Diagnostic value of aldosterone to renin ratio calculated by plasma renin activity or plasma renin concentration in primary aldosteronism: a meta-analysis

Zhenjie Liu1, 2, Xiaohong Deng1, 2, Li Luo3, Shaopeng Li1, 2, Man Li1, 2, Qingxin Deng1, 2, Weiguo Zhong1, 2, Qiang Luo1, 2

1Department of Clinical Laboratory, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510120, China; 2Department of Clinical Laboratory, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, Guangdong 510120, China; 3Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510120, China.

Abstract

Background: Since the diagnostic value of aldosterone to renin ratio (ARR) calculated by plasma renin concentration (PRC) or plasma renin activity (PRA) is still inconclusive, we conducted a meta-analysis by systematically reviewing relevant literature to explore the difference in the diagnostic efficacy of ARR calculated by PRC or PRA, so as to provide guidance for clinical diagnosis.

Methods: We searched PubMed, Embase, and Cochrane Library from the establishment of the database to March 2021. We included studies that report the true positive, false positive, true negative, and false negative values for the diagnosis of primary aldosteronism, and we excluded duplicate publications, research without full text, incomplete information, or inability to conduct data extraction, animal experiments, reviews, and systematic reviews. STATA 15.1 was used to analyze the data.

Results: The pooled results showed that ARR (plasma aldosterone concentration [PAC]/PRC) had a sensitivity of 0.82 (95% confidence interval [CI]: 0.78–0.86), a specificity of 0.94 (95% CI: 0.92–0.95), a positive-likelihood ratio (LR) of 12.77 (95% CI: 7.04–23.73), a negative LR of 0.11 (95% CI: 0.07–0.17), and symmetric area under the curve (SAUC) of 0.982, respectively. Furthermore, the diagnostic odds ratio (DOR) of ARR (PAC/PRC) was 180.21. Additionally, the pooled results showed that ARR (PAC/PRA) had a sensitivity of 0.91 (95% CI: 0.86–0.95), a specificity of 0.91 (95% CI: 0.90–0.93), a positive LR of 7.30 (95% CI: 2.99–17.99), a negative LR of 0.10 (95% CI: 0.04–0.26), and SAUC of 0.976, respectively. The DOR of ARR (PAC/PRA) was 155.52. Additionally, we conducted a subgroup analysis for the different thresholds (<35 or ≥35) of PAC/PRC. The results showed that the DOR of the cut-off ≥35 groups was higher than the cut-off <35 groups (DOR = 340.15, 95% CI: 38.32–3019.66; DOR = 116.40, 95% CI: 23.28–581.92).

Conclusions: The research results suggest that the determination of ARR (PAC/PRC) and ARR (PAC/PRA) was all effective screening tools for PA. The diagnostic accuracy and diagnostic value of ARR (PAC/PRC) are higher than ARR (PAC/PRA). In addition, within a certain range, the higher the threshold, the better the diagnostic value.

Keywords: Primary aldosteronism; Aldosterone to renin ratio; Plasma renin activity; Plasma renin concentration; Diagnostic value; Meta-analysis

Introduction

Primary aldosteronism (PA) is one of the most common endocrine causes of secondary hypertension.[1-3] PA was diagnosed in patients with a high aldosterone to renin (ARR) of 438 (ng/L·ng/L) and an inadequate high plasma aldosterone of 460 ng/L after fludrocortisone testing or 4100 ng/L after the saline infusion test.[4] Considering that PA patients have a higher prevalence of cerebrovascular and cardiovascular complications than patients with essential hypertension (EH),[5] it is important to diagnose hyperaldosteronism early and take specific treatment measures. To achieve accurate case detection, the Endocrine Society Guideline recommends that patients with a relatively high risk of PA should be screened for PA with the ratio of ARR.[6] Conventionally, the ARR (plasma aldosterone concentration [PAC]/plasma renin activity [PRA]) is calculated by measuring the PAC and PRA.[7] Recent studies have found that the use of PAC and plasma renin concentration (PRC) to calculate ARR can effectively avoid the influence of angiotensinogen concentration, incubation conditions, pH value, and other factors on the measurement results.[8] However, the diagnostic efficacy of ARR calculated by PRC or PRA is still inconclusive.
Meanwhile, the diagnostic value of ARR was varied in studies. The reason for this difference may be due to the different thresholds of different studies. Therefore, we conducted a meta-analysis by systematically reviewing relevant literature to explore the differences in the diagnostic efficacy of ARR calculated by PRC or PRA and analyze the influence of threshold on diagnostic efficacy, so as to provide guidance for clinical diagnosis.

