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Effect of Age on Aldosterone–Renin Ratio in Screening Primary Aldosteronism

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ABSTRACT

Primary aldosteronism (PA) is the most common endocrine cause of hypertension. The plasma aldosterone-to-renin ratio (ARR) is the most recommended screening tool for PA, but previous studies showed controversy regarding the influence of age on ARR. The aim of the study was to evaluate the impact of age on ARR measured using direct renin concentration (DRC) and its diagnostic value in patients with PA. We retrospectively collected patients with hypertension who attended Xiangya Hospital for PA screening using plasma aldosterone concentration (PAC)/DRC from January 1, 2017 to November 1, 2023. The patients were divided into the groups of PA and essential hypertension (EH) by confirmatory tests. We performed separate correlation analyses of age and DRC, PAC, and ARR, the patients were then further subdivided into four age groups: < 40, 40–49, 50–59, and ≥ 60 years old. Receiver operating characteristic curve and area under the curve (AUC) were used to determine age-specific ARR cutoff values for screening PA. We screened a total of 478 patients, comprising 255 diagnosed with PA (53.35%) and 176 with EH (36.82%). In patients with EH, PAC and DRC decreased with increasing age ($p < 0.001$, $r = -0.34$; $p < 0.001$, $r = -0.28$), whereas ARR increased with age ($p = 0.002$, $r = 0.22$). However, in patients with PA, DRC, PAC, and ARR did not show significant association with age ($p = 0.40$, 0.54, 0.33). The cutoff values of ARR for screening PA in four groups were 17.49, 20.79, 21.01, and 18.22. The optimal ARR cutoff was 22.52 in the all-ages, with an AUC of 0.948 (95% CI: 0.929, 0.966), sensitivity of 89.4%, and specificity of 85.2%. There was no significant correlation between age and DRC or PAC in patients with PA. Compared to the consensus-recommended cutoff of 37 (pg / mL)/(μIU/mL), a lower ARR cutoff may be more appropriate for screening PA.

1 | Introduction

Primary aldosteronism (PA), as the most common endocrine disorder leading to secondary hypertension, is primarily characterized by hypertension and hypokalemia. The prevalence of PA in the population is substantial, and compared to patients with essential hypertension (EH), PA causes more pronounced damage to target organs, including the cardiovascular system, kidneys, and vascular walls. Studies have shown that patients with PA have a 4.2-fold increased risk of stroke, a 6.5-fold increased risk of myocardial infarction, and a 12.1-fold increased risk of atrial fibrillation [1]. Therefore, early identification of PA and implementation of appropriate treatment are crucial to prevent or reverse the damage caused by elevated aldosterone levels on target organs, thereby reducing the incidence and mortality of cardiovascular, renal, and other complications [2]. Currently, the plasma aldosterone–renin ratio (ARR) is recommended by the American Endocrine Society as the primary

screening test for PA [3]. Numerous studies have demonstrated the ARR to be superior in measuring potassium or aldosterone (both of which have lower sensitivity) or renin (which is less specific) in isolation [4–6]. However, due to various factors such as population demographics, geographical location, study design (retrospective or prospective), medications, diet, posture, menstrual cycle, age, renal function, electrolytes, and timing of blood collection [7], and the lack of uniform testing methods internationally, the threshold values for ARR vary widely [8]. Currently, there is much controversy regarding the influence of age on ARR [9–13]. Whether different age groups of patients should use different thresholds for ARR remains contentious. In both healthy individuals and those with hypertension, renin levels decrease with age, leading to an increase in ARR [14, 15]. In patients with PA, considering that ARR may increase with age, using a lower ARR threshold in younger individuals may help identify more patients with PA [16]. Currently, less than 1% of adults with diagnosed primary hypertension are screened for PA [17]. It may result in a significant number of patients with PA remaining undiagnosed, this approach could be beneficial in improving detection rates.

As a result, this retrospective study collected hypertensive patients hospitalized for PA screening and assessed the differences in direct renin concentration (DRC), plasma aldosterone concentration (PAC), and ARR levels among different age groups in patients with PA and EH. Additionally, the study compared the diagnostic efficiency of age-related ARR threshold values in diagnosing PA.

