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Research Advances in Subtype Classification and Diagnosis of Primary Aldosteronism

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Abstract

Primary aldosteronism (PA), a prevalent form of secondary hypertension, compared with essential hypertension, PA patients exhibit significantly higher risks of cardiovascular/cerebrovascular events and renal impairment. The goal of subtype diagnosis is to clarify the etiology and determine subsequent treatment strategies. Due to inadequate understanding of PA among most clinicians and insufficient emphasis on its diagnosis and treatment, there is a lack of validated clinical research data. Current clinical studies on PA subtyping diagnosis are predominantly limited in scope. PA subtyping diagnosis has remained a clinical challenge. Future large-scale, multicenter clinical studies are required to further investigate PA subtyping diagnostic methods, thereby enhancing diagnostic and therapeutic approaches for PA patients. Regarding the subtyping methods for PA current commonly used methods include Adrenal CT, Adrenal Venous Sampling (AVS), Positron Emission Tomography-Computed Tomography (PET/CT), clinical prediction models, clinical trials, biochemical markers, and genetic testing. If AVS cannot be performed due to other factors, subtyping diagnosis may be conducted using the aforementioned alternative methods, with comprehensive analysis integrated with the patient's actual clinical data. For PA patients who meet the criteria for adrenal venous sampling (AVS), AVS remains the preferentially recommended method for subtype diagnosis. In conclusion, although multiple PA subtyping diagnostic methods have been proposed—including Adrenal CT, PET/CT, clinical prediction models, clinical trials, biochemical markers, and genetic testing—which can assist in PA subtyping diagnosis to some extent, all exhibit inherent limitations. None can match the sensitivity and specificity of Adrenal Venous Sampling (AVS). Therefore, AVS remains the gold standard for PA subtyping diagnosis. This article provides a comprehensive review of current PA subtyping diagnosis approaches. In order to provide clinicians with more

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choices for the classification diagnosis and treatment of patients with Primary aldosteronism.

Keywords

Primary Aldosteronism, Subtype Classification, Diagnosis, Adrenal Venous Sampling

1. Introduction

Primary aldosteronism (PA), a prevalent form of secondary hypertension, constitutes over 5% of newly diagnosed hypertensive cases [1] and accounts for 17% - 23% of resistant hypertension cases [2]. Compared with essential hypertension, PA patients exhibit significantly higher risks of cardiovascular/cerebrovascular events and renal impairment.

PA is etiologically classified into unilateral PA (unilateral primary aldosteronism, UPA), such as aldosterone-producing adenoma, aldosterone carcinoma, and unilateral adrenal cortical hyperplasia, as well as bilateral PA (bilateral primary aldosteronism, BPA), including idiopathic hyperaldosteronism and familial hyperaldosteronism [3]. The goal of subtype diagnosis is to clarify the etiology and determine subsequent treatment strategies. By identifying whether the adrenal lesion is unilateral or bilateral, different therapeutic approaches can be implemented: unilateral cases typically undergo surgical intervention, while bilateral cases are primarily managed with aldosterone receptor antagonists. Regarding the subtyping methods for PA [4], current commonly used methods include Adrenal CT, Adrenal Venous Sampling (AVS), Positron Emission Tomography-Computed Tomography (PET/CT), clinical prediction models, clinical trials, biochemical markers, and genetic testing. PA subtyping diagnosis has remained a clinical challenge. This article provides a comprehensive review of current PA subtyping diagnosis approaches.

2. Adrenal CT

Adrenal CT serves as the primary modality for PA subtype classification due to its advantages of visualization capabilities, non-invasiveness, rapidity, and cost-effectiveness. The 2016 Endocrine Society guidelines [5] recommended that all PA patients must undergo CT imaging. Furthermore, PA patients younger than 35 years with spontaneous hypokalemia, marked aldosterone hypersecretion, unilateral adrenal adenoma on Adrenal CT, and normal contralateral adrenal morphology may proceed directly to surgical treatment without requiring AVS [5].

