Review
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A clinical update on Primary Aldosteronism; Are we seeing only the tip of an iceberg?

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Abstract

Primary Aldosteronism (PA) is a common form of secondary hypertension, often undiagnosed, untreated, and overlooked leading to excess cardiovascular morbidity and mortality. Until recently it is being recognized as a binary disease. Recent evidence suggests PA is a disease spanning a continuum from subclinical stages to more florid disease manifesting as Conn's syndrome. Timely diagnosis and appropriate surgical intervention can cure hypertension in PA whereas it can reduce hypertension-related target organ damage and excess mortality and morbidity associated with aldosterone excess. Unfortunately, most clinicians are still in the dark with regard to the pitfalls of diagnosing PA, thus detecting only the tip of the iceberg.

Keywords: Primary Aldosteronism, Secondary Hypertension, Aldosterone Renin ratio, Adrenal Venous Sampling

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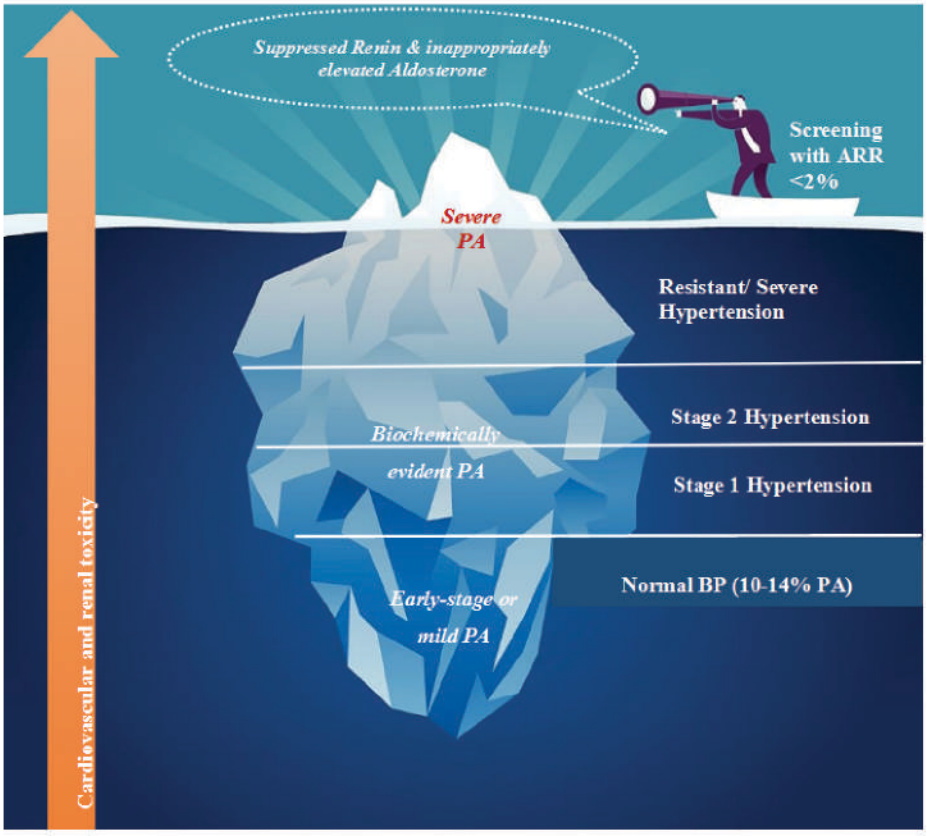
Graphical Abstract



Introduction

Primary aldosteronism (PA) is characterized by renin and angiotensin II independent non-suppressible aldosterone production leading to a status of sodium and volume overload.PA as first described by J. W. Conn in a 1955 paper was considered a rare cause of secondary hypertension. However, currently, PA is recognized as the leading cause of secondary hypertension. According to some experts the rising prevalence of hyperaldosteronism and associated cardiorenal morbidity, warrants excluding it at least once during the lifetime of every hypertensive patient[1]. Evolving knowledge of PA demonstrates a disease with a spectrum of clinical severity rather than a categorical disease. Thus, diagnosing it requires us to modify our screening strategies according to the newfound knowledge. The importance of diagnosing PA lies in the simplicity of its treatment. Treatment with either mineralocorticoid receptor antagonists (MRA) and /or adrenalectomy in unilateral cases will mitigate the toxic effects of aldosterone effectively. However current challenge in PA management is the delay or the non-diagnosis of the disease. It can be easily resolved by knowledge dissemination on the current concepts of PA. This review targets to address this gap between the existing knowledge of PA and its clinical application among clinicians.

