Int J Clin Exp Pathol 2015;8(6):6901-6909
www.ijcep.com /ISSN:1936-2625/IJCEP0006343

Original Article

Aldosterone-to-renin ratio acts as the predictor distinguishing the primary aldosteronism from chronic kidney disease

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Received January 26, 2015; Accepted March 23, 2015; Epub June 1, 2015; Published June 15, 2015

Abstract: Aldosterone-to-renin ratio (ARR) is a screening test for primary aldosteronism, but it was impacted by a bunch of clinical covariates. The ARR is associated with chronic kidney disease (CKD), renal artery stenosis, renin adenoma. This study aims to investigate relationship between ARR and primary aldosteronism in CKD patients. A retrospective observational analysis involves 253 attendees from Urology Department of Chengdu Military General Hospital (China), comprising 146 patients with confirmed primary aldosteronism, 56 patients with essential hypertension, and 55 patients with chronic kidney disease accounting for primary kidney disease. Blood samples were drawn from patients with particular restriction for measuring serum aldosteronism, plasma renin activity, and serum potassium. Receiver operating characteristic (ROC) curve of ARR was tested to establish cutoff values and to assess sensitivity and specificity. The results showed that LogARR values were significantly higher ($P < 0.001$), and PRA and serum potassium values were significantly lower ($P < 0.001$) in primary aldosteronism patients. By contrast, significantly higher serum aldosterone and plasma renin were observed in CKDs compared with the other two groups ($P < 0.001$). There was a significantly positive correlation between LogARR and serum potassium ($r = -0.0345$, $P < 0.001$, $R^2 = 0.093$). The AUC for plasma renin activity, logARR, and serum aldosterone are 0.855, 0.84, and 0.501, respectively. ROC curve of logARR and plasma renin activity in detection of primary aldosteronism with higher sensitivity and specificity. In conclusion, this study indicated that the ARR act as the biomarker for the primary aldosteronism, and could distinguish from chronic kidney disease.

Keywords: Aldosterone-to-renin ratio (ARR), primary aldosteronism, chronic kidney disease, receiver operating characteristic (ROC) curve

Introduction

It is suggested that primary hyperaldosteronism (PH) is a common, treatable, and potentially curable form of secondary hypertension. Some studies reported that primary aldosteronism could be more than 10% of hypertension patients [1-4], but the 2008 Endocrine Society Clinical Practice Guideline gave the overall prevalence about 6.1% [5]. This kind of hypertension is as high as 20% in patients with resistant hypertension [6-8], and is emphasized repeatedly due to the association with severe cardiovascular morbidity and mortality [9-11]. Primary aldosteronism is caused by adrenocortical adenomas (APA) or idiopathic hyperplasia (IHA) [5], however, the unilateral adrenal hyperplasia (UNAH) sometimes is defined the another subtype , which shows transition state between APA and IHA [12].

Aldosterone-to-renin ratio (ARR) is recommended as screening test for four groups of patients, those with blood pressure above 160/100 mmHg; resistance hypertension; hypokalemia whether spontaneous or diuretic-induced, or an adrenal incidental-loma [5]. Some hold that ARR, seen as a crude and unreliable bivariate analysis [3], is also influenced by a variety of internal and external factors, such as age [13], female sex, untreated hypertension, diuretic and other antihypertensive use, total/high-density lipoprotein cholesterol [14], time of day, and race [15, 16]. Many investigators require an elevated plasma aldosterone to consider the ARR as positive (90-91%) [17-19], whereas it

may make no clinical significance [20]. Furthermore, raising aldosterone can not give birth to the improvement of the value, because a bunch of secondary hypertension diseases can lead to aldosterone oversecretion, which sometimes induced the negative feedback on renin. A recent study led by the Ohasama [21], in which the patients with the development of chronic kidney disease (CKD) were reckoned it associated with lower PRA and higher ARR. A different but equally impressive phenomenon is renal artery stenosis, which was discovered that ARR was markedly high in bilateral (Bi)-renal artery stenosis (RAS) versus essential hypertensives [22].

