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Diagnostic Utility of Aldosterone/Direct Renin Concentration Ratio in Iraqi Patients with High Arterial Blood Pressure: A Pilot Study

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Abstract

Objectives: Primary aldosteronism is a prevalent contributor to secondary hypertension, posing an elevated risk of morbidity and mortality. The initial step in diagnosing this condition involves screening individuals suspected of having it.

Methods: In our study, we enrolled 50 patients who were suspected of having hyperaldosteronism. We provided specific recommendations and instructions to these patients concerning drug therapy and implemented measures to enhance testing accuracy. The tests were conducted using the Chemiluminescence Immunoassay (CLIA) system procedure, relying on plasma direct renin concentration rather than activity. Our findings were meticulously validated, compared, and aligned with the references from ARUP laboratories.

Results: Among our participants, 4 patients (8%) were unequivocally diagnosed with primary aldosteronism based on the Aldosterone Direct Renin Concentration (ADRR) criteria. These patients exhibited the trifecta of hypokalemia, elevated aldosterone levels, and diminished renin levels, obviating the need for further confirmatory testing. Furthermore, 13 patients (26%) were deemed likely candidates for primary aldosteronism, given their plasma aldosterone levels exceeding 15 ng/dl and renin levels below 2.5 pg/ml. Additionally, 7 patients (14%) displayed strong indications of primary aldosteronism, characterized by plasma aldosterone levels surpassing 21 ng/dl and plasma renin concentrations below 2.5 pg/ml, accompanied by high ADRR values. However, both the "likely" and "strong indication" groups necessitated confirmatory testing. Notably, our results revealed no significant disparities in age, gender, personal or family history of atherosclerotic cardiovascular disease (ASCVD), or the presence of adrenal adenomas between patients diagnosed with primary aldosteronism and those in the non-aldosteronism group within the study.

Conclusion: Primary aldosteronism is a prevalent health concern, warranting the screening of highly suspicious patients. Utilizing direct renin concentration, instead of renin activity, offers a straightforward, cost-effective, rapid, and reproducible method for diagnosis.

Keywords: Aldosterone, renin, arterial pressure, Iraq

Introduction

Hyperaldosteronism is one of the endocrine health problem which is underestimated and negligible by physicians and health professionals of developing countries, despite it is a big burden on patients health as their blood pressure stay uncontrol and lead to serious morbidities. Hypertension is the main presentation of hyperaldosteronism and is one of the leading causes of the global burden of disease as 1.13 billion person have hypertension worldwide.[1-3]

Many complications have been reported due to long stand untreated primary aldosteronism. Target organ damage of the heart and kidney and chronic kidney disease is more common in patients with primary aldosteronism in compare to general population. Greater LV mass measurements in compare with other types of hypertension (e.g., pheochromocytoma, Cushing syndrome and essential hypertension) and higher rate of cardiovascular events (e.g., stroke, atrial fibrillation, myocardial infarction) in matched patients with essential hypertension. Also the risk to develop new onset diabetes mellitus was documented in patients with primary aldosteronism. Primary aldosteronism have negative impact on quality of life, untreated patients have an impaired physical and mental quality of life, anxiety, demoralization, stress, depression and nervousness.[4,5]

Early detection and management of PA, whether by adrenalectomy or using mineralocorticoid receptor antagonists, carry a great improvement in morbidity and mortality.[6,7] Adult studies have shown that hypertension is cured in 30–60% of cases and significantly improved in 40–70% of cases, postoperatively.[7,8] Appropriate medical or surgical intervention in primary aldosteronism results in long-term reduction in blood pressure and left ventricle (LV) mass via LV inward remodeling.[6] Patient who underwent adrenalectomy had statistically significant reduced risk for incident diabetes and all cause of mortality compared with matched with hypertensive controls. Almost all quality of life measures had normalized for surgically managed patients after 1 year, while most measures improved for patients on medical treatment but not to the level of general population.[4]