Pathogenesis

Pathogenesis of PA is largely attributed to somatic mutations. Heritable germline mutations causing familial forms of hyperaldosteronism are rare. Identified somatic genetic mutations all encode ion channels whose activity signals for increased activity of CYP11B2/aldosterone synthase leading to unregulated aldosterone synthesis[1].

In sporadic PA, clinical spectrum of mild commonly unrecognized form to overt phenotype with severe hypertension with cardiorenal adverse effects is a result of the severity of the genetic mutation as well as their cumulative effect. A few examples of such genetic mutations contributing to familial as well as sporadic PA are mentioned in table 1.

Table 1: genetic mutations associated with primary aldosteronism [2]

Somatic mutations	Germline mutations	
Potassium Inwardly Rectifying Channel Subfamily J Member 5 (KCNJ5)	Familial hyperaldosteronism type	Genetic mutations
Calcium Voltage-Gated Channel Subunit Alpha1 D (CACNA1D)	FH1	Chimeric gene from crossover between CYP11B1(11β hydroxylase – cortisol biosynthetic enzyme) and CYPB11B2
Calcium Voltage-Gated Channel Subunit Alpha1 H (CACNA1H)	FH2	Chloride Voltage-Gated Channel 2 (CLCN2)
Chloride Voltage-Gated Channel 2 (CLCN2)	FH3	KCNJ5
ATPases: ATPase Na+/K+ Transporting Subunit Alpha 1 (ATP1A1)	FH4	CACNA1H
ATPase Plasma Membrane Ca2+ Transporting 3 (ATP2B3)	PASNA syndrome (PA, seizures & neurological abnormalities)	CACNA1D

CYP11B2 is the main enzyme responsible for aldosterone synthesis. In young adrenals, CYP11B2 is found continually. But in the aging adrenals, the enzyme is expressed in a discontinuous manner giving rise to aldosterone-producing micronodules (APM) harboring aldosterone-driver somatic mutations[3,4]. However, PA can be a result of lesions with diverse histological characteristics. These lesions can be an APM (previously called "aldosterone-producing cell cluster"), aldosterone-producing adenomas (APA), aldosterone-producing diffuse hyperplasia, and rarely, aldosterone-producing adrenocortical carcinoma[4]. Two or more histopathological types can coexist in the same adrenal. APA usually has the most severe clinical phenotype with more than 90% of APAs being positive for one or more somatic mutations[1].

Prevalence

Prevalence studies on PA are affected by the recommended indications for testing and the diagnostic thresholds used in screening and confirmatory tests. The screening and the confirmatory tests recommended in the 2016 guideline had cut-off values that would diagnose or exclude PA. But the problem with using these cut-offs from a single spot sample for aldosterone and renin is that even the unregulated aldosterone secretion in PA is influenced by diurnal and ultradian rhythms and it can vary from day to day. So, a negative/equivocal result on one day can easily convert to a positive one on repeat testing. Furthermore, these cutoffs are designed to diagnose a binary disease whereas the changing PA landscape reveals it to be a disease with varying degrees of severity. In one study among normotensive patients to hypertensive patients of every stage of severity there was a proportion with non-suppressible aldosterone with suppressed renin in the presence of high sodium balance who was diagnosed with PA. However, PA prevalence paralleled hypertension severity[5]. But, current indications for screening only recognize patients with the severe form of PA with resistant hypertension and organ toxicity[6]. The prevalence of PA in normotensive individuals varies from 11- 14%[5,7,8]. This group of people are at risk of developing hypertension later in life than normotensive people who do not have PA[8].