**Methods**

**Literature inclusion and exclusion criteria**

The inclusion criteria were as follows: the experimental group was patients with PA and has a clear diagnosis basis; the control group was patients with non-primary hyperaldosteronism and the diagnosis was clear; the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) values for the diagnosis of PA can be obtained directly or indirectly; the positive cut-off for diagnosing PA can be obtained directly or indirectly; the language is limited to English.

Exclusion criteria were as follows: duplicate publication; research without full text, incomplete information or inability to conduct data extraction; animal experiments; and reviews and systematic reviews.

**Search strategy**

In this meta-analysis, we searched PubMed, Embase, and Cochrane Library from the establishment of the respective database to March 2021. The search terms were mainly: “primary aldosteronism,” “aldosterone to renin ratio,” “plasma aldosterone concentration,” “plasma renin activity,” and “plasma renin concentration.” The substantial search strategy is shown in Supplementary Tables 1–3, http://links.lww.com/CM9/A858.

**Literature screening and data extraction**

The literature search, screening, and information extraction were all independently completed by two researchers. When there were doubts or disagreements, the decision was made after discussion or consultation with a third party. The data extraction content includes: author, year, sample size, gender, age, and the values of TP, FP, TN, and FN used to diagnose PA.

**Literature quality assessment**

Two researchers evaluated the quality of each included literature based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool,[9] involving a total of 11 items (for specific items, see the labeling of the bias risk diagram and the bias risk summary diagram in the results section). The evaluation results are divided into “high risk,” “low risk,” and “unclear”; after cross-checking, if opinions are inconsistent, the decision will be made through discussion or consultation with a third party. After the evaluation of all items is completed, Revman 5.3 software (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark) is used to draw a bias risk map and a bias risk summary map.

**Data synthesis and statistical analysis**

Firstly, the P value of Spearman correlation coefficient is used to judge the threshold effect. If the P value of the correlation coefficient is <0.05, it indicates that there is a threshold effect. Otherwise, it means that there is no threshold effect; then, we calculate the combined sensitivity, specificity, positive-likelihood ratio (LR), negative LR, diagnostic odds ratio (DOR), and other indicators and draw the total summary receiver operating characteristic (SROC) curve. The bivariate model or hierarchical SROC model was used to combine sensitivity and specificity. The I² value is used to evaluate the heterogeneity caused by non-threshold effects. If I² > 50%, the random-effects model is used; otherwise, the fixed-effects model is used. When I² is between 25% and 50%, the heterogeneity is low; when I² is between 50% and 75%, the heterogeneity is at a moderate level; and when I² > 75%, there is a high degree of heterogeneity. Subgroup analysis was performed to explore the causes of heterogeneity among the studies. All analyses were performed with STATA version 15.1 (Stata Corporation, College Station, TX, USA); the packages used in STATA are shown in the supplementary file, http://links.lww.com/CM9/A858. All statistical tests were two-sided, with a P value of 0.05 denoting statistical significance.

**Results**

**Literature search**

In this study, a total of 1270 studies were retrieved from the database. After eliminating duplicate studies, 638 were obtained. After browsing titles and abstracts, 385 studies were obtained. Finally, 14 articles were included in the meta-analysis through full-text reading [Figure 1].

**Baseline characteristics and quality assessment of the included studies**

**Baseline characteristics of the included studies**

A total of 14 studies were included in this meta-analysis, of which five studies reported ARR (PAC/PRA) and nine studies reported ARR (PAC/PRC). The sample size of patients was totally 2638, including 53 patients in the PA group and 2104 patients in the non-PA group. Patients in five studies were from Asia, and the patients in the nine studies were from Europe and America. The cut-off of ARR (PAC/PRA) ranges from 26.35 to 68.28, and the cutoff of ARR (PAC/PRC) ranges from 13.10 to 59.66 [Table 1].

