.044; P=0.018; 95% CI: 1.542-2.710), LVESD (OR=1.504; P=0.022; 95% CI: 0.956-2.053), LVEF (OR=2.790; P=0.008; 95% CI: 2.401-3.158), intima-media thickness of common carotid artery (OR=2.768; P=0.011; 95% CI: 2.266-3.137), and intima-media thickness of internal carotid artery (OR=2.303; P=0.026; 95% CI: 1.573-2.822) were all independent risk factors for PA (all P<0.05). ROC curve analysis showed that the AUC of ARR, LVEF, and medical thickness of common carotid artery media thickness were 0.741, 0.738 and 0.637 respectively, all of which were greater than 0.5, indicating their diagnostic value for PA. Besides, combined diagnosis could further improve the diagnostic efficacy, with an AUC of 0.845 and sensitivity and specificity of 91.46% and 88.42%, respectively (Z=2.079, P<0.05). The research about different treatment schemes revealed that total effective rate of group A was significantly higher than that in group B (P<0.05). After treatment, the blood pressure and cardiac function indexes in both groups were significantly improved (P<0.05 or P<0.001), but more significant improvement was found in group A (all P<0.05). At the same time, the incidence of total adverse reactions in group A was slightly lower than that in group B, but without statistically significant difference (P>0.05). What is more, the maintenance dose of spironolactone in group A was much lower than that in group B (P<0.05). Conclusion: ARR, LVEF and intima-media thickness of the carotid artery are all independent risk factors for PA, through which PA can be effectively screened and diagnosed. At the same time, combination of irbesartan and conventional clinical therapy can further improve the therapeutic effect with higher safety.

Keywords: Primary aldosteronism, clinical screening, plasma aldosterone/renin ratio, cardiac echocardiographic parameter, common carotid artery media thickness, intervention program

Introduction

Primary aldosteronism (PA) means excessive secretion of aldosterone by adrenal cortex, with main clinical presentation as hypertension with hypokalemia. PA was considered to be a rare disease previously, but the use of aldosterone-to-renin ratio (ARR) has greatly increased the detection rate of PA [1]. The latest research shows that PA accounts for 5-13% of all the hypertensive patients, and it goes up to 20% among patients with refractory hypertension [2, 3]. In addition to increased blood pressure, high plasma aldosterone levels in patients with PA also damage other body functions. Besides, patients with PA are more prone to heart, brain, kidney and other organ damage compared with patients with essential hypertension (EH) [4]. However, despite the high prevalence and risk, missed clinical diagnosis of PA is still very serious because some physicians still rely solely on hypertension with hypokalemia for diagnosis. In

fact, about half of the PA patients may not suffer from hypokalemia, thus a large number of PA patients were misdiagnosed as EH for a long time which delayed the treatment [5, 6]. Moreover, the insufficient capacity of ARR inspection has also markedly affected the detection of PA. Therefore, it is crucial to strengthen the screening of PA. Comprehensive report on the screening of patients with PA is rare at present, thus our study conducted associated exploration. At the same time, we also tested the therapeutic efficacy and safety of the combination of irbesartan and spironolactone with a view to provide a theoretical basis for clinical practice. The research results are presented as follows.

Materials and methods

General information

Seventy patients with PA who were admitted to The Second Hospital of Shijiazhuang during January 2020 to December 2014 were selected as the observation group.

Inclusion criteria: (1) all the patients were diagnosed according to the diagnostic criteria of the 2016 European Endocrine Association *Management of primary aldosteronism: Case screening, diagnosis and treatment* [7]. The patients were initially screened by ARR and diagnosed through intravenous saline load test or surgery; (2) the patient had complete clinical data related to this study; (3) the patients had undergone drug elution before PA screening: Diuretics were discontinued for at least 6 weeks prior; other drugs that might affect ARR screening such as beta-blockers, AT2 receptor antagonists, angiotensin-converting enzyme inhibitors, and dihydropyridine calcium channel blockers were stopped for at least 4 weeks; alpha-blockers and non-dihydropyridine calcium channel blockers were used to control the blood pressure; (4) all the patients voluntarily participated in this study and signed the informed consent.

Exclusion criteria: (1) patients with secondary hypertension such as renal parenchymal hypertension, pheochromocytoma, renal vascular hypertension, and hypercortisolism; (2) patients complicated with coronary heart disease.