2 | Materials and Methods

2.1 | Study Subjects

This study included hypertensive patients who were admitted to Xiangya Hospital, Central South University for PA screening from January 2017 to November 2023. This study adhered to the principles of the Helsinki Declaration and relevant ethical requirements, approved by the Ethics Committee of Xiangya Hospital, Central South University (ethics number: 202305357).

We screened for PA in patients exhibiting the following characteristics: (1) patients with sustained BP above 150/100 on each of three measurements obtained on different days, with hypertension (BP > 140/90) resistant to three conventional antihypertensive drugs (including a diuretic), or controlled BP (>140/90) on four or more antihypertensive drugs; (2) hypertension and spontaneous or diuretic-induced hypokalemia; (3) hypertension and adrenal incidentaloma; (4) hypertension and sleep apnea; (5) hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (< 40 years); (6) all hypertensive first-degree relatives of patients with PA.

Meanwhile, we excluded the following patients: (1) other common secondary hypertensive patients, such as renal artery stenosis, EH, pheochromocytoma, and Cushing syndrome; (2) patients with severe heart failure, liver dysfunction, renal dysfunction, advanced tumors, and hyperthyroidism; (3) incomplete data, patients who did not strictly discontinue medications that significantly affect the renin–angiotensin–aldosterone system.

Patients with hypertension undergoing PA screening were required to maintain a normal sodium intake before the test. Patients with hypokalemia were supplemented with potassium to achieve normal levels (>3.5 mmol/L) or close to normal levels and discontinued medications that significantly affect ARR, including loop diuretics, thiazides, and spironolactone, for ≥4 weeks, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, contraceptives, and licorice preparations for ≥2 weeks. Alpha-blockers (such as terazosin) and/or non-dihydropyridine calcium channel blockers (such as verapamil) could be used for patients with poorly controlled blood pressure.

We screened a total of 478 patients. Finally, patients were divided into two groups: group of PA (255) and EH (176) (Figure 1). General characteristics of the patients, including gender, age, body mass index (BMI), maximum systolic blood pressure (SBP), maximum diastolic blood pressure (DBP), duration of hypertension, albumin, serum potassium, calcium, phosphorus, magnesium, 24-h urinary potassium, urinary calcium, uric acid, creatinine, lipid profile, standing PAC, standing DRC, and ARR were collected.

2.2 | DRC and PAC Detection Methods

Patients remained in a supine position overnight from 22:00 and stood upright for 4 h from 6:00 the next morning. Blood samples were collected at 10:00 in the morning in an upright position to measure DRC and PAC and calculate the ARR value. The LIAISON XL fully automated chemiluminescence immunoassay (CLIA) analyzer was used for all measurements, strictly following the instructions of the reagent kits. PAC and DRC were detected using CLIA technology. The reagent kits were provided by DiaSorin S.p.A., Italy. The detection range for PAC was 3–100 ng/dL, with intra-batch and inter-batch coefficients of variation (CV) of 2.1%–4.2% and 5.8%–10.5%, respectively. The detection of DRC could reach 500 μIU/mL, with intra-batch and inter-batch CVs of 0.2%–2.7% and 1.9%–12.2%, respectively.

2.3 | Captopril Challenge Test (CCT)

Patients maintained a seated position for 1 h in the early morning on an empty stomach, then orally took 50 mg of captopril and remained seated for 2 h. Blood samples were collected before medication, as well as 1 and 2 h after medication to measure blood potassium concentration, DRC, PAC, and cortisol concentration. An ARR > 30 (pg/mL)/(μIU/mL) or PAC suppression rate < 30% or PAC > 110 pg/mL was considered positive after CCT.