In the present study, we collected clinical data of the patients who were examined serum aldosteronism and plasma renin activity ,and those were transformed ARR for screening primary aldosteronism. Subsequent to this investigation, we set out to estimate the value of serum aldosteronism, plasma renin activity, and serum potassium in common secondary hypertension by investigating the difference between the primary aldosteronism and chronic kidney disease. Given that the assessment of ARR can not keep pace with the specificity of diagnosis in primary aldosteronism, a study of the clinical characteristic correlate of PH in the community and the different changes of imaging on disease progression and the effective identification among secondary hypertension subjects could have diagnostic, therapeutic, and prognostic importance. Our study was conducted to reassess the clinical diagnostic value of serum aldosteronism, plasma renin activity, and ARR in a general sample. In addition, we also detected the association of serum aldosteronism and plasma renin activity, and ARR with the CKD.

Materials and methods

Study participant

Study participants undergo detailed medical history, assessment of medication use, physical examination, assessment of laboratory tests, imaging study, and assessment of family heredity. A retrospective observational study was performed on patients diagnosed with PH, CKD and EH. The clinical diagnosis had been established by raised aldosterone/renin ratio together with positive confirmatory tests and lateralization studies (CT, MRI and adrenal vein sampling) according to the routine protocols at our center. The histopathological diagnosis had been confirmed by expert endocrine pathologists.

Participants were excluded if they were missing for plasma rennin (n = 7), serum aldosterone (n = 16), or any of the covariates (n = 11). After exclusions, 253 participants were eligible for the study of clinical correlates. The protocol was approved by our local ethics committee, and all of the participants gave their written informed consent.

Laboratories assays

Fasting whole blood samples were drawn by venipuncture after 10 minutes of rest in a supine position in the morning, typically between 6:30 and 8:30 AM. Blood was collected in EDTA tubes for plasma renin activity and serum aldosterone measurement, maintained at 0°C temperature during delivery to the laboratory, and rapidly frozen at -20°C after centrifugation. Plasma renin activity and serum aldosterone were measured using radioimmunoassay at laboratory at baseline, in erect position, in the supine position after a 30-min rest. Spot urinary sodium and potassium concentration was measured using an automated ion-electrode method and indexed to urinary creatinine (expressed as millimoles of sodium per gram of urinary creatinine). Aldosterone-to-renin ratio was natural-log transformed because of their positively skewed distributions .The most valuable serum potassium level was measured before the start of the treatment, especially the use of diuretic and potassium supply.

Clinical characteristics

All participants were measured height and weight, and then the body mass index was calculated. BP was measured twice consecutively using a mercury column sphygmomanometer in a sitting position, after a 5 min rest interval, by trained nurses. The average of 2 readings constituted the examination BP. Information on age of onset, use of antihypertensive medication, smoking, imaging examinations and history of family heredity, diabetes mellitus and proportion of dyslipidemia.

Imaging study

All patients undergo computed tomography before a definite diagnosis was made. Patients with primary aldosteronism (PA) who are suit-

Table 1. Characteristics comparison among the three subtypes

characteristic*	Adrenocortical adenocarcinoma N=72	Idiopathic hyperplasia N=25	Unilateral adrenal hyperplasia N=49	*P* value
Age when PHA was diagnosed (years)				
	42.9±11.4	46.7±15.8	45.1±11.8	
Hypertension, n (%)	61	22	46	
Serum aldosterone, pg/ml	602.22±229.7	680.63±212.50	581.68±252.28	
Plasmarenin, pg/ml.h	0.83±0.95	0.85±0.70	1.0±1.0	
LogARR	2.09±0.59	2.11±0.54	1.96±0.57	
Serum potassium	3.22±0.77	3.41±0.86	3.57±0.58	P=0.043
Hypokalemia, n (%)	42	13	19	
Operation, n (%)	58	7	27	

*Shown are the clinical characteristics of primary kidney disease inducing CKD.