At the same time, 90 patients with EH admitted to The Second Hospital of Shijiazhuang during the same time period were randomly selected as the control group. Diagnosis of EH was made according to the Guidelines for the Prevention and Treatment of Hypertension: systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg without taking antihypertensive drugs in the absence of any apparent reason [8].

According to the different treatment regimens, the patients with PA were divided into groups A and group B. Group B (38 cases) received routine clinical therapies and group A (32 cases) adopted additional irbesartan on the basis of routine clinical therapies. This study was reviewed and approved by the Ethics Committee of The Second Hospital of Shijiazhuang.

Methods

Clinical data collection: The clinical data of the patients including age, gender, body mass index, symptoms, systolic/diastolic blood pressure, blood biochemical indexes, ARR, echocardiographic parameters of heart, and cervical vascular ultrasound parameters were collected. A mercury sphygmomanometer was used for blood pressure measurement, which was calibrated before use. Patients were forbidden to consume strong tea and coffee, or smoke 30 minutes before the measurement, and were advised to take rest quietly for at least 5 minutes and not to hold urine or speak during the measurement. During the measurement, the patients were kept in a sitting position. Two consecutive measurements were taken on different days and the average value was noted. All the patients had finished drug elution before the blood samples were collected. The patients need to rest on lying position from 22:00 on the day of admission and the venous blood was drawn in a lying position at 06:00 the next day after admission. After the blood was drawn, the patients were asked to maintain a sitting position for another 2 hours. Then, the venous blood was drawn at 08:00 for aldosterone, renin activity, and ARR measurement.

In addition, fasting cubital venous blood was collected in the morning. Blood biochemical indicators were detected by automatic bio-

chemical analyzer (Shandong Boke Biological Industry Co., Ltd. BK200).

ARR assay method: Radioimmunoassay was used to determine plasma renin activity (Renin kit: Beijing North Institute of Biotechnology) and aldosterone (Beijing North Institute of Biotechnology).

Ultrasound examination (Philips iE Elite color Doppler ultrasound diagnostic apparatus; Phillips, US): Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fractions (LVEF), and other indicators were collected by echocardiography. Intima-media thickness of common carotid artery and internal carotid artery were measured through carotid ultrasonography, which were examined according to the Guidelines for Carotid Ultrasound Examination, and the mean values on both sides were used as experimental data. Ultrasound examination and report issuance were performed by physicians above the intermediate level in The Second Hospital of Shijiazhuang [9].

Treatment methods: Group B was treated with routine clinical therapies, including taking spironolactone (manufacturer: Hangzhou Minsheng Pharmaceutical Group Co., Ltd.) and calcium channel blockers (levamlodipine maleate tablets, manufacturer: CSPC Ouyi Pharmaceutical Co., Ltd.) and symptomatic treatment for complications. Group A was treated with irbesartan (manufacturer: Hangzhou Sanofi Aventis Minsheng Pharmaceutical Co., Ltd.) 150 mg/d based on the routine methods in group B. The initial dose of spironolactone was 80 mg/d, to be completed for 2-3 times orally. During the treatment period, the changes in serum potassium levels were monitored, and the dose of spironolactone was adjusted to insure that the serum potassium concentration should not exceed 5.5 mmol/L, and at last the selected dose was taken as maintenance dose. The adverse reactions in both groups during treatment were observed, and the efficacy was evaluated 3 months after treatment. At last, the blood pressure and echocardiographic results before and after the treatment were compared.

Outcome measures

(1) Comparison of clinical data between observation group and control group; (2) Analysis of the risk factors of PA; (3) Receiver operating characteristic (ROC) analysis of the diagnostic value of independent risk factors; (4) Comparison of efficacy between group A and group B; (5) Comparison of maintenance dose of spironolactone between group A and group B and incidence of adverse reactions during treatment.

Efficacy evaluation criteria

Efficacy evaluation criteria: According to the Expert Consensus on Diagnosis and Treatment of Primary Aldosteronism, markedly effective was defined as systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and complete disappearance of symptoms; effective was defined as a reduction in systolic and diastolic blood pressure of >10 mmHg but did not reach the normal level, and an improvement in symptoms; ineffective was defined as no significant improvement in blood pressure and symptoms [10]. The total effective rate = markedly effective rate + effective rate.