Primary hyperaldosteronism is a state of suppressed plasma renin activity (PRA), and increased aldosterone excretion, which was first fully described in 1955, by Dr. Jerome W. Conn, a professor of medicine at the University of Michigan. He suggested that up to 20% of patients with essential hypertension might have primary aldosteronism. Later, Conn decreased his predicted prevalence of primary aldosteronism to 10% of hypertensives.[4] The main causes of primary aldosteronism are; Bilateral idiopathic hyperplasia (IHA) 60% of cases, aldosterone-producing adenoma (APA) 30% of cases, primary (unilateral) adrenal hyperplasia 2% of cases, aldosterone-producing adrenocortical carcinoma <1% of cases, familial hyperaldosteronism (FH) <7% and ectopic aldosterone-producing adenoma or carcinoma <0.1% of cases.[4,5]

The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decades of life, it is a rare condition in children.[9] As causes of hyperaldosteronism is

either primary or secondary, early detection and diagnosis of primary aldosteronism is a main concern for physicians and endocrinologists because it is not strait forward, may need more than one step and cost effect.[6]

The diagnostic approach to primary aldosteronism can be considered in three phases: case detection tests, confirmatory tests and subtype evaluation tests.[4,9]

Case-detection phase represent the first step in detecting and diagnosis of primary aldosteronism. All patients with hypertension should be screened for primary aldosteronism at least once in life[4] but in order to increase the sensitivity of screening primary aldosteronism it is recommended to specify special criteria to select highly suspected patients, these are; drug-resistant hypertension (defined as systolic BP >140 and diastolic BP >90 despite treatment with 3 hypertensive medications); hypertension and spontaneous or diuretic-induced hypokalemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early onset hypertension or atherosclerotic cardiovascular disease (ASCVD) at a young age (<40 y); and all hypertensive first-degree relatives of patients with PA. Additionally, in patients younger than 20 years or those with a family history of PA or stroke at a young age (<40 y), or with an onset at a young age (eg., <20 y).[8,10]

In the early time after discovery of primary aldosteronism, the use of hypokalemia as a diagnostic requirement, as advocated by some authorities, may have led to under recognition of some cases of hyperaldosteronism. Later, studies shows 72% of patients with primary aldosteronism are normokalaemia. So all patients with hypertension are candidate for this disorder and patients with APA tend to have higher blood pressures than those with IHA.[5]

The spontaneous hypokalemia/no antihypertensive drug diagnostic approach resulted in predicted prevalence rates of less than 0.5% of hypertensive patients. However, it is now recognized that most patients with primary aldosteronism are not hypokalemic and that case-detection testing can be completed with a simple blood test (plasma aldosterone concentration PAC-to-plasma renin activity PRA or plasma renin concentration PRC ratio) while the patient is taking most of antihypertensive drugs.[5]

It can be accomplished by paired measurements of plasma aldosterone and plasma renin activity in a random morning ambulatory blood sample (preferably obtained between 8 and 10 am) and calculate the aldosterone renin ratio (ARR).[5] While the ARR is generally considered the most reliable means of screening for primary aldosteronism, its interpretation is not straightforward.[11] However, new direct renin assays that measure plasma renin concentration (PRC) are progressively replacing PRA because these are faster, simpler, and more reproducible.[12]

Plasma aldosterone measured by nanogram per deciliter while plasma renin activity measured by nanogram per milliliter per hour,[4,5] while measurement of direct renin concentration is by picogram per milliliter (pg/ml) or by milli international unit per litter (mU/L) and the ratio will be aldosterone direct renin concentration ratio (ADRR),[11] and in a study of aldosterone/direct renin concentration ratio as a screening test for primary aldosteronism: A meta-analysis, shows (ADRR) is 95% sensitive and 95% specific and reliable to be used instead of (ARR), although antihypertensive drugs can interfere with the interpretation of (ADRR) and it is recommended to interrupt therapy or at least replace with analogues that do not significantly affect the ADRR value.[13]

Yet, as general physicians not familiar with hyperaldosteronism, can our simplified screening plan be easily to perform? Can we detect cases of high suspicion of hyper aldosteronism with using ADRR instead of using ARR?

Our aim is to study the frequency of primary aldosteronism in highly suspected sample of patients with uncontrolled hypertension by case-detection test.