**Quality assessment of the included studies**

The quality assessment of the included studies uses the QUADAS-2 tool, which mainly includes four aspects: patient selection, index test, reference standard, and flow and timing. Only one study of “patient selection” is high-
risk, and most of them are low-risk. In the two aspects of “reference standard” and “flow and timing,” the vast majority of studies are low-risk [Figures 2 and 3].

Results of meta-analysis

ARR (PAC/PRC)

There was no threshold effect because the Spearman correlation coefficient showed no correlations between sensitivity and specificity ($r = 0.467, P = 0.205 > 0.05$). Since the $I^2$ for sensitivity (97.4%), specificity (97.4%), positive LR (74.4%), negative LR (93.9%), and DOR (79.9%) was >50%, representing a high level of inconsistency among studies, a meta-analysis was conducted through a random-effects model. The pooled sensitivity and specificity of the studies overall were 0.97 (95% CI: 0.75–1.00) and 0.98 (95% CI: 0.90–0.99), respectively [Figure 4A]. The pooled positive LR and negative LR of the studies overall were 12.77 (95% CI: 7.94–23.73) and 0.10 (95% CI: 0.04–0.26), respectively [Figure 4C and 4E]. The pooled DOR of the studies overall was 180.21 (95% CI: 51.63–629.04) [Figure 4G]. In the random-effects model, the symmetric area under the curve (SAUC) of nine studies was 0.99 (95% CI: 0.98–1.10) [Figure 5A].

ARR (PAC/PRA)

There was no threshold effect because the Spearman correlation coefficient showed no correlations between sensitivity and specificity ($r = 0.200, P = 0.747 > 0.05$). Since the $I^2$ for sensitivity (32.6%), specificity (94.6%), positive LR (93.4%), and DOR (71.7%) was >50%, representing a high level of inconsistency among studies, a meta-analysis was conducted through a random-effects model. Since the $I^2$ for negative LR (0.0%) was <50%, a meta-analysis was conducted through a fixed-effects model. The pooled sensitivity and specificity of the studies overall were 0.93 (95% CI: 0.86–0.97) and 0.92 (95% CI: 0.63–0.99), respectively [Figure 4B]. The pooled positive LR and negative LR of the studies overall were 7.30 (95% CI: 2.99–17.99) and 0.11 (95% CI: 0.07–0.17), respectively [Figure 4D and 4F]. The pooled DOR of the studies overall was 155.52 (95% CI: 22.51–1074.74) [Figure 4H]. In the random-effects model, the SAUC of five studies was 0.95 (95% CI: 0.92–0.96) [Figure 5B].

Subgroup analysis

Due to the high diagnostic value of PAC/PRC, we conducted a subgroup analysis for the different thresholds (<35 or ≥35) of PAC/PRC. The results showed that the DOR of the cut-off ≥35 groups was higher than the cut-off <35 groups (DOR = 340.15, 95% CI: 38.32–3019.66; DOR = 116.40, 95% CI = 23.28–581.92) [Figure 6].

Publication bias

The $P$ value of Deek Funnel plot of the studies reporting ARR (PAC/PRC) was 0.06, indicating that there is no obvious publication bias in this study; the $P$ value of Deek Funnel plot of the studies reporting ARR (PAC/PRA) was
Table 1: Baseline characteristics of the included studies.