Statistical methods

The statistical analysis was performed using SPSS 25.0. The enumeration data was expressed as percentage (n, %), and was compared with Chi-square test. Measurement data was expressed as mean ± standard deviation ($\bar{x}$ ± sd), and independent-samples t-test and paired-samples t-test were used for inter-group comparison and intra-group comparison, respectively. A multivariate logistic regression model was used to evaluate risk factors. ROC curve was drawn to evaluate the diagnostic efficiency, and Z test was used to compare the area under the curve (AUC). $P<0.05$ was considered as statistically significant.

Results

Comparison of clinical data between the observation group and control group

The comparison between the two groups showed that there existed significant differences in periodic paralysis, serum potassium levels, sitting aldosterone levels, sitting renin activity, ARR, LVEDD, LVESD, LVEF, common carotid artery media thickness, and internal carotid artery media thickness between the two groups (all $P<0.05$). As shown in **Table 1**.

Table 1. Comparison of clinical data between observation group and control group [n (%)/($\bar{x}$ ± sd)]

Index	Observation group (n=70)	Control group (n=90)	χ^2/t	P
Gender			0.423	0.515
Male	44 (62.86)	52 (57.78)		
Female	26 (37.14)	38 (42.22)		
Age (years)	46.5±8.2	44.4±7.9	1.657	0.100
BMI (kg/m^2)	25.81±3.15	25.18±3.62	1.175	0.242
Symptoms				
Dizziness and headache	41 (58.57)	52 (57.78)	0.010	0.920
Fatigue	33 (47.14)	46 (51.11)	0.248	0.618
Palpitation	38 (54.29)	44 (48.89)	0.459	0.498
Chest tightness	19 (27.14)	25 (27.78)	0.008	0.929
Periodic paralysis	8 (11.43)	0 (0.00)	8.555	0.003
Systolic blood pressure (mmHg)	161.34±21.07	159.82±19.15	0.471	0.638
Diastolic blood pressure (mmHg)	96.84±14.67	97.20±14.16	0.156	0.876
Serum potassium (mmol/L)	3.74±0.33	3.95±0.36	3.837	<0.001
Serum sodium (mmol/L)	141.35±1.68	140.98±1.72	1.368	0.174
Triglycerides (mmol/L)	2.57±0.28	2.61±0.31	0.855	0.394
Total cholesterol (mmol/L)	2.08±0.57	2.15±0.71	0.692	0.490
High density lipoprotein (mmol/L)	1.33±0.32	1.31±0.26	0.425	0.672
Low density lipoprotein (mmol/L)	3.03±0.69	3.12±0.74	0.793	0.429
Fasting blood glucose (mmol/L)	5.21±1.20	5.26±1.24	0.258	0.797
Serum creatinine (μmol/L)	69.18±16.43	68.95±15.57	0.090	0.929
Sitting aldosterone (ng/mL)	0.45±0.33	1.71±1.20	9.510	<0.001
Sitting renin activity (ng/mL•h)	24.21±10.57	13.25±7.17	7.445	<0.001
ARR (ng/dL)/(ng/mL•h)	83.29±66.18	16.40±14.38	8.305	<0.001
LVEDD (mm)	55.41±3.17	48.37±5.62	10.011	<0.001
LVESD (mm)	36.11±3.10	30.54±3.58	10.532	<0.001
LVEF (%)	58.23±5.49	66.37±6.40	8.649	<0.001
Intima-media thickness of common carotid artery (mm)	0.66±0.15	0.59±0.12	3.190	0.002
Intima-media thickness of internal carotid artery (mm)	0.57±0.11	0.52±0.10	2.967	0.004

Note: BMI: body mass index; ARR: aldosterone-to-renin ratio; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fractions.

Analysis of risk factors of PA

Indicators with inter-group differences were analyzed by univariate analysis, including serum potassium, sitting aldosterone, sitting renin activity, ARR, LVEDD, LVESD, LVEF, common carotid artery media thickness, and internal carotid artery media thickness. These above indicators were included as independent variables for multivariable logistic regression analysis. The results showed that ARR (OR=3.149; P=0.015; 95% CI: 2.359-3.911), LVEDD (OR=2.044; P=0.018; 95% CI: 1.542-2.710), LVESD (OR=1.504; P=0.022; 95% CI: 0.956-2.053), LVEF (OR=2.790; P=0.008; 95% CI: 2.401-3.158), common carotid artery media thickness (OR=2.768; P=0.011; 95% CI: 2.266-3.137), and internal carotid artery media thickness (OR=2.303; P=0.026; 95% CI: 1.573-2.822) were all independent risk factors for PA (all P<0.05). See **Table 2**.