Patients and Methods

A 50 hypertensive patients with suspected secondary cause of hypertension were included in our study that they match the criteria for the study. Patient data collection last for one year, from September 2021 till August 2022 and took place in two places, Emamein Kadhimein medical city/endocrine and diabetes outpatient clinic and national diabetes center/Mustansiriya university.

The study is of cross-sectional type, to collect data of specific criteria that included in case-detection phase only of primary aldosteronism.

Guidelines recommend case-detection testing in high-risk groups for primary aldosteronism.[14]

When to consider testing for primary aldosteronism? All patients with hypertension should be tested, but in order to increase the sensitivity of case-detection testing we follow an inclusion and exclusion criteria to select more specific candidate in this survey.[5,11,15]

Inclusion Criteria

1. Patients with drug-resistant hypertension (defined as systolic BP >140 and diastolic BP >90 despite treatment with 3 hypertensive medications or more).
2. Sustained hypertension (systole blood pressure equal or more than 160 mmHg and/or diastolic blood pressure equal or more than 100 mmHg) firstly diagnosed in age before 40 years.
3. Sustained hypertension with spontaneous or diuretic-induced hypokalemia, serum potassium equal or less than 3.4 mEq/L, at any age.
4. Sustained hypertension with adrenal incidentaloma, at any age.
5. Sustained hypertension and premature onset of atherosclerotic cardiovascular disease (ASCVD) or cerebrovascular disease, personal or familiar (first or 2nd degree relatives).
6. Sustained hypertension with obstructive sleep apnea.

Exclusion Criteria

1. Patients diagnosed with heart failure.
2. Patients diagnosed with chronic kidney disease with eGFR less than 60 ml/min.
3. Pregnant women.

The reason to exclude these conditions is that plasma renin level, serum sodium and serum potassium markedly affected in these conditions and lead to false negative or false positive results.[11]

Patient is advised to use his/her anti-hypertensive therapy specially if blood pressure is not controlled but modulation in therapy is performed before testing, and this is by stopping mineralocorticoids receptors antagonist (spironolactone and eplerenone) for at least 40 days before testing, these drugs prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in renin, which can lead to false-negative case-detection testing.[4,11,15] Also stop diuretics, specially amiloride, for at least 14 days as diuretics tend to induce secondary hyperaldosteronism. Patients using ACE inhibitors or angiotensin receptor blockers can still keep using them, although they may lead to increase in renin level, patients with low renin despite using these agents may strengthen our results in new case detection. Using Beta-adrenergic blockers, although they may cause false positive results, they may not interfere with our results if they used in a low to moderate doses. Patients with uncontrolled or sub-optimal control blood pressure advised to use Alpha-adrenergic blockers, Calcium channel blockers and vasodilators.[16]

Patients encouraged not to restrict salt intake and advised to consume around 3 g of table salt 3 to 5 days before testing,[11,15] and hypokalemia should be corrected before testing because low potassium suppresses aldosterone secretion so potassium supplement given to patients with tested low serum potassium.[11,15]

Blood sample is obtained between 8 AM – 10 AM while the patient in fasting state, advised to walk for 60 minute and then rest for 30 minute before collecting the blood sample, according to test kit manufacturer advise, and without posture stimulation.[4]

The sample analyzed using MAGLUMI 800 analyzer machine that deepened on Chemiluminescence immunoassay (CLIA) system.

We used to perform aldosterone-to-direct renin concentration ratio (ADRR) which is calculated by direct renin concentration (DRC) instead of aldosterone-to-plasma renin activity ratio (ARR).

Our results are corrected, compared and followed the references of ARUP laboratories, which is national nonprofit and academic reference laboratory at the forefront of diagnostic medicine, founded In 1984 by a group of University of Utah pathologists in USA.[17]

Results

This study included fifty hypertensive patients presented with mean age of 35.8 ± 11.1 years and range of (14–60 years); 30% of patients were less than 30 years age, 44% of them were in age group 30–39 years, 10% of them were in age group 40–49 years and 16% of patients were 50 years age and more. Male hypertensive patients were more than females (56% vs. 44%) (Table 1 and Figures 1 and 2).