able for surgery should undergo adrenal computerized tomography (CT). Adrenocortical adenomas tend to be small, smooth, homogeneous, and round to oval in shape. High-resolution computed tomography (CT) with fine (2-3 mm) cuts of the upper abdomen is the best available technique for the identification of adrenal nodules, which can be found in APA. When a mean limb width of greater than 3 mm was used to diagnose bilateral adrenal hyperplasia, and a specificity of 100% was achieved when the mean limb width was 5 mm or greater [23]. We measured each limb width and size of adrenal gland in order to detect the Paranephrosmorphologic change among the participants.

Data analysis

All data were analyzed with SPSS statistical software version 17.0. Continuous variables with normal distribution were expressed as mean ± SD. Missing BMI values were interpolated from the regression slope on age by sex. The comparison of continuous variables between three subtype patients with primary aldosteronism was performed using the Student t-test. Categorical variables were expressed by frequency distribution and were compared using the Pearson's chi-square tests (or Fisher exact test for cells less than 5). To analyze the relationships between tertiles of ARR and participant characteristics, means and proportions were compared using analysis of variance (ANOVA) and the chi-square test for univariate analysis. ARR were natural log-transformed because of their positively skewed distributions. We evaluated the specific distributions of log ARR in several participant subgroups: primary aldosteronism (PHs), chronic kidney disease (CKDs), essential hypertension (EHs). We used univariable logistic regression to evaluate the clinical correlates of logARR in the entire sample of 146 participants with primary aldosteronism. The optimal discriminator from receiver operating characteristic (ROC) curve was tested to establish cutoff values and to assess sensitivity and specificity. For the ROC curves, chronic kidney disease and essential hypertension results were pooled to assess specificity. The threshold for statistical significance was predefined as $P < 0.05$.

Results

Basic characteristics

A total of 257 patients were enrolled in this trial, comprising 146 patients with confirmed primary aldosteronism, 56 patients with essential hypertension, and 55 patients with chronic kidney disease due to primary kidney disease developed.

Characteristics comparison among three subtypes

Table 1 showed the comparison among the three subtypes used to observed characteristics and basal biochemical determinations in primary aldosteronism. Only serum potassium was discovered the significant difference between Adrenocortical adenocarcinoma and Unilateral adrenal hyperplasia (**Table 1**, P < 0.001).

Table 2 presents characteristics and biochemical determinations. The mean age and BMI of PH subjects were not significantly different from the other two groups. LogARR values were significantly higher ($P < 0.001$), and PRA and serum potassium values were significantly

Table 2. Characteristics and biochemical determinations of patients

characteristic*	Primary aldosteronism n=146	Chronic kidney disease* n=55	Essential hypertension n=56	*P* value
Sex (M/F)	74/72	40/16	33/12	
Age when HT was diagnosed (years)				
	N=131	N=53	N=55	
Mean ± SD	43.9±11.8	35.6±11.9	41.4±16.3	
Range	12-76	6-66	12-80	
Years of diagnosing HT				
Mean ± SD	5.7±6.0	2.9±3.5	5.6±7.4	
Range	1-30	6-66	1-30	
Hypertension, n	131	53	55	
Systolic BP, mm Hg	177.9±31.2	189.0±37.1	191.7±31.3	
Diastolic BP, mm Hg	104.3±19.4	115.7±23.9	113.1±17.7	
Family heredity, n	46	20	34	
BMI, kg/m^2	23.6±3.3	23.4±4.2	24.6±4.39	
Serum aldosterone pg/ml	608.75±235.67	844.67±310.45	447.78±174.65	0.001
Plasma renin, pg/ml.h	0.89±0.93	3.36±3.06	2.98±2.01	0.001
ARR$^+$	313.91±624.0	52.08±51.49	24.8±38.26	
LogARR	2.05±0.58	1.53±0.42	1.24±0.31	0.001
ARR ≥ 35, n	130	27	6	0.001
Serum potassium, mmol/L	3.37±0.74	4.50±0.78	3.93±0.45	0.001
Hypokalemia, n	74	4	7	0.001
Dyslipidemia, n	89	23	47	
Diabetes, n	12	6	8	
Smoking, n	27	12	15	
Paranephrosmorphologic change on CT				0.001
Unilateral, n	115	9	0	
Bialateral, n	31	5	0	