ROC curve analysis for diagnosis of PA by independent risk factors

The index with the most contributive OR in these independent risk factors for PA was used as the diagnostic index, and the ROC curve was

Table 2. Multivariate logistic regression analysis of patients with PA (n=160)

Factors	B	Wald	P	OR (95% CI)
Serum potassium	0.141	3.512	0.084	1.152 (0.761-1.743)
Sitting aldosterone	0.335	1.647	0.126	1.398 (0.742-1.890)
Sitting renin activity	0.497	1.318	0.147	1.644 (0.818-2.255)
ARR	1.147	6.681	0.015	3.149 (2.359-3.911)
LVEDD	0.715	6.282	0.018	2.044 (1.542-2.710)
LVESD	0.408	6.157	0.022	1.504 (0.956-2.053)
LVEF	1.026	8.360	0.008	2.790 (2.401-3.158)
Intima-media thickness of common carotid artery	1.018	8.253	0.011	2.768 (2.266-3.137)
Intima-media thickness of internal carotid artery	0.834	5.972	0.026	2.303 (1.573-2.822)

Note: PA: primary aldosteronism; ARR: aldosterone-to-renin ratio; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fractions; OR: odds ratio; CI: confidence interval.

Table 3. ROC curve analysis for diagnosis of PA by independent risk factors

Index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	Cut-off value
ARR	75.38	74.37	80.46	70.69	0.741 (0.658, 0.824)	50.242
LVEF	71.52	74.13	81.35	72.84	0.738 (0.660, 0.815)	64.353
Medical thickness of common carotid artery	61.79	68.82	82.14	73.71	0.637 (0.549, 0.725)	0.630
Combination	91.46	88.42	90.73	85.45	0.845 (0.780, 0.910)	

Note: PA: primary aldosteronism; ARR: aldosterone-to-renin ratio; LVEF: left ventricular ejection fractions; AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value.

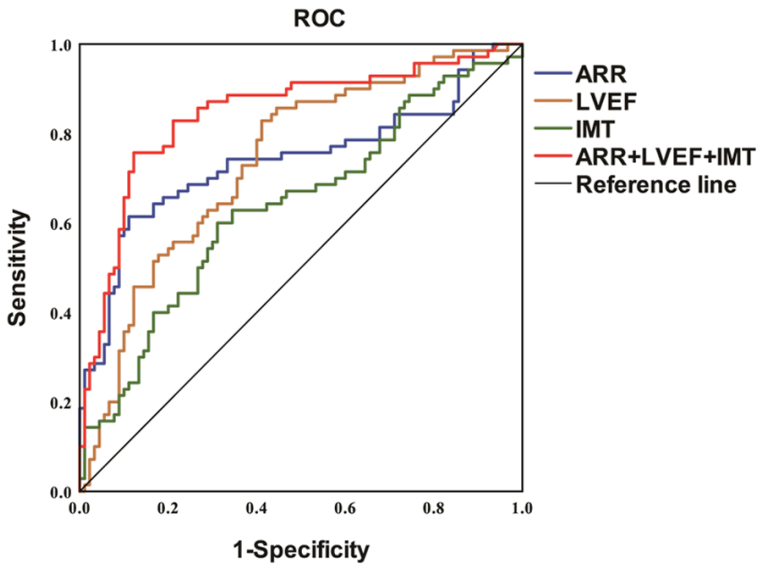

Figure 1. ROC curve for PA diagnosis. PA: primary aldosteronism; ARP: angiotensin-to-renin ratio; LVEF: left ventricular ejection fraction; IMT: Intima-media thickness; ROC: receiver operating characteristic.

drawn to analyze its diagnostic efficacy for PA. The results showed that AUCs of ARR, LVEF, and intima-media thickness of the carotid artery were 0.741, 0.738 and 0.637, respectively, which were all greater than 0.5, indicting high diagnostic efficacy. According to the Youden index calculation rule, the cut-off values of ARR, LVEF, and medial thickness of the common carotid artery were 50.242, 64.353 and 0.630, respectively. The results showed that the AUC of combined diagnosis was 0.845, which was significantly higher than that of ARR, LVEF, and medial thickness of the common carotid artery alone (Z=2.079, P<0.05), with the sensitivity and specificity of 91.46% and 88.42%, respectively, as shown in **Table 3** and **Figure 1**.