Numerous studies have demonstrated that adrenal CT has very limited value in PA subtyping diagnosis. Aya *et al.* [6] have reported that the consistency rate between adrenal CT and AVS in adrenal subtype diagnosis is merely 51%. A 2019 study conducted by the First Affiliated Hospital of Xi'an Jiaotong University in

China [7] also demonstrated that among 42 PA patients, the concordance rate between Adrenal CT and AVS in PA subtyping diagnosis was 64% (16/25). If treatment decisions were based solely on Adrenal CT findings, it may result in inappropriate treatment for 32% (8/25) of patients, including 12% (3/25) undergoing unnecessary adrenalectomy and 20% (5/25) who should have undergone surgery being recommended for medical management. Furthermore, Tracy *et al.* [8] conducted a retrospective study comparing treatment outcomes of adrenalectomy based on Adrenal CT findings (235 cases) versus AVS (526 cases) showed that the biochemical remission rate was significantly lower in the former group compared to the latter (80% vs. 93%, $P < 0.001$). This indicates discrepancies in the consistency between adrenal CT and AVS for PA subtyping diagnosis. Furthermore, Gian *et al.* [9]'s cohort study revealed that 28% of surgically cured unilateral PA patients showed no adrenal CT abnormalities, with adrenal CT demonstrating low specificity in distinguishing aldosterone-producing tumors from non-functional adenomas. Additionally, its detection rate for small tumors remains suboptimal. Therefore, relying solely on adrenal CT for PA subtyping proves unreliable, potentially leading to clinical misjudgments that may compromise treatment efficacy and prognosis.

3. Adrenal Venous Sampling (AVS)

AVS is currently recognized as the most reliable and accurate method for determining adrenal functional lateralization, and is widely regarded as the "Gold Standard" for PA subtyping diagnosis [3]. Currently, both the sensitivity and specificity of AVS can exceed 90%. Moreover, AVS demonstrates greater advantages in diagnosing PA patients where Adrenal CT fails to determine subtypes, and is more conducive to accurate PA classification. According to the 2020 Expert Consensus on Adrenal Venous Sampling [10], it is recommended that PA patients with surgical indications should undergo AVS to guide treatment selection.

AVS can currently be categorized into ACTH-stimulated AVS and non-ACTH-stimulated AVS (*i.e.*, conventional AVS). Silvia *et al.* [11] had an analysis of 76 PA patients undergoing conventional AVS and ACTH-stimulated AVS revealed that ACTH stimulation improved bilateral adrenal vein cannulation success rates. The consistency in diagnostic outcomes between the two AVS methods reached 88%. Studies have indicated that ACTH stimulation enhances bilateral adrenal vein cannulation success rates without significantly affecting the determination of the dominant side [12]. However, a Japanese study demonstrated that ACTH stimulation increased AVS success rates from 67% to 89%, while the proportion of dominant side identification decreased from 62% to 28% [13]. Additional research has shown that ACTH stimulation may reduce the lateralization index during AVS [14] [15]. Currently, there is no consensus regarding which AVS method is superior. Meanwhile, AVS sampling results can be influenced by multiple factors including emotional state, stress, hypokalemia, and certain antihypertensive medications. Therefore, AVS findings require cautious interpretation considering these

variables, particularly in patients where AVS measurements indicate no dominant lateralization. If the influence of prior medication use or other factors cannot be excluded, blood sampling should be repeated after medication adjustment followed by a 4 - 6 weeks washout period [10]. Furthermore, as an invasive procedure, AVS is not only time-consuming and labor-intensive but also technically demanding, which hinders its widespread clinical implementation. In China, only a few dozen hospitals routinely perform adrenal venous sampling (AVS), with additional challenges including poor patient compliance, low accessibility, and the absence of unified standardized protocols. Different medical institutions may adopt varying operational procedures and diagnostic cutoff points, leading to heterogeneous interpretations of results [4]. Therefore, it is imperative to enhance clinicians' understanding of PA and AVS, particularly among specialists in cardiovascular medicine, endocrinology, and urology. This will advance the diagnosis and management of PA patients within China's hypertensive population, ensuring proper treatment for undiagnosed PA cases and ultimately improving patients' quality of life.

4. Nuclear Medicine Imaging (PET/CT)

PET/CT is an emerging nuclear medicine imaging technology that offers higher sensitivity and specificity compared to traditional CT. Its greatest advantage over AVS lies in its non-invasive nature. According to the current expert consensus [3], it is recommended that patients aged > 35 years, likely to have unilateral aldosterone-producing adenoma (APA) with surgical intentions but refusing AVS, may directly undergo PET/CT examination.