*shown are the clinical characteristics of primary kidney disease inducing CKD. +Aldosterone-to-renin ratio (ARR) is skew distribution and make natural-log transform for statistics.

lower ($P < 0.001$) in primary aldosteronism patients compared to the other groups (**Table 2**, $P < 0.001$). However, hypokalemia was not significantly different between CKDs (n) and EHs. By contrast, significantly higher serum aldosterone and plasma renin activity were observed in CKDs compared with the other two groups (**Table 2**, $P < 0.001$).

Optimal critical values of biomarkers

In order to explore the diagnostic values of the above biomarkers, the optimal critical values have been investigated. **Figure 1** depicts individual values for plasma aldosterone, ARC, serum potassium and ARR from the subjects in all three groups.

By examining the expression of distribution of plasma aldosterone, ARC, serum potassium and ARR, we analyzed the statistical distribution. The mobility scale for the primary aldosteronism group, chronic kidney disease group and essential hypertension group were listed in **Figure 1**.

LogARR correlates negatively with serum potassium

We also analyzed the correlations between the biomarkers in the three groups. The results indicated that there was a significantly inverse correlation between LogARR and serum potassium ($r = -0.0345$, $P < 0.001$, $R^2 = 0.093$, **Figure 2**).

Diagnostic accuracy

The diagnostic accuracy of plasma aldosterone activity, ARR, and Serum aldosterone, in terms of sensitivity and specificity, are presented by receiver operating characteristic (ROC) curve