Comparison of clinical efficacy between groups A and B

There were 21 cases (65.63%) markedly effective, 7 cases effective (21.88%), and 4 cases ineffective (12.50%) in group A, with the total effective rate of 87.50%. There were 15 cases

Table 4. Comparison of echocardiography parameters and blood pressure before and after treatment between group A and group B ($\bar{x} \pm sd$)

	Cases	LVEDD (mm)	LVESD (mm)	LVEF (%)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Pre-treatment						
Group A	32	54.78±3.52	36.08±3.16	58.49±5.62	160.28±22.49	96.94±13.52
Group B	38	55.37±3.66	36.95±3.39	57.94±5.81	162.47±21.15	96.11±14.79
t		1.384	1.110	0.402	0.417	0.245
P		0.171	0.271	0.689	0.678	0.807
Post-treatment						
Group A	32	47.27±2.93***	29.14±2.58***	68.46±5.53***	142.38±15.60***	81.56±10.03***
Group B	38	49.55±3.10***	33.19±3.25***	63.17±5.40***	151.84±17.73*	88.36±12.44*
t		3.143	5.698	4.038	2.374	2.531
P		0.002	<0.001	<0.001	0.021	0.014

Note: Compared with the same group before treatment, *P<0.05, ***P<0.001. LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fractions.

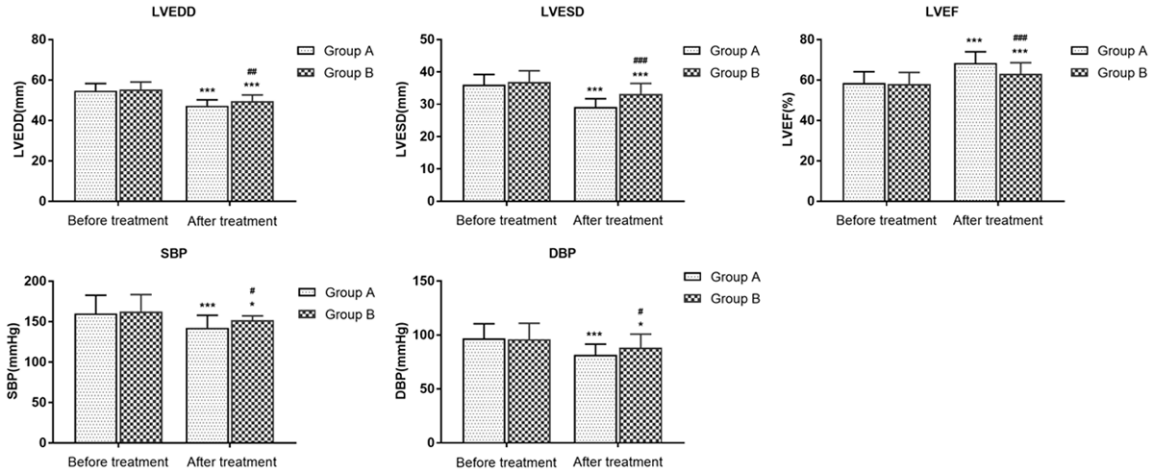

Figure 2. Comparison of heart function and blood pressure. Pre-treatment comparison, *P<0.05, ***P<0.001; compare with group A after treatment, #P<0.05, ##P<0.01, ###P<0.001. LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure.

(39.47%) markedly effective, 9 cases effective (23.68%), and 14 cases ineffective (36.84%) in group B, with the total effective rate was 63.16%. Thus, the total effective rate in group A was significantly higher than that in group B (χ^2=4.190, P=0.041). Before treatment, no significant differences were shown in LVEDD, LVESD, LVEF, and blood pressure values between the two groups (P>0.05). After treatment, the LVEDD, LVESD, systolic blood pressure, and diastolic blood pressure of group A and group B were all much lower than those before treatment and LVEF was higher than that before treatment, all with statistically significant differences (all P<0.05 or P<0.001). After treatment, LVEDD, LVESD, systolic blood pressure, and diastolic blood pressure in group A were all significantly lower than those in group B, while LVEF was significantly higher than that in group B (all P<0.05). See **Table 4** and **Figure 2** for details.