| Author          | Year | Country | PA   | Non-PA | Age (years) | Gender | Detection method of aldosterone | Indicator | Cut-off (ng/L)/[ng/L] | Conditions of controls | Diagnostic criteria for PA |
|----------------|------|---------|------|--------|-------------|--------|---------------------------------|-----------|------------------------|--------------------------|---------------------------|
| Balas et al    | 2010 | Spain   | 28   | 33     | 55.71 ± 9.11 | 52.41 ± 11.29 | 12/16 | PAC/PRA                        | 26.35      | EH                      | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4100 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4100 ng/L (faline infusion test) |
| Diederich et al| 2007 | China   | 31   | 32     | 52.5 ± 12.3  | 59.6 ± 11.9  | 18/13 | PAC/PRC                        | 59.6       | EH                      | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4101 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4101 ng/L (faline infusion test) |
| Fischer et al  | 2011 | Germany | 25   | 25     | 53 ± 2       | 55 ± 3       | 17/8  | RIA                             | PAC/PRA    | 31.54                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4102 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4102 ng/L (faline infusion test) |
| Gan et al      | 2018 | China   | 97   | 345    | 49.69 ± 11.40| 42.91 ± 13.98| /     | RIA                             | PAC/PRA    | 28.6                    | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4103 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4103 ng/L (faline infusion test) |
| Li et al       | 2019 | China   | 64   | 386    | 49 ± 10      | 48 ± 12      | 30/34 | RIA                             | PAC/PRC    | 46.2                    | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4104 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4104 ng/L (faline infusion test) |
| Lin et al      | 2020 | China   | 58   | 180    | 48.59 ± 11.25| 45.83 ± 15.96| 29/29 | PAC/PRC                        | 28          | EH                      | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4105 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4105 ng/L (faline infusion test) |
| Corbin et al   | 2011 | Canada  | 38   | 95     | 53 ± 11      | 51 ± 12      | 29/13 | RIA                             | PAC/PRC    | 46.93                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4106 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4106 ng/L (faline infusion test) |
| Jansen et al   | 2014 | Netherlands | 27   | 151    | 47.6 ± 9.4   | 49.9 ± 9.7   | 15/12 | RIA                             | PAC/PRC    | 51.82                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4107 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4107 ng/L (faline infusion test) |
| Pilz et al     | 2019 | Austria | 18   | 364    | 48.9 ± 9.3   | 50.3 ± 15.1  | 9/9   | RIA                             | PAC/PRC    | 68.28                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4108 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4108 ng/L (faline infusion test) |
| Perschel et al | 2004 | Germany | 28   | 76     | 5.10 ± 13.1  | /             | 16/12 | RIA                             | PAC/PRA    | 40.34                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4109 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4109 ng/L (faline infusion test) |
| Teruya et al   | 2020 | Japan   | 52   | 23     | 61 (52–68)   | 59 (49–73)   | 24/51 | CLIA                           | PAC/PRA    | 13.1                    | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4110 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4110 ng/L (faline infusion test) |
| Tzanela et al  | 2007 | Greece  | 17   | 106    | 55.5 ± 1.4   | 58.7 ± 1.4   | 9/8   | RIA                             | PAC/PRA    | 50.46                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4111 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4111 ng/L (faline infusion test) |
| Vorselaars et al| 2018 | Netherlands | 16   | 217    | 53.6 ± 13.4  | /             | 123/110 | RIA                             | PAC/PRA    | 26.75                   | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4112 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4112 ng/L (faline infusion test) |
| Willenberg et al| 2008 | Germany | 35   | 71     | 57.4 ± 10.1  | 57.5 ± 12.8  | 17/18 | RIA                             | PAC/PRA    | 33                      | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4113 ng/L (faline infusion test) | ARR > 438 ([ng/L]/[ng/L]) and plasma aldosterone < 460 ng/L (fludrocortisone testing)/4113 ng/L (faline infusion test) |
0.01, indicating that there may be publication bias in this study [Figure 7].

**Sensitivity analysis**

Sensitivity analysis eliminates each included study one by one and performs a summary analysis on the remaining studies to assess whether a single included study has an excessive impact on the results of the entire meta-analysis. The result of the sensitivity analysis is shown in Figure 8. The results showed that none of the studies had an excessive impact on the results of the meta-analysis, indicating that the results of the remaining studies are stable and reliable.

**Discussion**

In the hypertension population, the prevalence of PA has reached 5% to 10%.[24] Compared with EH patients, PA patients are more likely to suffer from cardiovascular disease and cerebrovascular disease, so early and accurate diagnosis of PA is of great importance.[25-27] However, the diagnostic efficacy of ARR calculated by PRC or PRA is still inconclusive. This meta-analysis pooled 14 studies evolving 2638 patients to explore the difference in the diagnostic efficacy of ARR calculated by PRC or PRA.