The take-home message from the epidemiolocal aspect of PA is that it is a more common disease than previously thought of. The patient will go through varying stages of severity presenting to the physician with abundant opportunities to diagnose and treat PA before the irreversible end-organ damage. So, suspecting it and testing it at least in high-risk populations and repeated periodic testing if the clinical suspicion is high is important if we are to tackle PA effectively.

Clinical relevance of PA

Effects of PA extend beyond those expected from elevated blood pressure alone. This is explained by the excessive mineralocorticoid receptor activation in several target organs causing fibrosis, necrosis, and endothelial dysfunction. In a meta-analysis comparing essential hypertensive patients with PA patients of the same degree of hypertension, an increased risk of stroke, coronary artery disease, atrial fibrillation, heart failure, and left ventricular hypertrophy was demonstrated in PA patients[9]. Intravascular volume expansion because of high sodium balance in PA can lead to glomerular hyperfiltration causing chronic kidney disease. Due to hyperfiltration, the GFR can be falsely normal. Once the PA is treated it can unmask the underlying renal dysfunction[10,11]. Excessive oxidative stress of PA leads to albuminuria[10].

The risk of developing diabetes mellitus is heightened in PA patients[9]. PA reduces insulin secretion and increases insulin clearance[12]. Another contributory factor could be the co-secretion of cortisol associated with PA in a subset of patients[13]. Obstructive sleep apnea (OSA) has a bidirectional association with hyperaldosteronism. PA patients are more likely to develop OSA. A recent study found a 30% prevalence of PA among patients with OSA and hypertension[14]. On the other hand, OSA patients are also more likely to have secondary hyperaldosteronism because of the RAA system activation due to hypoxia and increased sympathetic drive. PA leads to hypercalciuria and secondary hyperparathyroidism causing nephrolithiasis [15] and osteoporosis[16] respectively.

Current indications for PA screening recognize these adverse health outcomes. But diagnosing PA before these irreversible clinical manifestations will require detecting milder but clinically relevant phenotypes. Several studies worldwide have shown that screening for PA even in high-risk populations is alarmingly low. Thus, diagnosing milder phenotype of PA/earlier stages of PA is going to be impossible in the current setup. Thus, there is a dire need for a change in testing practices for PA.

Diagnostic Approach

Diagnosing PA requires clinicians to have a high degree of suspicion and continuous screening.

With the growing body of evidence, some experts suggest, every hypertensive patient should undergo PA screening at least once in their lifetime. The answer to the cost-effectiveness of such a strategy is the reduction in morbidity associated with hyperaldosteronism. But in resource-constrained Sri Lanka, at least the high-risk populations should undergo testing[17]. It includes patients with,

a. Severe or resistant hypertension
b. Spontaneous or diuretic-induced hypokalemia
c. Hypertension and an adrenal mass
d. Hypertension and sleep apnea
e. Hypertension and atrial fibrillation
f. Strong family history of young-onset (<40 years) hypertension or intravascular hemorrhage

ARR can be done and interpreted without changing antihypertensives and as an outpatient procedure irrespective of the time of the day. A false positive result in a walk-in ARR is unlikely. But a negative result in a high-risk patient warrants repeating ARR after withholding MRA or epithelial sodium channel (ENAC) blockers for 4 weeks and correction of hypokalemia[1,2,6]. In 2016 case detection guidelines recommends using ARR for the screening of PA. But using absolute aldosterone and renin values in screening for PA is found to be more sensitive[1].

With this new interpretation (Figure 1), even if you are unable to perform further testing, as it is PA unless proven otherwise there is an opportunity for medical management. Necessity for further confirmation of PA depends on the aldosterone value (Figure 2). The opinion on absolute aldosterone value in confirming "overt PA" without further testing varies among experts as some suggest the cutoff of >20ng/dl and spontaneous hypokalemia as an absolute prerequisite[6]. However, the higher the aldosterone values more confident we can be about the PA diagnosis. Saline loading and salt loading were previously known as confirmatory testing. But they better serve the purpose of excluding PA diagnosis in this newly proposed algorithm when it is negative, as we will be doing these suppression testing in patientswho are already 'diagnosed with PA' [1].