2.4 | Saline Infusion Test (SIT)

Patients maintained a seated position for 1 h, and blood potassium concentration, DRC, PAC, and cortisol concentration were measured. Within 4 h, 2 L of 0.9% normal saline was infused at a constant rate, while the patient remained seated. Blood samples were collected again to check the above indicators. Blood pressure and heart rate changes were closely monitored through-

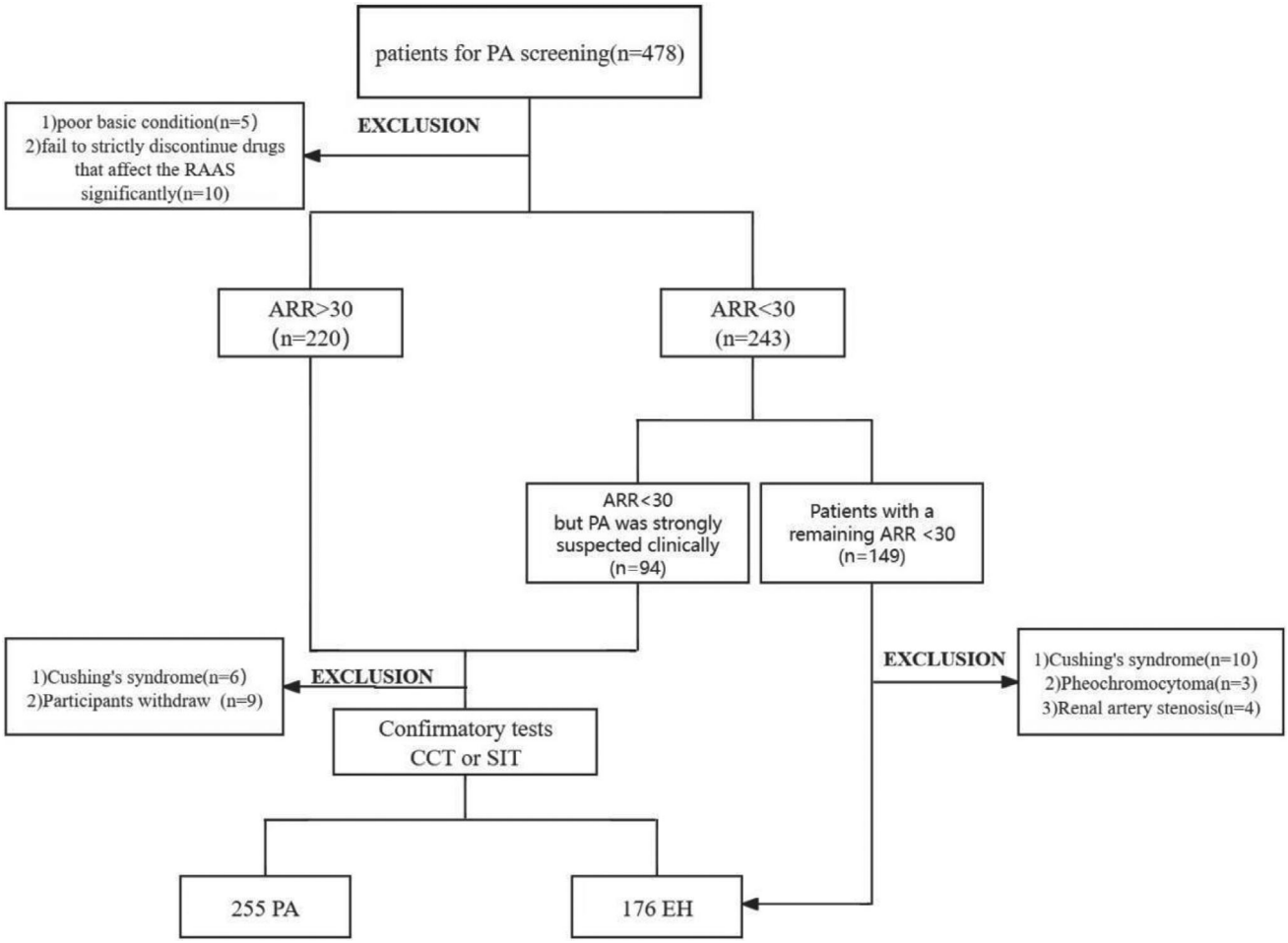

FIGURE 1 | Flowchart of patients with EH and PA were included.

out the process. A PAC > 10 ng/dL after SIT was considered positive.