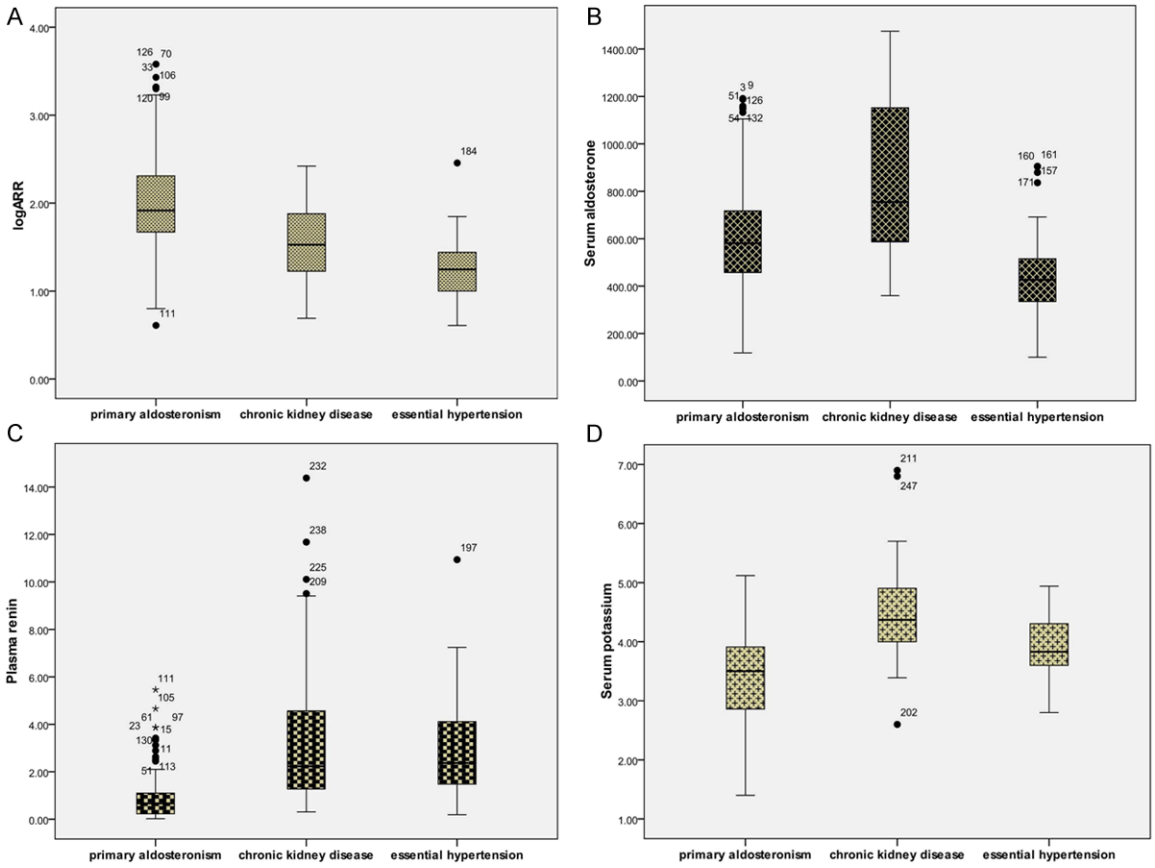

Figure 1. Optimal critical values for logARR (A), serum aldosterone (B), plasma renin (C), and serum potassium (D) from the subjects in all three groups.

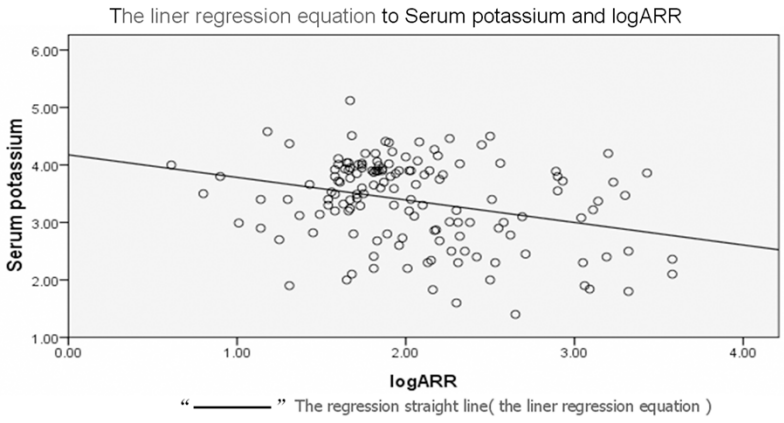

Figure 2. Correlation analysis between serum potassium and log ARR.

analysis. **Figure 3** showed the ROC curves for plasma aldosterone activity, ARR, and Serum aldosterone. The prediction values for primary aldosteronism are shown in **Table 3**. The area under the ROC curve (AUC) for plasma aldosterone activity, ARR, and Serum aldosterone are 0.855, 0.84, and 0.501, respectively. In **Figure 3**, corresponding to ARR (**Figure 3A**) and PRA (**Figure 3B**), the area under the curve for PRA is little better than for ARR in detecting primary aldosteronism when CKD group is involved. ROC curve of ARR in detection of prior treatment-ARR from primary aldosteronism in our study (AUC = 0.84) (sensitivity = 89.7%, specificity = 70.4%, cut-off value ≥ 35).

Discussion

The goal of ARR is to provide a balance between missing clinically cancer and performing unnecessary adrenal venos sampling (AVS) in primary aldosteronism. Unfortunately, the cutoff value of ARR as screening for primary aldosteronism remains controversial. ARR was positively asso-