Comparison of spironolactone maintenance dose and adverse reactions during treatment between group A and group B

The maintenance dose of spironolactone in group A was significantly lower than that in group B (127.46±25.18 mg/d vs 143.61±34.75 mg/d; t=2.249, P=0.028). The incidence

Table 5. Adverse reactions during treatment in group A and group B (n (%))

Group	Gastrointestinal dysfunction	Hyponatremia	Hepatic injury	Swelling of lower limbs	Myalgia	Total incidence
Group A (n=32)	1 (3.13)	1 (3.13)	0 (0.00)	1 (3.13)	1 (3.13)	4 (12.50)
Group B (n=38)	2 (5.26)	3 (7.89)	1 (2.63)	2 (5.26)	2 (5.26)	10 (26.32)
χ^2						1.299
P						0.254

of adverse reactions in group A was also lower than that in the control group, but without statistically significant difference (P>0.05). See **Table 5** for details of adverse reactions in two groups.

Discussion

Our present study revealed that the symptoms of periodic paralysis and serum potassium levels between patients with PA and EH were both significantly different, however, neither of them are independent risk factors for patients with PA. Therefore, periodic paralysis and hypokalemia should not be used as the only basis for the diagnosis of patients with PA [11, 12]. Multivariate logistics regression analysis and ROC analysis results suggest that ARR, LVEDD, LVESD, LVEF, intima-media thickness of the carotid artery and internal carotid artery media thickness are all independent risk factors for PA, and could be used to effectively distinguish PA from EH.

Increased aldosterone secretion is one of the main features of PA. By enhancing inflammatory response and oxidative stress response, inhibiting vascular endothelial function, and promoting fibroblast proliferation and collagen production, aldosterone can lead to myocardial hypertrophy and fibrosis, as well as vascular injury [13-15]. However, plasma renin activity is decreased with the increasing aldosterone secretion. According to the above characteristics, ARR was firstly proposed by Hiramatsu et al. in 1981, through which the detection rate of PA in clinical practice was greatly improved. At present, patients with PA were preliminarily screened using ARR which was approved by Chinese consensus and American guidelines, and further measures such as confirmatory tests and surgery can effectively improve the rate of diagnosis for the initially screened patients [16]. However, due to complexity of the detection of aldosterone and renin activity, ARR application is largely restricted in many primary hospitals [17]. Therefore, research on effective methods to improve the detection efficiency of aldosterone and renin activity is a hot spot in this field. For instance, Morimoto et al. had proposed a chemiluminescent immunoassay (CLIA) that can screen PA rapidly [18]. A recent study showed that the optimal cut-point of ARR in erect position for predicting PA was 40 ($ng \cdot dL^{-1}$)/($ng \cdot mL^{-1} \cdot h^{-1}$), with a sensitivity of 93% and a specificity of 76% [19]. In our study, the cut-off value of ARR was 50.242 ($ng \cdot dL^{-1}$)/($ng \cdot mL^{-1} \cdot h^{-1}$), which was slightly higher than that in the previous study. Given that ARR could be greatly affected by age, we speculated that it was related to the age of the patients in our study. Therefore, establishing appropriate cut-points for age-related ARR may be more essential for clinical practice. Besides, it is also worth noting that the determination of plasma aldosterone concentration and renin is greatly affected by certain antihypertensive drugs, menstrual cycle, body position, serum potassium level, etc. [20]. Thus, appropriate preparation should be made according to the condition of patients before screening, and these factors above should be fully taken into consideration for confirming the diagnosis. Moreover, ROC analysis showed that combined measurement of ARR, cardiac LVEF, and intima-media thickness of the common carotid artery could effectively improve the ability to distinguish PA and EH, and the sensitivity and specificity of the combined diagnosis can even reach 91.46% and 88.42%. Therefore, combined diagnosis could be considered to further improve the detection ability of the initial screening.