2.5 | Statistical Analysis

All statistical analyses were conducted using SPSS statistical software version 26.0 (Chicago, IL, USA). Data are presented as mean ± standard deviation or median (interquartile range). For comparisons between groups of continuous variables, *t*-tests and analysis of variance (ANOVA) were used, with LSD post-hoc tests for estimating intergroup differences. Categorical variables were analyzed using chi-square tests. The relationship between age and DRC, PAC, and ARR was assessed using Spearman correlation analysis. Receiver operating characteristic (ROC) curves were used to determine the ARR cutoff values for diagnosing PA in different age groups and to assess their sensitivity and specificity. Graphs were plotted using GraphPad Prism 8.0.1 software. A significance level of $p < 0.05$ was considered statistically significant.

3 | Results

The general characteristics of the two groups of patients were compared in Table 1. In the group of PA, the average age of patients was (49.45 ± 11.05) years, while in the EH, the average age was (47.41 ± 12.69) years. There were no statistically significant differences in gender, age, blood pressure (systolic and diastolic) between the two groups. However, compared to EH with patients, PA exhibited significantly higher PAC, ARR, and a longer duration of hypertension ($p < 0.001$). Conversely, DRC and serum potassium levels were significantly lower in PA with patients compared to EH ($p < 0.001$). Additionally, patients with PA had lower serum calcium levels and relatively higher levels of urinary potassium, urinary calcium, and creatinine.

In patients with EH, DRC and PAC are negatively correlated with age ($r = -0.34$, $p < 0.001$ for DRC; $r = -0.28$, $p < 0.001$ for PAC), while ARR is positively correlated with age ($r = 0.22$, $p = 0.002$) (Figure 2). DRC and PAC decrease with increasing age, with significant differences observed between the ≥60 years group and the ≤ 39 years, 40–49 years, and 50–59 years groups (Figure 3, Table 2). However, the decline in PAC is less pronounced compared to DRC, resulting in an increase in ARR with age (Figure 3, Table 2). Significant differences in ARR are also observed between the ≤ 39 years and ≥ 60 years groups (Figure 3, Table 2). In contrast, in patients with PA, PAC, DRC, or ARR is not correlated with age (Figure 2, Table 3).

Then we conducted ROC curve analysis for the four groups to evaluate the optimal cutoff value of ARR and the accuracy of ARR

TABLE 1 | Comparison of General Information among the Two Groups.

	PA	EH	
	***N* = 255**	***N* = 176**	***p***
male/female	156/99	106/70	0.843
Age (years)	49 ± 11	47 ± 13	0.076
BMI (kg/m2)	25.38 ± 3.31	25.03 ± 3.86	0.318
SBP (mmHg)	170.00 (160.00, 190.00)	176.00 (160.00, 190.00)	0.211
DBP (mmHg)	100.00 (100.00, 110.00)	100 (90.00, 110.00)	0.217
Duration of hypertension (years)	6.00 (2.00, 10.00)	2.00 (1.00, 7.00)	<0.001
Serum potassium (mmol/l)	3.32 (2.97, 3.58)	3.80 (3.57, 3.95)	<0.001
serum calcium (mmol/l)	2.29 (2.23, 2.37)	2.34 (2.26, 2.39)	0.003
Serum phosphorus (mmol/l)	1.05 ± 0.21	1.07 ± 0.21	0.373
serum magnesium (mmol/l)	0.85 (0.79, 0.90)	0.86 (0.86, 0.91)	0.121
urinary potassium (mmol/24 h)	40.39 (28.19, 51.62)	26.29 (18.41, 33.72)	<0.001
urinary calcium (mmol/24 h)	4.83 (3.45, 6.01)	3.68 (2.48, 5.16)	0.001
creatinine (μmol/L)	82.15 (67.95, 95.65)	77.40 (66.00, 90.00)	0.03
uric acid (umol/l)	351.85 (281.33, 413.93)	359.50 (301.80, 42.40)	0.054
LDL (mmol/L)	2.94 ± 0.78	3.05 ± 0.81	0.140
TG (mmol/L)	1.71 (1.11, 1.32)	1.64 (1.13, 2.44)	0.953
TC (mmol/L)	4.54 (3.84, 5.16)	4.53 (3.94, 5.27)	0.423
HDL (mmol/L)	1.03 (0.90, 1.21)	1.06 (0.94, 1.26)	0.166
DRC (μIU/mL)	3.30 (1.82, 7.11)	13.43 (6.64, 28.83)	<0.001
PAC (pg/mL)	265.00 (172.00, 389.00)	129.00 (79.88, 184.00)	<0.001
ARR (pg/mL)/(μ IU/mL)	70.90 (35.07, 146.99)	9.92 (4.73, 15.76)	<0.001

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, cholesterol; TG, triglycerides.