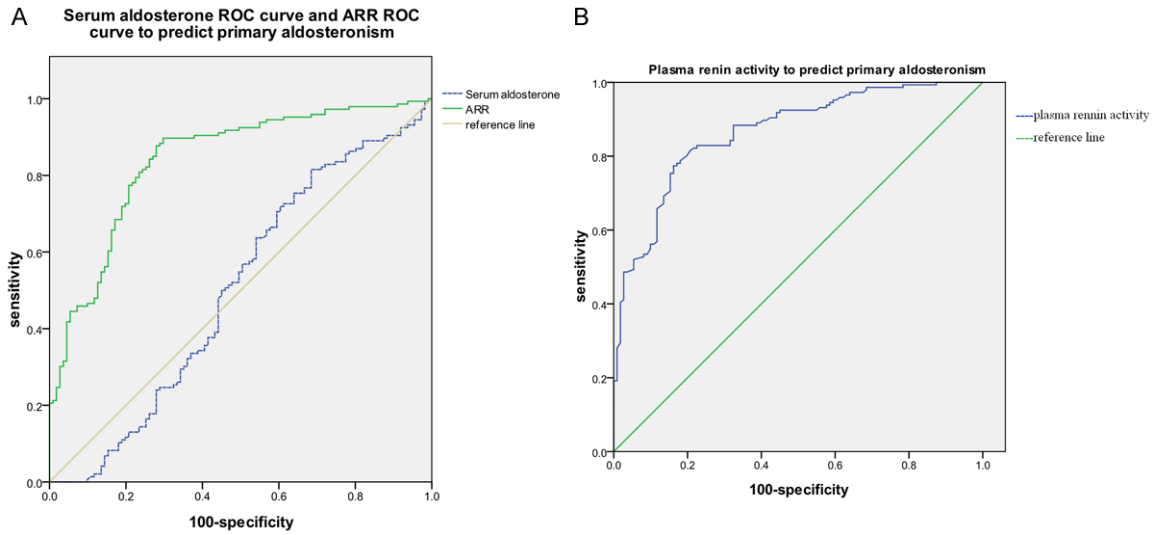

Figure 3. ROC curves predict the primary aldosteronism. A. Serum aldosterone ROC curve and ARR ROC curve to predict primary aldosteronism. B. Plasma rennin activity to predict primary aldosteronism.

Table 3. The prediction values for primary aldosteronism

Characteristic	AUC	95%-confidence intervals	*P* value
Plasma-renin activity	0.855	0.82-0.90	< 0.001
ARR	0.84	0.71-0.89	< 0.001
Serum aldosterone	0.501	0.47-0.58	0.97

ciated with age, female sex, untreated hypertension, total/high-density lipoprotein cholesterol ratio, hormone replacement therapy, and β-blocker use, but negatively associated with angiotension-converting enzyme inhibitor and diuretic [24]. However, even AVS can be problematic beyond its cost and the aggressive damage, on which experts didn't reach a consensus [25]. Nevertheless, screening for this secondary hypertension is widespread. The hitherto aldosterone-to-renin ratio (ARR) is insisted to be a more valuable test than aldosterone levels for primary aldosteronism, and it could be an index for inappropriate aldosterone activity and salt sensitivity.

Now few laboratories have attempted to compare the difference among primary aldosteronism, chronic primary kidney disease and essential hypertension. Compared with the Ohasama study and other new researches [23, 26], higher serum aldosterone and plasma renin concentration, as well as middle ARR were associated with the chronic kidney disease in our three groups. By contrast, the patients who developed CKD indeed have been found their higher serum aldosterone and ARR than essential hypertension controls. While the primary aldosteronism patients accompanying chronic Kidney disease still have been demonstrated high serum aldosterone and ARR levels, low PRA, and no clear association of hypokalemia. Aldosterone-induced renal injury has been demonstrated in previous clinical study that a mineralocorticoid receptor inhibitor reduced albuminuria independent of blood pressure reduction [27-29]. Indeed, there are a large number of patients (14/56) with chronic kidney disease presented abnormal shaped in adrenal gland, which was defined as full shape not hyperplasia. We suggested that this shape of form abnormal was related to renin-oriented aldosterone hypersecretion, which could not be reckoned as Independent incretion.