The past history of atherosclerotic cardiovascular disease (ASCVD) was positive in 12% of hypertensive patients. Family history of ASCVD was positive in 30% of hypertensive patients. The adrenal adenoma was positive in 18% of hypertensive patients (Table 2 and Figure 3).

Mean serum potassium level of hypertensive patients was (3.9 mEq/L); 24% of them had low serum potassium level. Mean plasma aldosterone level of hypertensive patients was (18.2 ng/dl); 28% of them had high serum aldosterone level. Mean plasma direct renin concentration level of hypertensive patients was (20.4 pg/ml); 32% of them had low plasma direct renin concentration level. Mean Aldosterone/renin ratio of hypertensive patients was (5.5); 32% of them had Aldosterone/renin ratio of more than 3.7 (Table 3).

The final diagnosis of primary aldosteronism was detected in 4 (8%) hypertensive patients, while favorable diagnosis of primary aldosteronism was shown by 13 (26%) hypertensive patients and high suspicion of primary aldosteronism was detected in 7 (14%) hypertensive patients (Table 4 and Figure 4).

No significant differences were observed between hypertensive patients with final primary aldosteronism diagnosis and hypertensive patients without final primary aldosteronism diagnosis regarding age (P = 0.13), gender (P = 0.8), past history of ASCVD (P = 0.44), family history of ASCVD (P = 0.36) and adrenal adenoma (P = 0.08) (Table 5).

No significant differences were observed between hypertensive patients with primary aldosteronism favorable diagnosis and hypertensive patients without primary aldosteronism

Table 1. **ARUP reference interval**[15,18]

Component	Reference Interval			
	Age	Posture unspecified	Supine	Upright
Serum aldosterone	0–6 days	5–102 ng/dL		
	1–3 weeks	6–179 ng/dL		
	1–11 months	7–99 ng/dL		
	1–2 years	7–93 ng/dL		
	3–10 years	4–44 ng/dL		
	11–14 years	4–31 ng/dL		
	15 years and older	Less than or equal to 21 ng/dL	Less than or equal to 16 ng/dL	4–21 ng/dL
Direct renin concentration	2.5–45.7 pg/mL			
Aldosterone/direct renin concentration		0.1–3.7		
	Aldosterone/direct renin ratio of greater than 3.7 is suggestive of hyperaldosteronism			