Spironolactone is a classical drug for clinical treatment of PA, which not only helps to lower the blood pressure, but also inhibits cardiomyocyte apoptosis and hamper or even reverse myocardial remodeling [21, 22]. However, stud-

ies have shown that long-term use of spironolactone may induce unilateral or bilateral breast development in men, whose incidence and severity were positively correlated with the dosage taken [23]. Veeregowda et al. had reported a case of a 52-year-old male patient who had developed painful swelling in the right breast after taking spironolactone, and the pain and swelling were significantly reduced one month after withdrawal [24]. Irbesartan, an angiotensin II inhibitor, can not only help reduce vascular resistance and cardiac load directly, but also reduce aldosterone secretion [25]. In 2001, Stokes et al. pointed out that irbesartan had a better therapeutic effect on patients with PA and could further enhance the blood pressure control of patients [26]. Our present study showed that both the blood pressure control and cardiac function of patients in group A were significantly improved after irbesartan was added to the regimen. Besides, no significant difference existed in the incidence of adverse reactions between the two groups and no breast development was observed. However, sample size of this study was small, and the maintenance dose of spironolactone in group A was significantly lower than that in group B. Therefore, effects of irbesartan on breast development in patients treated with spironolactone at a maintenance dose need to be further compared with a larger sample.

There are some limitations in this study, including small sample size and short observation time, which could cause some ambiguity in the results of this study. Besides, this is a single-center retrospective study, which does not necessarily represent the characteristics of the whole population. Therefore, further studies with larger samples and longer observation periods are required.

In summary, ARR, cardiac echocardiography parameters, cervical vascular ultrasound parameters, etc. are all independent risk factors for patients with PA, and have high value for early diagnosis of PA. Combined diagnosis can further improve the diagnostic efficiency. In terms of treatment, irbesartan combined with clinical routine treatment can further improve the therapeutic effect with higher efficacy and helps to reduce the maintenance dose of spironolactone.

Disclosure of conflict of interest

None.

Address correspondence to: Yuwei Xing, Department of Endocrinology, The Second Hospital of Shijiazhuang, No. 53 Huaxi Road, Shijiazhuang 050000, Hebei Province, China. Tel: +86-158-31162796; E-mail: xingyuwei05en@163.com

References

[1] Ahmed AH, Gordon RD, Ward G, Wolley M, McWhinney BC, Ungerer JP and Stowasser M. Effect of combined hormonal replacement therapy on the aldosterone/renin ratio in postmenopausal women. J Clin Endocrinol Metab 2017; 102: 2329-2334.

[2] Allison SJ. Hypertension: CLCN2 chloride channel mutations in primary aldosteronism. Nat Rev Nephrol 2018; 14: 213.

[3] Song Y, Yang SM, He WW, Hu JB, Cheng QF, Wang Y, Luo T, Ma LQ, Zhen QN, Zhang SH, Mei M, Wang ZH, Qing H, Bruemmer D, Peng B and Li QF. Confirmatory tests for the diagnosis of primary aldosteronism: a prospective diagnostic accuracy study. Hypertension 2018; 71: 118-124.

[4] Aragao-Santiago L, Gomez-Sanchez CE, Mulatero P, Spyroglou A, Reincke M and Williams TA. Mouse models of primary aldosteronism: from physiology to pathophysiology. Endocrinology 2017; 158: 4129-4138.

[5] Caroccia B, Prisco S, Seccia TM, Piazza M, Maiolino G and Rossi GP. Macrolides blunt aldosterone biosynthesis: a proof-of-concept study in kcnj5 mutated adenoma cells ex vivo. Hypertension 2017; 70: 1238-1242.

[6] Mulatero P, Monticone S, Burrello J, Veglio F, Williams TA and Funder J. Guidelines for primary aldosteronism: uptake by primary care physicians in Europe. J Hypertens 2016; 34: 2253-2257.

[7] Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M and Young WF. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016; 101: 1889-1916.

[8] Aronow WS. Hypertension guidelines. Hypertension 2011; 58: 347-348.

[9] Crişan S. Carotid ultrasound. Med Ultrason 2011; 13: 326-330.

[10] Vetshev SP, Polunin GV and Sotnikova VA. Diagnosis and treatment of primary hyperaldosteronism. Khirurgiia (Mosk) 2004; 14: 61-69.