Once the diagnosis is consolidated next step is localization to determine the unilateral or bilateral nature of the disease. It is done through CT- adrenals with or without adrenal venous sampling. (Refer to figure 3)

AVS is the gold standard investigation for localization. It is indicated in all PA patients who are willing to undergo surgery. However, in a resource-limited setting like Sri Lanka, amidst the current health economic crisis choosing the best candidates for AVS will be determined by the expected outcome after surgery. If hypertension associated with PA is likely to be cured /well controlled following surgery, those patients will benefit more from undergoing AVS. The following factors predict a better response to adrenalectomy in PA patients [18,19].

a. Fewer number of antihypertensives preoperatively (less than 2)
b. Hypertension duration of fewer than 5 years
c. Higher aldosterone levels
d. One or no first-degree family members with hypertension
e. Younger age

When PA is secondary to an adenoma the clinical severity is much higher compared to cases of unilateral /bilateral hyperplasia[6].

The clinical outcome after the adrenalectomy will be better in such cases if there is no irreversible end-organ damage. Even though guideline recommendation for AVS in every PA patient is there considering the cost and benefit we ought to be more selective in deciding to go ahead with AVS.

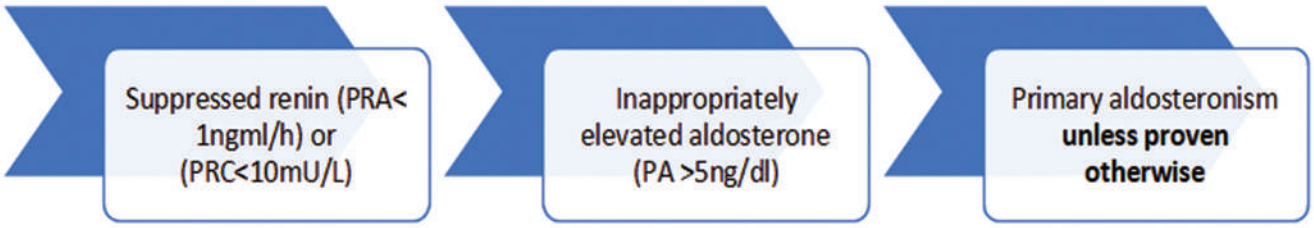


Figure 1 : Proposed interpretation of ARR testing in suspected PA
PRA- plasma renin activity, PRC- plasma renin concentration, PAC-Plasma Aldosterone Concentration