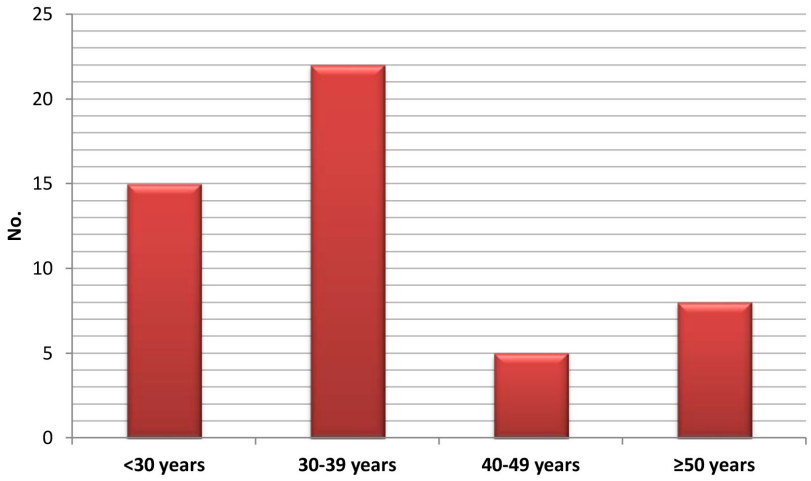

Fig. 1 **Age distribution.**

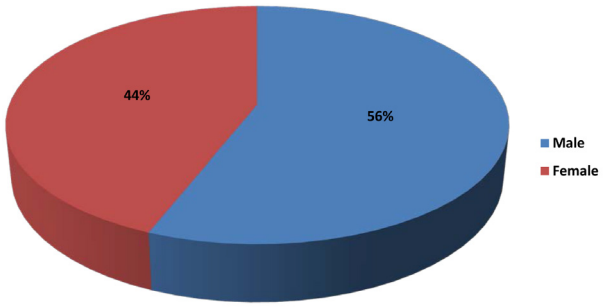

Fig. 2 **Gender distribution.**

Table 2. **Demographic characteristics of hypertensive patients**

Variables	No.	%
Age Mean ± SD (35.8 ± 11.1 years)		
<30 years	15	30.0
30–39 years	22	44.0
40–49 years	5	10.0
≥50 years	8	16.0
Total	50	100.0
Gender		
Male	28	56.0
Female	22	44.0
Total	50	100.0

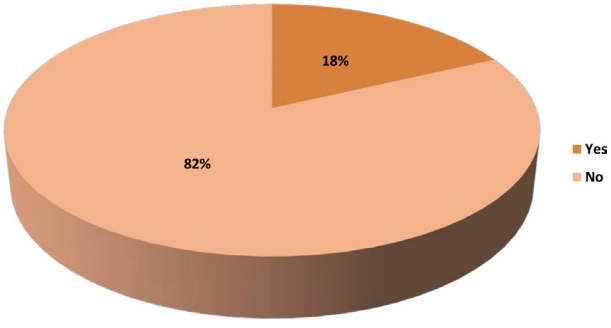

Fig. 3 **Adrenal adenoma.**

Table 3. **Clinical characteristics of hypertensive patients**

Variables	No.	%
Past history of ASCVD		
Positive	6	12.0
Negative	44	88.0
Total	50	100.0
Family history of ASCVD		
Positive	15	30.0
Negative	35	70.0
Total	50	100.0
Adrenal adenoma		
Positive	9	18.0
Negative	41	82.0
Total	50	100.0

Table 4. **Investigations measures findings of hypertensive patients**

Variables	No.	%
Serum potassium Mean ± SD (3.9 ± 0.65 mEq/L)		
Normal	38	76.0
Low	12	24.0
Total	50	100.0
Plasma aldosterone Mean ± SD (18.2 ± 12.5 ng/dl)		
Normal	36	72.0
High	14	28.0
Total	50	100.0
Direct renin concentration Mean ± SD (20.4 ± 53.9 pg/ml)		
Normal	34	68.0
Low	16	32.0
Total	50	100.0
Aldosterone/renin ratio Mean ± SD (5.5 ± 8.9)		
≤3.7	34	68.0
>3.7	16	32.0
Total	50	100.0

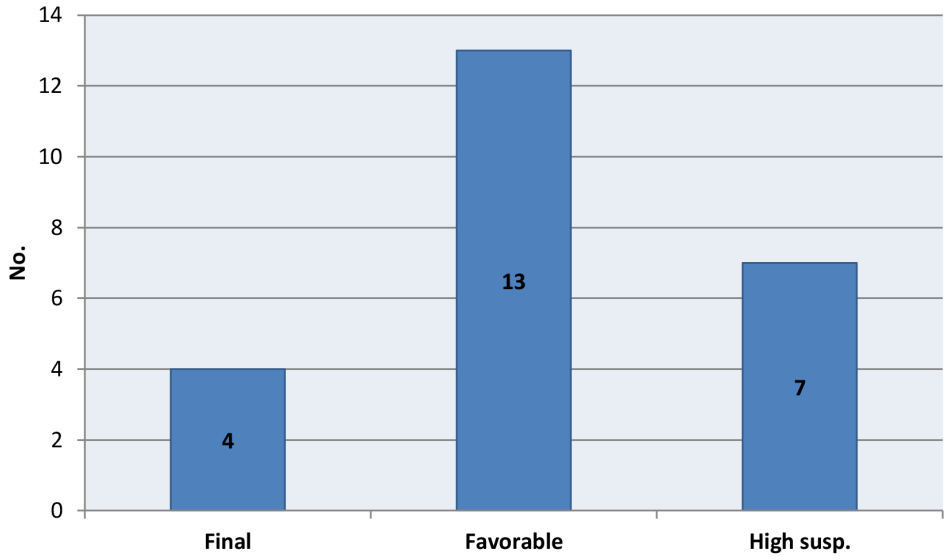

Fig. 4 **Primary aldosteronism diagnosis.**

Table 5. **Interpretation of investigations findings**

Variables	No.	%
Primary aldosteronism		
Yes	4	8.0
No	46	92.0
Total	50	100.0
Favorable primary aldosteronism		
Yes	13	26.0
No	37	74.0
Total	50	100.0
High suspicion primary aldosteronism		
Yes	7	14.0
No	43	86.0
Total	50	100.0