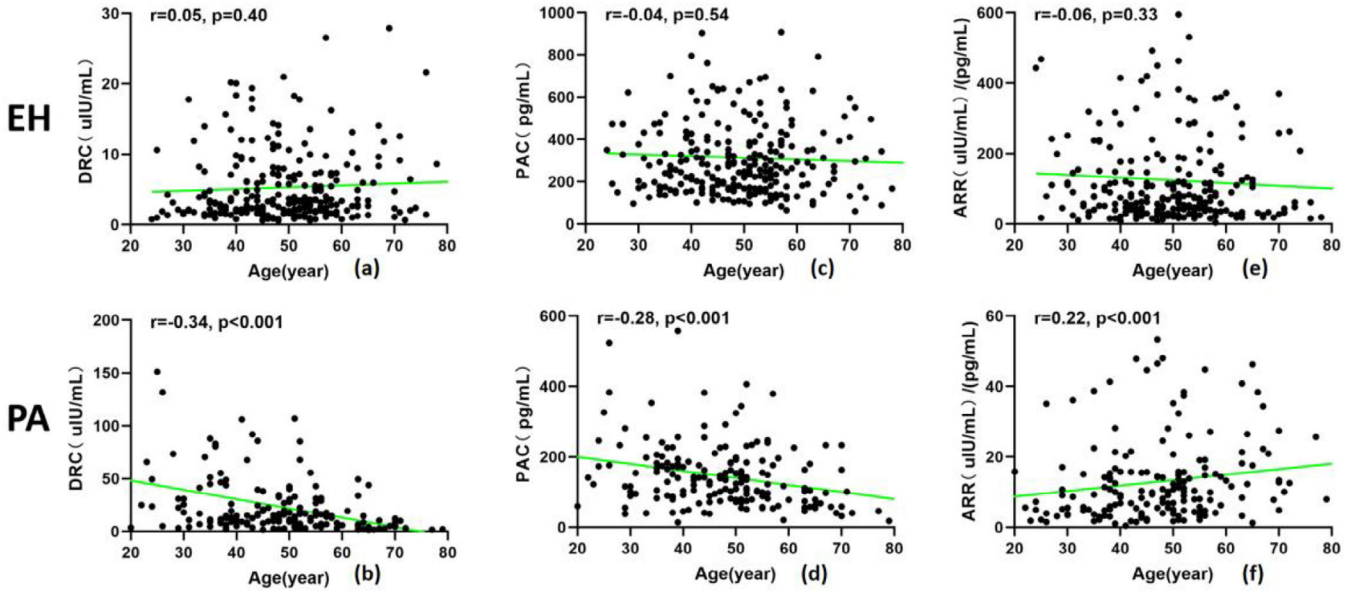

FIGURE 2 | Correlation between age and DRC, PAC, and ARR levels in EH (a, c, and e) and PA (b, d, and f).