[11] Yang T, Zhang HL, Liang Q, Shi Y, Mei YA, Barrett PQ and Hu C. Small-conductance Ca2+-activated potassium channels negatively regulate aldosterone secretion in human adrenocortical cells. Hypertension 2016; 68: 785-795.
[12] Freel EM and Connell JM. Primary aldosteronism: an update. Expert Rev Endocrinol Metab 2010; 5: 389-402.
[13] Czepiel M, Kania G, Diviani D, Diestler O, Eriksson U, Siedlar M and Blyszczuk P. P6295 role of angiotensin II receptor type 1 in TGF-beta-mediated fibrogenesis in mouse model of experimental autoimmune myocarditis. Eur Heart J 2017; 53: 647-655.
[14] Bounthavong M, Butler J, Dolan CM, Dunn JD, Fisher KA, Oestreicher N, Pitt B, Hauptman PJ and Veenstra DL. Correction to: cost-effectiveness analysis of patiromer and spironolactone therapy in heart failure patients with hyperkalemia. Pharmacoeconomics 2019; 37: 1071.
[15] Rossignol P, Claggett BL, Liu J, Vardeny O, Pitt B, Zannad F and Solomon S. Spironolactone and resistant hypertension in heart failure with preserved ejection fraction. Am J Hypertens 2018; 31: 407-414.
[16] Monticone S, Losano I, Tetti M, Buffolo F, Veglio F and Mulatero P. Diagnostic approach to low-renin hypertension. Clin Endocrinol (Oxf) 2018; 89: 385-396.
[17] Vecchiola A, Fuentes CA, Barros ER, Martínez-Aguayo A, García H, Allende F, Solari S, Olmos R, Carvajal C, Tapia-Castillo A, Campino C, Kalergis AM, Baudrand R and Fardella CE. The aldosterone/renin ratio predicts cardiometabolic disorders in subjects without classic primary aldosteronism. Am J Hypertens 2019; 32: 468-475.
[18] Morimoto R, Ono Y, Tezuka Y, Kudo M, Yamamoto S, Arai T, Gomez-Sanchez CE, Sasano H, Ito S and Satoh F. Rapid screening of primary aldosteronism by a novel chemiluminescent immunoassay. Hypertension 2017; 70: 334-341.
[19] Deltombe C, Gillaizeau F, Anglicheau D, Morelon E, Trébern-Launay K, Le Borgne F, Rimbert M, Guérif P, Malard-Castagnet S, Foucher Y and Giral M. Is pre-transplant sensitization against angiotensin II type 1 receptor still a risk factor of graft and patient outcome in kidney transplantation in the anti-HLA Luminex era? A retrospective study. Transpl Int 2017; 30: 1150-1160.
[20] Wang J, Hanada K, Gareri C and Rockman HA. Mechanoactivation of the angiotensin II type 1 receptor induces β-arrestin-biased signaling through Gα(i) coupling. J Cell Biochem 2018; 119: 3586-3597.
[21] Rieber-Mohn AB, Sugulle M, Wallukat G, Alnæs-Katjavivi P, Leite Størvold G, Bolstad N, Redman CW, Dechend R and Staff AC. Autoantibodies against the angiotensin II type I receptor in women with uteroplacental acute atherosis and preeclampsia at delivery and several years postpartum. J Reprod Immunol 2018; 128: 23-29.
[22] Fichtner A, Süsal C, Schröder C, Höcker B, Rieger S, Waldherr R, Westhoff JH, Sander A, Dragun D and Tönshoff B. Association of angiotensin II type 1 receptor antibodies with graft histology, function and survival in paediatric renal transplant recipients. Nephrol Dial Transplant 2018; 33: 1065-1072.
[23] Mackenzie IS, Morant SV, Wei L, Thompson AM and MacDonald TM. Spironolactone use and risk of incident cancers: a retrospective, matched cohort study. Br J Clin Pharmacol 2017; 83: 653-663.
[24] Veeregowda SH, Krishnamurthy JJ, Krishnaswamy B and Narayana S. Spironolactone-induced unilateral gynecomastia. Int J Appl Basic Med Res 2018; 8: 45-47.
[25] Yousif NG, Hadi NR, Al-Amran F and Zigam QA. Cardioprotective effects of irbesartan in polymicrobial sepsis: the role of the p38MAPK/NF-κB signaling pathway. Herz 2018; 43: 140-145.
[26] Stokes GS, Monaghan JC, Ryan M and Woodward M. Efficacy of an angiotensin II receptor antagonist in managing hyperaldosteronism. J Hypertens 2001; 19: 1161-1165.