11C-metomidate (MTO) PET/CT can be applied in the subtype diagnosis of PA. Timothy *et al.* [16] indicate that when the maximum standardized uptake value (SUV max) cutoff in the target lesion area of bilateral adrenal glands during PET/CT scanning is set at 1.25, the sensitivity and specificity of 11C-MTO-PET/CT in diagnosing APA are 76% and 87%, respectively; if the SUV max on the adenoma side is >17, the specificity can reach 100%. However, the production of short-acting 11C-metomidate tracers requires a specialized cyclotron, which is rarely available in general medical centers. Consequently, this technique has rarely been studied since its proposal.

The specific ligand targeting chemokine receptor 4 (68Ga-Pentixafor) PET/CT also contributes to PA subtyping diagnosis, particularly demonstrating high diagnostic value in patients with unilateral adrenal nodules >10 mm on CT. A multicenter prospective study [17] enrolled 100 PA patients and evaluated the diagnostic value of 68Ga-Pentixafor PET/CT in PA subtype classification using AVS as the gold standard for subtype diagnosis. The study [17] found that using the ratio of 10-minute high-side SUVmax to low-side SUVmax in adrenal glands for diagnosing unilateral primary aldosteronism (UPA) demonstrated an area under the receiver operating characteristic (ROC) curve of 0.90. With a cutoff ratio of 1.65, this method achieved a sensitivity of 77% and specificity of 100% for UPA diag-

nosis, while 68 Ga-Pentixafor PET/CT showed a 90% concordance rate with adrenal venous sampling (AVS). In patients with unilateral adrenal nodules larger than 10 mm, the concordance rate between 68Ga-Pentixafor PET/CT and AVS can reach 100%. This study demonstrated that 68Ga-Pentixafor PET/CT exhibits high accuracy in PA subtyping diagnosis, with superior sensitivity and specificity compared to adrenal CT, and shows strong consistency with AVS results. However, its diagnostic efficiency still requires further validation through more prospective, multicenter population-based studies.

In addition, Tsutomu *et al.* [18] revealed that the novel tracer ^{18}F-CDP2230 is a new PET/CT imaging agent with the advantages of a long half-life and no requirement for dexamethasone pretreatment. It demonstrates high selectivity for both 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2). However, there is currently a lack of clinical studies on CDP2230, and its applicability in the subtype diagnosis of PA remains unclear.

One of the most realistic and important problems is the high cost of PET/CT examination, and the general application during follow-up is inconsistent with the economic development level of China [19]. Meanwhile, it has a relatively high missed diagnosis rate, and faces restricted use of radioisotopes, making it difficult to implement widely in most hospitals.

5. Predictive Models

In recent years, clinical predictive models for PA subtype classification have gradually increased. Most models are constructed based on analyses of patients' general demographics, clinical manifestations, laboratory findings, and imaging examination results. The most widely used model is the Küpers scoring system from Japan [20], which incorporates three clinical predictors (typical imaging findings of adenoma, serum potassium < 3.5 mmol/L, and estimated glomerular filtration rate (eGFR) > 100 ml·min^{-1}·1.73 m^{-2}). When the score exceeds 5, the sensitivity for diagnosing unilateral primary aldosteronism (UPA) is 53% with 100% specificity. However, subsequent studies revealed that its specificity significantly decreased in elderly populations [21]. Consequently, researchers have revised the model proposed by Küpers *et al.* They enrolled 406 patients who successfully underwent adrenal venous sampling (AVS), selecting urinary aldosterone as a replacement for eGFR. The results demonstrated that the revised model exhibited a larger area under the ROC curve (AUC = 0.745, 95% CI: 0.667 - 0.813) compared to the Küpers model (AUC = 0.635, 95% CI: 0.552 - 0.713). The optimal cutoff value for distinguishing the presence of dominant secretion lateralization was determined to be 5 points, demonstrating a sensitivity of 45.3% and specificity of 90.5%. Notably, when applied to patients aged ≤ 40 years with a score of 6 points, the specificity reached 100% [22]. However, this model's prerequisite requires patients' serum potassium to be maintained within normal ranges during urinary aldosterone measurements, rendering it inapplicable to patient populations with refractory hypokalemia.