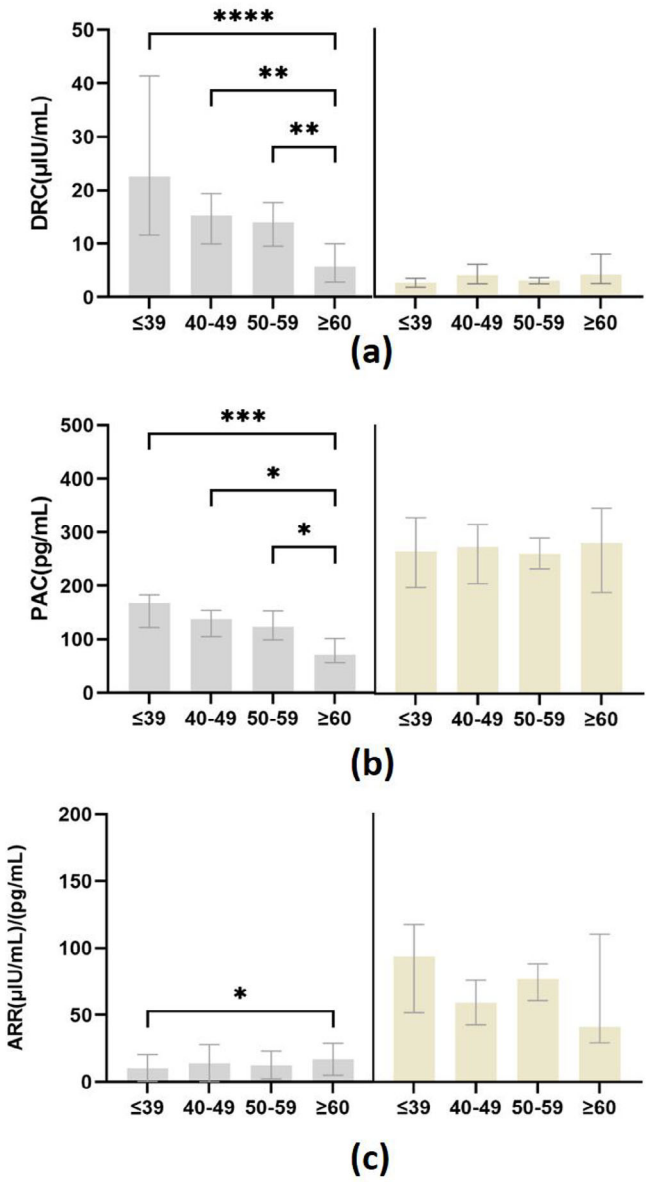

FIGURE 3 | Levels of DRC (a), PAC (b), and ARR (c) in different age groups of PA and EH. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

as a screening indicator. As shown in Table 4, the cutoff values for each age group ranged between 17.49 and 21.00. AUC for ARR decreased gradually from 0.966 to 0.885, indicating a decrease in diagnostic accuracy. The Youden index and positive likelihood ratio also decreased progressively from 0.785 to 0.617 and from 7.01 to 2.73, respectively, suggesting a reduction in the reliability of the diagnosis.

4 | Discussion

PA is characterized by excessive aldosterone production by the adrenal glands. Aldosterone binds to mineralocorticoid receptors, inducing sodium reabsorption through epithelial sodium channels (ENaC), leading to water reabsorption and consequent potassium and hydrogen excretion. This process results in elevated blood pressure, increased glomerular filtration rate, and suppression of renin and angiotensin II. Angiotensin II is an important mediator of sodium reabsorption in the proximal renal tubule; its inhibition amplifies aldosterone-driven water and sodium reabsorption, accelerating potassium and acid excretion [18]. Consequently, PA typically presents with varying degrees of hypertension and/or hypokalemia. However, hypokalemia is not universally present, and the frequency of normokalemia in patients with PA may be higher than expected. A meta-analysis showed that normokalemic patients with PA can comprise up to 33% [19]. Similarly, several studies indicate that 6% to 25% of normotensive patients are ultimately diagnosed with PA [20, 21]. Research also suggests an increased risk of developing hypertension within 5 years for these patients [22]. PA often remains undiagnosed until patients present with difficult-to-control hypertension, weakness, or target organ damage in the cardiovascular system. In this study, patients with PA experienced a longer duration of hypertension compared to patients with EH. Patients with PA exhibited lower potassium levels and higher urinary potassium levels, consistent with the typical features reported in the literature, particularly evident in patients with aldosterone-producing adenoma (APA) due to higher aldosterone secretion, resulting in more severe hypertension and hypokalemia. Additionally, this study found that patients with PA had lower blood calcium levels and increased urinary calcium excretion. Calcium and sodium reabsorption are coupled processes; elevated blood pressure in PA reduces sodium reabsorption in the proximal convoluted tubule, affecting calcium reabsorption [23]. Although calcium is also reabsorbed in the distal convoluted tubule, excretion outweighs reabsorption. Furthermore, decreased blood potassium levels can affect phosphate reabsorption, stimulating calcitriol synthesis, enhancing intestinal calcium absorption, or increasing bone resorption, leading to hypercalciuria [24, 25].