favorable diagnosis regarding age ($P = 0.62$), gender ($P = 0.13$), past history of ASCVD ($P = 0.57$), family history of ASCVD ($P = 0.9$) and adrenal adenoma ($P = 0.58$) (Table 6).

No significant differences were observed between hypertensive patients with primary aldosteronism high suspicion and hypertensive patients without primary aldosteronism high suspicion regarding age ($P = 0.76$), gender ($P = 0.9$), past history of ASCVD ($P = 0.29$), family history of ASCVD ($P = 0.9$) and adrenal adenoma ($P = 0.06$) (Tables 7, 8).

Discussion

Our study is cross-sectional of sample of hypertensive patients in order to establish a screening modality for primary aldosteronism. Although hyperaldosteronism represents the most common cause of endocrine causes of hypertension and represents a risk factor for cardiovascular diseases, it is still under diagnosed and untreated.

Full fit the work up to confirm the diagnosis of primary aldosteronism is costly, require time and preparation, so specify the target patient according to specific criteria and follow specific recommendations in case-detection phase will help to increase the sensitivity of case-detection, these are correction of hypokalemia, advice for sodium consumption before the test and modulate anti-hypertensive therapy before testing in a way that not affecting blood pressure control.[11]

The first problem in this study is how to unify lab results in order to get a correct results as most references use renin activity not renin concentration and by using renin concentration the whole numbers and ratios should be changed, so we used the ARUP laboratories as references (which is national nonprofit and academic reference laboratory at the forefront of diagnostic medicine, founded In 1984 by a group of University of Utah pathologists in USA),[17] and the test kit used for renin concentration was in international unit (micro IU/ml) and in order to change it to (pg/ml) as in reference to calculate the aldosterone direct renin concentration ratio (ADRR) we should multiply by (0.6) which is the conversion factor and the normal range of the ADRR is 0.1–3.7 (ng/dl)/(pg/ml) which is totally different from normal range of aldosterone renin activity ratio (ARR) which should be less than 20. Using renin concentration instead of renin activity carry some advantages in that it is faster, simpler, more reproducible[12] and has good sensitivity (95%) and specificity (95%) as shown by meta-analysis of Aldosterone/direct renin concentration ratio as a screening test for primary aldosteronism done by the Department of Endocrinology, The First Affiliated Hospital of Chongqing Medical University, China.[13]

Using aldosterone direct renin concentration ratio (ADRR) alone make the screen less sensitive, while using other variables, serum potassium; plasma aldosterone and the (ADRR) with recommendations given before testing, salt consumption; 1 hour ambulation before testing and upright positioning during testing,[11] make the screen more sensitive even with the use of direct renin concentration instead of renin activity.[12]

The patients that show positive screen results subdivided into 3 groups,[19] first patients that confirmed with primary aldosteronism from screen results because they show the 3 criteria, hypokalemia; high plasma aldosterone and low plasma

Table 6. **Distribution of general characteristics according to primary aldosteronism final diagnosis**

Variables	Diagnosis				*P*
	Yes		No		
	No.	%	No.	%	
Age					0.13*NS
<30 years	0	–	15	32.6	
30–39 years	4	100.0	18	39.1	
40–49 years	0	–	5	10.9	
≥50 years	0	–	8	17.4	
Gender					0.8*NS
Male	2	50.0	26	56.5	
Female	2	50.0	20	43.5	
Past history of ASCVD					0.44*NS
Positive	0	–	6	13.0	
Negative	4	100.0	40	87.0	
Family history of ASCVD					0.36*NS
Positive	2	50.0	13	28.3	
Negative	2	50.0	33	71.7	
Adrenal adenoma					0.08*NS
Positive	2	50.0	7	15.2	
Negative	2	50.0	39	84.8	

*Fishers exact test, NS = Not significant.