The pooled results showed that ARR (PAC/PRC) had a sensitivity of 0.97 (95% CI: 0.75–1.00), a specificity of 0.98 (95% CI: 0.90–0.99), a positive LR of 12.77 (95% CI: 7.04–23.73), a negative LR of 0.11 (95% CI: 0.07–0.17), and SAUC of 0.982, respectively. Furthermore, the DOR of 180.21 also showed ARR (PAC/PRC) to be an efficient test. Additionally, the pooled results showed that ARR (PAC/PRA) had a sensitivity of 0.93 (95% CI: 0.86–0.97), a specificity of 0.92 (95% CI: 0.63–0.99), a positive LR of 7.30 (95% CI: 2.99–17.99), a negative LR of 0.10 (95% CI: 0.04–0.26), and SAUC of 0.976, respectively. The DOR of 155.52 also showed ARR (PAC/PRA) to be an efficient test. The quality of the studies was good according to the QUADAS-2 criteria,[28] showing that the pooled results were valuable. The results of the study first show that the ARR calculated by PRC or PRA has good diagnostic performance. Second, ARR (PAC/PRC) has a higher diagnostic value. This is consistent with the results of the previous studies, which showed that the DRC assay provides several advantages compared with PRA, for example, specimen handling, shorter turnaround time, better reproducibility, and easier standardization.[29] However, we also noticed that PRA has a higher sensitivity than PRC. If doctors in the clinical diagnosis of PA pay more attention to the sensitivity of diagnosis, PRA can be the first choice.

Moreover, the analysis also demonstrated a massive heterogeneity. It is worth noting that the cut-off value of the 14 studies is variable. ARR (PAC/PRA) ranges from 26.35 ([ng/L]/[ng/L]) to 68.28 ([ng/L]/[ng/L]), while ARR (PAC/PRC) ranges from 13.1 ([ng/L]/[ng/L]) to 59.66 ([ng/L]/[ng/L]), which may be the cause of the large heterogeneity. Since PRC has a higher diagnosis in the diagnosis of PA, we further carried out a subgroup analysis for the different cut-offs. According to the distribution of the threshold, we artificially divide the threshold into a cut-off < 35 groups and a cut-off ≥ 35 groups. The results showed that the DOR of the cut-off ≥ 35 groups was higher than the cut-off < 35 groups (DOR = 340.15, 95% CI: 38.32–3019.66; DOR = 116.40, 95% CI = 23.28–581.92). This suggests that within a certain range, the higher the threshold, the better the diagnostic performance.

This study has certain limitations: first, there is the fact of its large heterogeneity. The reasons for the heterogeneity may first be related to the difference in cut-off; and second, it may be related to the selection of the control group. The non-PA group includes patients with EH and healthy people. Second, the P value of Deek Funnel plot of the studies reporting ARR (PAC/PRA) was 0.01, indicating that there may be publication bias in this study. Moreover, since only nine studies reporting ARR (PAC/PRC) and five studies reporting ARR (PAC/PRA), it was not enough to detect publication bias, and this article only carried out a bias analysis on five documents, which meant that some potential eligible studies might be omitted. Therefore, in the future analysis, new documents that meet the requirements need to be further included for analysis to eliminate publication bias.

**Conclusion**

The research results suggest that the determination of ARR (PAC/PRC) and ARR (PAC/PRA) was all effective screening tools for PA. The diagnostic accuracy and
Figure 4: (A) Forest plot of sensitivity and specificity of the studies reporting ARR (PAC/PRC). (B) Forest plot of sensitivity and specificity of the studies reporting ARR (PAC/PRA). (C) Forest plot of positive LR of the studies reporting ARR (PAC/PRC). (D) Forest plot of positive LR of the studies reporting ARR (PAC/PRA). (E) Forest plot of negative LR of the studies reporting ARR (PAC/PRC). (F) Forest plot of negative LR of the studies reporting ARR (PAC/PRA). (G) Forest plot of DOR of the studies reporting ARR (PAC/PRC). (H) Forest plot of DOR of the studies reporting ARR (PAC/PRA). ARR: Aldosterone to renin; DOR: Diagnostic odds ratio; LR+: Positive-likelihood ratio; LR–: Negative-likelihood ratio; PAC: Plasma aldosterone concentration; PRA: Plasma renin activity; PRC: Plasma renin concentration.
Figure 5: (A) SROC curve of the studies reporting ARR (PAC/PRC). (B) SROC curve of the studies reporting ARR (PAC/PRA). ARR: Aldosterone to renin; PAC: Plasma aldosterone concentration; PRA: Plasma renin activity; PRC: Plasma renin concentration.