In 2018, Hiroki *et al.* [23] enrolled 1936 PA patients and established a scoring system for diagnosing bilateral PA, incorporating indicators including serum potassium levels, plasma aldosterone concentration (PAC) < 210.0 pg/ml (1 ng/dl = 1 pg/ml), aldosterone-to-renin ratio (ARR) < 620 (renin unit: $ng \cdot ml^{-1} \cdot h^{-1}$), adrenal CT findings, and gender. The model demonstrated an area under the receiver operating characteristic curve (AUC-ROC) of 0.87, outperforming the Küpers score (0.790). Net reclassification index (NRI) analysis further confirmed its superiority over previous models.

In 2019, the endocrinology team at Shanghai Ruijin Hospital developed a more streamlined prediction model incorporating body mass index (BMI), serum potassium levels, and Adrenal CT findings into a nomogram. The model achieved sensitivity and specificity of 86.59% and 87.38% respectively, with an AUC-ROC of 0.894. When the cut-off value was set at 0.9, the specificity reached 100% [24]. While this model shows potential clinical reference value, its generalizability requires further validation due to the current lack of large-scale clinical studies.

In 2024, Chongqing Medical University validated several reported prediction models for idiopathic hyperaldosteronism (IHA), considering aspects such as simplicity, safety, accuracy, and generalizability. The study ultimately concluded that the Hiroki2018 scoring model remains the most suitable for predicting IHA in Chinese populations [25].

Although clinical prediction models are simple, convenient, and non-invasive—with some demonstrating high specificity—this advantage comes at the expense of reduced sensitivity. Moreover, the same predictive model may yield significantly different results across diverse regions and populations, hence there is currently no widely adopted clinical prediction model in practice.

6. Clinical Trials

Recent literature has confirmed that clinical trials also contribute to PA subtyping diagnosis. Research data indicate that the supine saline infusion test (SIT) can not only confirm PA diagnosis but also aid in subtype classification. Study results demonstrate that patients with persistently non-suppressed aldosterone levels after supine SIT are more likely to have aldosterone-producing adenoma (APA) [26]. Other studies have shown that patients with post-SIT plasma aldosterone levels < 300 pmol/L and decreased aldosterone-to-renin ratio (ARR) are more likely to have idiopathic hyperaldosteronism (IHA), with corresponding sensitivity, specificity, and positive predictive values of 48.6%, 96.8%, and 94.7%, respectively [27]. However, this study had an insufficient sample size and unverifiable external validity, making the diagnostic accuracy unable to be reliably assessed.

A recent cross-sectional study by the Chinese PLA General Hospital involving 82 PA patients demonstrated that the APA group showed higher plasma aldosterone concentrations (PAC) and PAC/Cortisol ratios at 30, 60, 90, and 120 minutes after combined 1 mg dexamethasone suppression test and ACTH stimulation test at midnight compared to the IHA group. The study revealed this protocol achieved

91.8% sensitivity and 84.8% specificity in differentiating APA from IHA. This study demonstrates substantial clinical value in effectively differentiating APA and IHA, with the 90-minute PAC and PAC/Cortisol ratio showing optimal diagnostic performance [28].

Additionally, a study conducted by West China Hospital of Sichuan University involving 370 PA patients demonstrated that post-captopril challenge test (CCT) plasma aldosterone concentration (PAC) > 17.0 ng/dL may assist in diagnosing the APA subtype. Patients with post-CCT PAC < 11.7 ng/dL combined with an aldosterone-to-renin ratio (ARR) < 2.8 (ng/dL)/(mU/L) could be excluded from the APA subtype diagnosis [29].

Other research proposed utilizing the adrenocorticotropic hormone (ACTH) stimulation test (AST) as a confirmatory diagnostic for PA. A post-AST PAC > 37.9 ng/dl demonstrated diagnostic sensitivity and specificity of 91.3% and 80.6%, respectively, for predicting unilateral adenomas [30]. Some scholars have proposed that using a post-AST maximum PAC to cortisol ratio < 18.3 ng/L for predicting bilateral hyperplasia demonstrates sensitivity and specificity of 83% and 88% respectively, with an area under the ROC curve of 0.918 [31].