The measurement of ARR is a commonly recommended method for screening PA according to current guidelines. However, various medications and physiological factors can lead to false-positive or false-negative results. The potential impact of age on PA screening has been a topic of debate. Luo et al. [9] found that ARR is not significantly correlated with age, and the optimal cutoff value for ARR in PA screening was highest in the 50–59 age group, at 28 (ng/dL)/(ng/mL/h). For individuals aged 60 or older, the ARR cutoff value was 25. The ROC curve of ARR showed a decreasing trend in AUC, sensitivity, specificity, and Youden index with increasing age. Yin et al. [10] conducted a study comparing 39 patients to PA, 274 patients with EH, and 153 healthy volunteers. They found no significant difference in PA screening using ARR between those aged 40 or older and those younger than 40. Using ARR and PAC together helped improve the screening rate for elderly patients with PA. However, scholars discovered that ARR values are significantly higher in the elderly in the Japanese population (≥65 years old), suggesting that the screening criteria for ARR in the elderly population may need to be higher than in non-elderly individuals [11]. In the above-mentioned studies, ARR calculations were based on plasma renin activity (PRA). However, a recent study by Ma et al. [12] utilized DRC for ARR calculations. They determined that for patients aged 60 years or older, setting the ARR cutoff at 37 (pg/mL)/(μIU/mL) achieved a sensitivity of 100% and specificity of 80%. For the age groups of 40–59 years, the ARR cutoff was lowered to 20 (pg/mL)/(μIU/mL), and for patients younger than 40 years, the critical ARR threshold was set at 10

TABLE 2 | Levels of PAC, DRC, and ARR in EH of different age groups.

	≤39 *N* = 53	40-49 *N* = 43	50-59 *N* = 52	≥60 *N* = 28	*p*
DRC	22.51 (9.13, 50.34)	15.27 (9.18, 24.63)	14.02 (6.99, 2.73)	5.75 (2.41, 10.63)	<0.001
PAC	168.00 (96.45, 226.00)	138.00 (95.10, 176.00)	123.00 (79.88, 191.25)	71.30 (48.43, 109.25)	0.001
ARR	5.95 (3.40, 14.23)	9.21 (5.51, 15.73)	10.30 (4.66, 15.55)	13.03 (8.09, 24.81)	0.042

TABLE 3 | Levels of PAC, DRC, and ARR in PA of different age groups.

	≤39 *N* = 48	40-49 *N* = 75	50-59 *N* = 94	≥60 *N* = 38	*p*
DRC	2,74 (1.56, 4.41)	4.07 (1.92, 9.32)	3.11 (1.84, 5.49)	4.17 (2.03, 8.75)	0.113
PAC	266 (175.50, 410.25)	274.00 (174.00, 396.00)	261.00 (168.00, 377.75)	282.00 (162.00, 362.25)	0.945
ARR	93.75 (39.84,187.97)	59.46 (29.50, 146.83)	77.06 (45.02, 145.79)	41.35 (26.35, 128.24)	0.155

TABLE 4 | Different cutoff values of ARR for screening PA in different age groups.

age	AUC	Cutoff value	Sensitivity	Specificity	Youden index	PLR
≤39	0.966	17.49	0.917	0.868	0.785	6.94
40–49	0.922	20.79	0.933	0.814	0.747	5.02
50–59	0.968	21.01	0.947	0.865	0.762	7.01
≥60	0.885	18.22	0.974	0.643	0.617	2.73
All	0.948	22.52	0.894	0.852	0.746	6.04

Abbreviation: PLR, positive likelihood.

(pg/mL)/(μIU/mL). These thresholds resulted in sensitivities of over 90% and specificities of over 80%, reducing the risk of missing PA diagnoses. However, Ma et al. did not analyze specific cutoff values for ARR in different age groups. Their analysis focused on achieving a sensitivity of > 90% while ensuring test performance, but they did not fully consider the specificity in evaluating the diagnostic test.