Table 7. **Distribution of general characteristics according to primary aldosteronism favorable diagnosis**

Variables	Favorable diagnosis				*P*
	Yes		No		
	No.	%	No.	%	
Age					0.62*NS
<30 years	5	38.5	10	27.0	
30–39 years	4	30.8	18	48.6	
40–49 years	1	7.7	4	10.8	
≥50 years	3	23.1	5	13.5	
Gender					0.13*NS
Male	5	38.5	23	62.2	
Female	8	61.5	14	37.8	
Past history of ASCVD					0.57*NS
Positive	1	7.7	5	13.5	
Negative	12	92.3	32	86.5	
Family history of ASCVD					0.9*NS
Positive	4	30.8	11	29.7	
Negative	9	69.2	26	70.3	
Adrenal adenoma					0.58*NS
Positive	3	23.1	6	16.2	
Negative	10	76.9	31	83.8	

*Fishers exact test, NS = Not significant.

Table 8. **Distribution of general characteristics according to primary aldosteronism high suspicion**

Variables	High suspicious diagnosis				*P*
	Yes		No		
	No.	%	No.	%	
Age					0.76*NS
<30 years	2	28.6	13	30.2	
30–39 years	4	57.1	18	41.9	
40–49 years	0	–	5	11.6	
≥50 years	1	14.3	7	16.3	
Gender					0.9*NS
Male	4	57.1	24	55.8	
Female	3	42.9	19	44.2	
Past history of ASCVD					0.29*NS
Positive	0	–	6	14.0	
Negative	7	100.0	37	86.0	
Family history of ASCVD					0.9*NS
Positive	2	28.6	13	30.2	
Negative	5	71.4	30	69.8	
Adrenal adenoma					0.06*NS
Positive	3	42.9	6	14.0	
Negative	4	57.1	37	86.0	

*Fishers exact test, NS = Not significant.

renin concentration, the second group was patients with high suspension of primary aldosteronism those who show high plasma aldosterone, above normal reference, low direct renin concentration and ADRR above 5.55 ng/dl/pg/ml, and the third group was those with favorable primary aldosteronism those who show plasma aldosterone above 15 ng/dl, low direct renin concentration and ADRR above 3.7 ng/dl/pg/ml.

Four patients (8%) were confirmed to have primary aldosteronism by using (ADRR) as they full fit the 3 criteria, without further confirmatory testing, while 13 patients (26%) were favorable to have primary aldosteronism and 7 patients (14%) with high suspicion of primary aldosteronism but both need confirmatory testing. And so using all the recommendations and instructions during screening for primary aldosteronism can help to reach the diagnosis.

Our results show no significant differences between patients favorable, high suspicion or diagnosed with primary aldosteronism and other patients in the study regarding age, gender, personal or family history of ASCVD and presence of adrenal adenoma.

Too many difficulties and limitations we face in our study, first and most important was the cost of the screen, time of patient preparation for the laboratory testing and lack of resources, second was how to unify the laboratory work and numbers to get an accurate results, specially we are using direct renin concentration not activity as most references did,[20] and third was lack of both patients and medical staff knowledge about primary aldosteronism and how common this condition is so it is not easy to find a proper patient for screening.

Conclusion

Primary aldosteronism is not uncommon health problem, screening by following the recommendation result in diagnosing and detecting highly suspected hypertensive patients more accurately. Using direct renin concentration instead of renin activity is simple, cheap, fast and reproducible.

Recommendations

1. Notify and educate primary health providers and internists about primary aldosteronism as a major secondary cause of hypertension and as a cause of important morbidity.
2. Proper recommendations of testing procedure can make the screen easier, cheaper and shorter in time.
3. Focusing on laboratory results and unify results units make our results and screen more accurate.
4. Screening of larger number of patients in future in important in order to improve our results.

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