These clinical experimental results provide novel insights for simplifying PA subtype classification workflows and show potential to become alternative approaches for subtype diagnosis of primary aldosteronism.

7. Biochemical Markers

Growing evidence suggests that 18-oxocortisol (18oxoF) and 18-hydroxycortisol (18OHF) hold clinical significance in the subtype diagnosis of PA. Given their high expression in APA, these compounds have been identified as biomarkers for APA and are consequently employed in PA subtype diagnosis.

A study demonstrated that Fumitoshi *et al.* [32] used high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) to measure peripheral blood 18-oxocortisol (18oxoF), researchers found that APA patients exhibited significantly higher peripheral 18oxoF levels than BPA patients. At a cutoff value of 4.7 ng/dl, the diagnostic Sensitivity and Specificity for APA reached 0.83 and 0.99, respectively. Subsequently, Graeme *et al.* [33] revealed that modeling multiple steroid hormones in peripheral plasma measured by mass spectrometry could achieve over 80% accuracy in subtype classification. These studies indicate that mass spectrometry-derived peripheral blood steroid hormone profiles in PA patients contain potential biomarkers for subtype differentiation. However, many medical institutions currently lack the capability to measure 18oxoF and 18-hydroxycortisol (18OHF). Moreover, differences in detection methodologies may lead to inconsistent conclusions, necessitating further clinical research data for validation.

Furthermore, studies have demonstrated a bidirectional stimulatory relationship between parathyroid hormone (PTH) and aldosterone. PA patients exhibit elevated PTH levels and decreased serum calcium levels, with APA patients

demonstrating higher PTH levels compared to IHA patients. This differential PTH expression enables its utilization for subtype diagnosis in PA patients. Under vitamin D-deficient conditions with a cutoff value of 56.44 ng/L, the sensitivity was 66.5% and specificity reached 83.0%. When vitamin D levels were sufficient and using a cutoff of 48.81 ng/L, the sensitivity increased to 70.5% while specificity decreased to 72.6% [34]. However, subtype diagnosis based solely on biochemical markers has weak evidentiary support, necessitating comprehensive evaluation combined with patients' general clinical data and imaging examinations.

8. Genetic Testing

Recent studies have identified gene mutations in sporadic aldosterone-producing adenomas, with KCNJ5 mutations being the most prevalent. A research study reported that [35] among 206 APA patients, 166 cases exhibited gene mutations, of which 158 carried KCNJ5 mutations. The mutation rate of KCNJ5 reached 91% (131/144 cases) in adenoma tissues from aldosterone-producing adenoma patients accompanied by hypokalemia. This indicates that KCNJ5 mutations suggest a higher likelihood of aldosterone-producing adenomas, providing valuable assistance in subtype classification of PA.

With research advancements, multiple genes including the ATP1A1 gene encoding the α1 subunit of Na+/K+ ATPase and the CTNNB1 gene encoding β-catenin have been identified to harbor mutations in APA [36], however, the specific mechanisms have not yet been elucidated. Current research on gene mutations in PA remains actively exploratory and may potentially become one of the methods for PA subtyping diagnosis in the future.

In conclusion, although multiple PA subtyping diagnostic methods have been proposed—including Adrenal CT, PET/CT, clinical prediction models, clinical trials, biochemical markers, and genetic testing - which can assist in PA subtyping diagnosis to some extent, all exhibit inherent limitations. None can match the sensitivity and specificity of Adrenal Venous Sampling (AVS). Therefore, AVS remains the gold standard for PA subtyping diagnosis. For PA patients who meet the criteria for adrenal venous sampling (AVS), AVS remains the preferentially recommended method for subtype diagnosis. If AVS cannot be performed due to other factors, subtyping diagnosis may be conducted using the aforementioned alternative methods, with comprehensive analysis integrated with the patient's actual clinical data. Due to inadequate understanding of PA among most clinicians and insufficient emphasis on its diagnosis and treatment, there is a lack of validated clinical research data. Current clinical studies on PA subtyping diagnosis are predominantly limited in scope. Future large-scale, multicenter clinical studies are required to further investigate PA subtyping diagnostic methods, thereby enhancing diagnostic and therapeutic approaches for PA patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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