PRA is measured by radioimmunoassays (RIAs), which indirectly reflects the level of reactive renin in plasma by the amount of angiotensinogen converted to angiotensin I per unit volume per unit time, which is affected by the concentration of angiotensinogen, etc. [26]. Whereas DRC is measured by CLIA, which is not influenced by substrate concentration, and it offers rapid detection, high stability, and strong repeatability [27]. In our study, we aimed to control for medications, blood potassium levels, timing of blood draws, and other conditions to focus on assessing the relationship between age and ARR. Our study results revealed that in the group of PA, ARR is independent of age. The ARR cutoff values for different age groups did not show an increasing trend with age; rather, the cutoff values fluctuated between 17 and 22. This finding may be attributed to the dysregulation of aldosterone secretion in PA, which is not controlled by the renin–angiotensin–aldosterone system, leading to renin suppression. As a result, the increase in ARR is not related to age.

The incidence of PA is primarily concentrated in middle-aged and younger populations, with a relatively lower incidence among elderly patients. Additionally, the elderly population often presents with complex physiological conditions and comorbidities that could potentially influence ARR. In patients with EH, both DRC and PAC levels exhibit a significant downward trend with increasing age. As individuals age, they become more salt-sensitive, and plasma renin levels tend to decrease, leading to an increase in ARR. This age-related decrease in DRC and PAC levels in patients with EH contrasts with the findings in primary aldosteronism, where ARR levels do not show a consistent relationship with age. This discrepancy underscores the unique pathophysiological mechanisms underlying primary aldosteronism, where aldosterone secretion is dysregulated and not controlled by age-related changes in the renin–angiotensin–aldosterone system.

This study determined that the optimal cutoff value for screening using ARR is 22.52, with corresponding sensitivity of 89.8% and specificity of 85.2%. This figure is significantly lower than that recommended by the American College of Endocrinology [3]. Rossi et al. [28] conducted a prospective study including 254 patients to screen for PA and found that the optimal cutoff value for ARR was 20.6 (pg/mL)/(μIU/mL), achieving 92% sensitivity and 91.6% specificity. Similarly, Pizzolo et al. [29] proposed a cutoff of 20 (pg/mL)/(μIU/mL). In our study cohort, we tested the previously recommended cutoff values based on DRC for PA screening. The cutoff value of 37 (pg/mL)/(μIU/mL) demonstrated a specificity of 92.61% but a lower sensitivity of only 72.94%. Conversely, the cutoff proposed by Pizzolo (20 (pg/mL)/(μIU/mL)) showed a sensitivity of 91.76% but a specificity of only 80.68%. Compared

to previous studies, our research implemented comprehensive screening preparations, including pharmacological washout and correction of blood potassium levels, ensuring quality control of the study. As a result, our study achieved higher sensitivity and specificity, thereby suggesting a more reasonable cutoff value for ARR in PA screening.

However, this study also has certain limitations. In this retrospective study conducted in a provincial tertiary hospital center, the prevalence of PA was higher than that in ordinary areas. The incidence of PA is lower in elderly patients (≥60 years old) and younger patients (≤30 years old), and elderly patients often have multiple comorbidities, which reduced the sample size of patients with PA in these age groups in our study. However, we screened the subjects strictly according to the inclusion and exclusion criteria. Some patients whose ARR < 30 but strongly suspected clinically also underwent the confirmatory tests. This improved the detection rate of PA and reduced the false-negative rate of ARR to some extent. The procedures of screening and confirmation were standardized according to the guidelines. Additionally, our study did not consider the potential influence of gender and hormonal fluctuations during the menstrual cycle on DRC testing, which could impact the determination of ARR cutoff values for patients with PA. The study also did not account for the influence of gender on ARR, which could affect ARR cutoff values. This study fully and truthfully reflects the real situation of our center. Future large-scale multicenter prospective cohort studies are needed to further confirm the above conclusions.

Author Contributions

Tiejian Jiang and Min Luo participated in the design of the study. Ning Peng, Zhen Zhang, and Yao Xiao drafted and revised the manuscript and performed the statistical analysis. Qianwen Ye, Geru Liu, Mengling Zhen, and Yanqing Zheng collected the samples. Dr. Ning Peng (proposed sole first author); Led >90% of manuscript writing and revisions; Performed primary data analysis and interpretation; Initiated and coordinated all critical revisions. Dr. Zhen Zhang (proposed contributor); Assisted with manuscript polishing and formatting; Provided supplementary data analysis support; Participated in technical discussions.

Ethics Statement

This study adheres to the guidelines set forth by the Hospital Ethics Committee.

Consent

All participants in this study have signed an informed consent document.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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