To our knowledge, among the three subtypes of primary aldosteronism, there are no remarkable differences in clinical characteristics except serum potassium .Our findings clearly demonstrated that high ARR levels, low PRA and serum potassium were significantly and independently associated with primary aldosteronism in most of patients. We observed that 15 of 146 primary aldosteronism patients had a raised ARR, who did not have Hypertension only accompanying Hypokalemia, or even without any clinical symptoms. According to present study, Only a small proportion of patients (between 9 and 37%) were hypokalemia [30].

Nearly half patients (74/146) have hypokalemia in our study, but we found there was a linear relationship between LogARR and serum potassium. Imaging studies have shown that approximately 100% of patients have abnormal shape in their bilateral or (and) unilateral adrenal gland, but these have different anatomic abnormality (adenomas, hyperplasia, tubercle).

In our other studies we found the association of polymorphisms in angiotensin II receptor genes with the risk for aldosterone-producing adenoma (APA) in a Chinese Han population, and rs5194 polymorphism at AT (2) R gene was associated with the risk for APA, which may constitute a genetic marker of APA [31, 32]. From this study, the proportion of EHs involved higher difference than the PHs in Family heredity ,however, we defined any history of familial hypertension as Family heredity ascribed to the posterior awareness of primary aldosteronism. The same phenomenon was observed in dyslipidemia between primary aldosteronism and essential hypertension. An increasing prevalence of diabetes mellitus (DM) has been reported in patients with primary aldosteronism (PA), and they suggested that diabetic dyslipidemia and modification of circulating lipoproteins should promote adrenocortical aldosterone synthesis [33]. On the contrary, the other study insisted that it is unlikely that the prevalence of metabolic syndrome differs significantly between patients with primary aldosteronism and those with essential hypertension [34], and we also presented the same point.

The ROC curve analysis was clearly the best performing test, and ARR showed the middling sensitivity and specificity in detecting primary aldosteronism due to the kind of hypertension with CKD involved, as well as PRA showed a little better. The combination of an ARR cutoff value with a plasma aldosterone threshold (> 416 pmol/l or > 15 ng/dl) has been recommended by some investigations [35,36]. Actually, ARR as screening test in primary aldosteronism is suffering great challenges, the influence not only comes from inherence, but also exterior has been verified. Ultrahigh serum aldosterone also has been detected in renal artery stenosis and renin adenoma, and the numeric of PRA was not low also. Consequently, urologists and physicians should consider the other possibility more than primary aldosteronism, especially chronic kidney disease, when the moderately high ARR was detected, in spite of some existing methods of differential diagnoses.

Our study has limitations. Most of these are primary tied to the limitation in the studies we reviewed. Firstly, PRA and ARR were measured under nonstandardized condition that contributing to their special status of the chronic kidney disease, and the samples size should be expanded. Susceptible ARR should be limited diuretic at the least for screening test [5]. Unfortunately, the CKD patients were recommended the use of aldosterone antagonists [32]. Secondly, the lack of evidences to verify the cause of full shape of adrenal gland. As the disease develops, we spontaneously believed that it was secondary changes. However, aldosterone-induced renal injury was reported, we should actively observe the dysfunction of paranephros in early stage of primary kidney disease included serum aldosterone, PRA, and imaging examination was necessary also. The motivation is increased stimulated surveillance in next step for the development of kidney disease. Furthermore, we only have finite clinical data about renal artery stenosis and renin adenoma, as we know they still account for the suggestible reason of ARR. It means that we will expand the proportion of these in future researches.

Finally, identifying and measuring all the resources, especially ARR, used in screening for secondary hypertension is still significant. According to the 2008 guideline recommends ARR screening for four particular groups of patients [5], we should take into account the possibility of chronic kidney disease, which does not attribute to the primary aldosteronism, when we observed the moderately high ARR.

Acknowledgements

The authors are grateful to the residents of Urology Department of Chengdu Military General Hospital and The Xiamen Urology Center, all related investigators and study staff, and clinical laboratory for their valuable support on this project. This work was supported by Urology Department of Chengdu Military General Hospital and The Xiamen Urology Center.

Disclosure of conflict of interest

None.

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