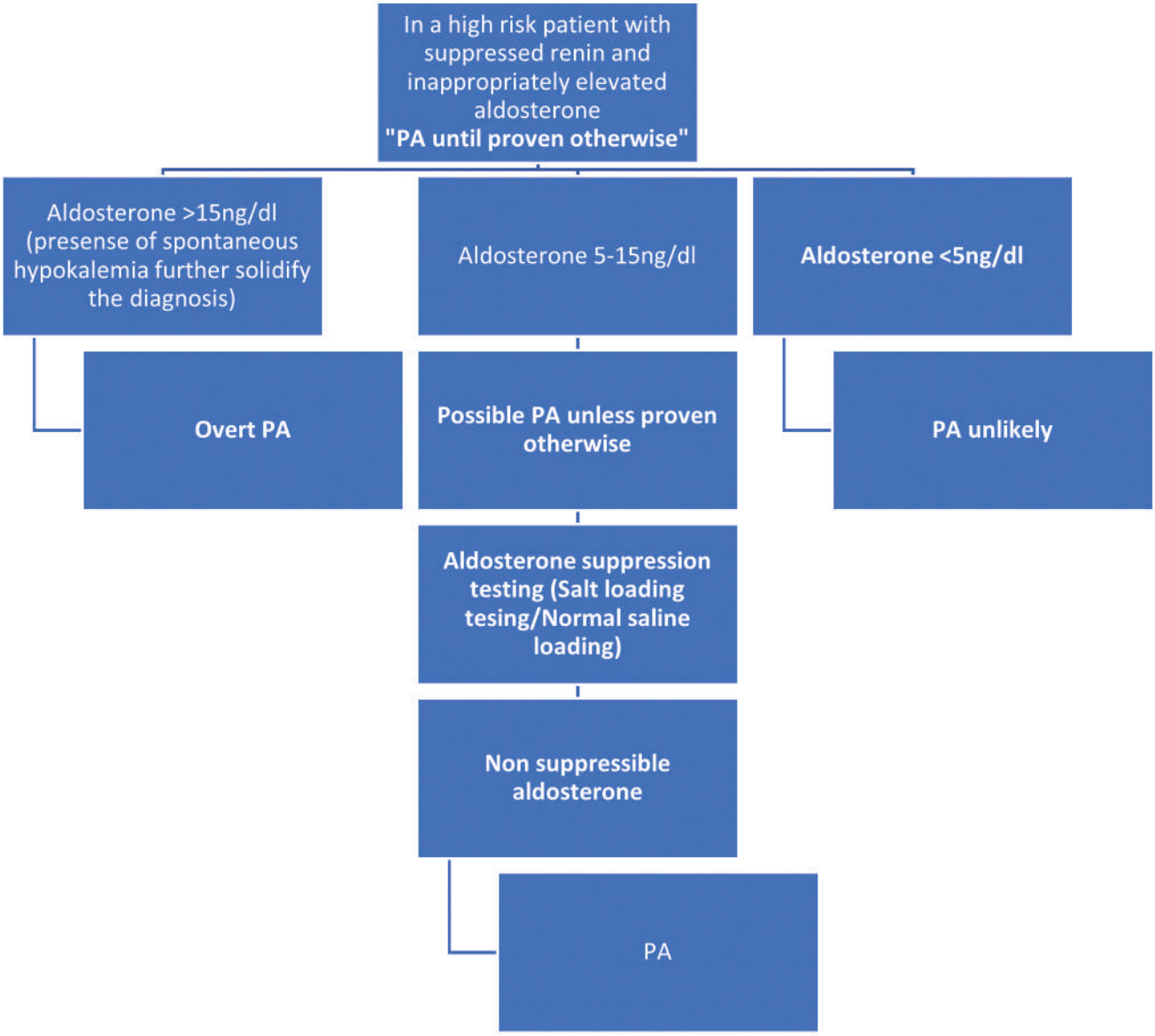


Figure 2: Proposed New Algorithm for Diagnosis of PA

Adrenal Venous Sampling

AVS is a minimally invasive procedure, but it is technically challenging, and requiring expertise. Doing it in a high-volume center with a dedicated interventional radiologist will achieve the best possible outcome. Even though the procedural aspect of AVS is beyond the scope of this article, the interpretation of AVS will be discussed briefly. There is no standardized protocol for AVS. Various centers use various protocols depending on available facilities which include stimulated AVS with corticotrophin infusion and unstimulated AVS. Catheterization of adrenal veins also can be sequential or simultaneous[20]. Interpretation of AVS results depends on the selectivity index, lateralization index, and contralateral suppression index[20]. Before AVS, performing overnight dexamethasone suppression testing to exclude autonomous cortisol secretion is important as it can influence the interpretation. When there is co-secretion of cortisol, depending on the adrenal lesion characteristics and degree of cortisol burden surgery may be warranted without further investigations for hyperaldosteronism.[18]

Treatment

Treatment of PA will depend on whether the disease is unilateral or bilateral. In unilateral disease laparoscopic adrenalectomy is the treatment of choice. Whereas bilateral disease is managed medically with MRA and if necessary with ENAC blockers. Adenectomy for unilateral disease or adrenal-sparing surgery is not recommended considering the improved understanding of the histopathological basis of PA. For example, the adenoma can be nonfunctioning with APM being the source of autonomous aldosterone which is in the normal-looking adjacent adrenal tissue[21].

Table 2: Interpretation of AVS results

Selectivity index (SI)	Adrenal vein cortisol/IVC cortisol	SI of 2 or more for unstimulated AVS (5 or more for stimulated AVS) indicate successful adrenal vein catheterization.
Lateralization index (LI)	$\frac{PAC_{dominant}/PCC_{dominant}}{PAC_{non\ dominant}/PCC_{non\ dominant}}$	LI of >2 in unstimulated AVS (>4 in a stimulated AVS) indicates an aldosterone-secreting lesion on the dominant side.
Contralateral suppression index	$\frac{PAC_{cannulated\ side}/PCC_{cannulated\ side}}{PAC_{IVC}/PCC_{IVC}}$	A contralateral suppression index of <0.5 indicates an aldosterone-secreting lesion on the non-cannulated side. This is used when only one adrenal vein is successfully cannulated.

** PAC - plasma aldosterone concentration, PCC - plasma cortisol concentration, IVC - Inferior vena cava*

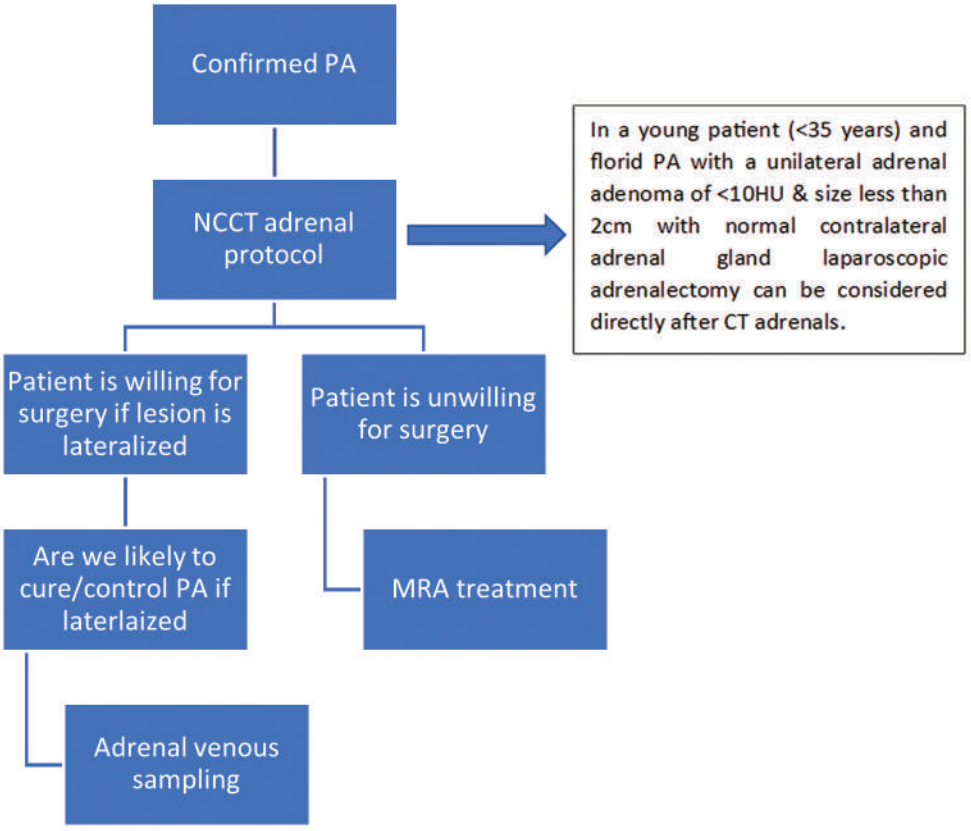


Figure 3: Subtype Classififcation in PA

Salt restriction is advised along with MRAs in medically managed PA. Spironolactone and eplerenone are the commonly used MRAs. Spironolactone is more potent, longer-acting, and cheaper than eplerenone. But antiandrogenic side effects, including painful gynecomastia and decreased libido in males and menstrual irregularities in females, may require the use of eplerenone. When these are inadequate ENAC blockers can be added[1]. The target of medical therapy would be to maintain a potassium level in the upper normal range without replacement and to keep renin levels non-suppressed as it will indirectly indicate the adequate blockade of aldosterone activity[6]. When both the medical and surgical management options are available surgery seems to have better outcomes, especially concerning renal outcomes and quality of life[11,22].

Conclusion

PA is more prevalent than previously thought of and thinking of it as a disease spectrum rather than a binary disease will help in detecting more PA cases. As PA can be managed effectively with either surgery or MRAs, diagnosing it will reduce the excess cardiovascular and renal morbidity associated with hyperaldosteronism and improve the quality of life.

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