Figure 6: Subgroup analysis of DOR of the studies reporting ARR (PAC/PRC). ARR: Aldosterone to renin; DOR: Diagnostic odds ratio; PAC: Plasma aldosterone concentration; PRC: Plasma renin concentration.
diagnostic value of ARR (PAC/PRC) are higher than ARR (PAC/PRA). In addition, within a certain range, the higher the threshold, the better the diagnostic performance.

**Funding**

This study was supported by a grant from the Science and Technology Project of Guangdong Province (No. 2016A020215136).

**Conflicts of interest**

None.

**References**

1. Yang Y, Reincke M, Williams TA. Prevalence, diagnosis and outcomes of treatment for primary aldosteronism. Best Pract Res Clin Endocrinol Metab 2020;34:101365. doi: 10.1016/j.bepm.2019.101365.
2. Byrd JB, Turcu AF, Auchus RJ. Primary aldosteronism: practical approach to diagnosis and management. Circulation 2018;138:823–835. doi: 10.1161/CIRCULATIONAHA.118.033597.
3. Vaidya A, Mulatero P, Baudrand R, Adler GK. The expanding spectrum of primary aldosteronism: implications for diagnosis, pathogenesis, and treatment. Endocr Rev 2018;39:1057–1088. doi: 10.1210/er.2018-00139.
4. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008;93:3266–3281. doi: 10.1210/jc.2008-0104.
5. Kohler A, Sarkis AL, Henrich DA, Muller L, Handgriff L, Deniz S, et al. Renin a marker for left ventricular hypertrophy in primary aldosteronism: a cohort study. Eur J Endocrinol 2021;185:663–672. doi: 10.1530/EJE-21-0018.
6. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101:1889–1916. doi: 10.1210/jc.2015-4061.
7. Hung A, Ahmed S, Gupta A, Davis A, Kline GA, Leung AA, et al. Performance of the aldosterone to renin ratio as a screening test for primary aldosteronism. J Clin Endocrinol Metab 2021;106:2423–2435. doi: 10.1210/clinem/dgab348.
8. Gruson D, Maisin D, Lison P, Maiter D, Persu A. Two-site automated chemiluminescent assay for measurement of immunoreactive renin. Biomarkers 2011;16:605–609. doi: 10.3109/1354750X.2011.614015.
9. Ryan D, Giele H. The scratch collapse test: a QUADAS-2 assessment of a systematic review. J Plast Reconstr Aesthet Surg 2019;72:1418–1433. doi: 10.1016/j.bjps.2019.03.021.
10. Balas M, Zoum J, Maser-Gluth C, Hermens D, Cupisti K, Schott M, et al. Indicators of mineralocorticoid excess in the evaluation of primary aldosteronism. Hypertens Res 2010;33:850–856. doi: 10.1038/hr.2010.76.
11. Diederich S, Mai K, Bahr V, Helfrich S, Pfeiffer A, Perschel FH. The simultaneous measurement of plasma-aldosterone- and -renin-
concentration allows rapid classification of all disorders of the renin-aldosterone system. Exp Clin Endocrinol Diabetes 2007;115:433–438. doi: 10.1055/s-2007-973061.

12. Fischer E, Beuschlein F, Bidlingmaier M, Reinecke M. Commentary on the endocrine society practice guidelines: consequences of adjustment of antihypertensive medication in screening of primary aldosteronism. Rev Endocr Metab Disord 2011;12:43–48. doi: 10.1007/s11154-011-9163-7.

13. Gan W, Lin W, Ouyang J, Li Y, Chen D, Yao Z, et al. High efficiency of the aldosterone-to-renin ratio in precisely detecting primary aldosteronism. J Hum Hypertens 2019;33:57–61. doi: 10.1038/s41371-018-0112-8.

14. Li T, Ma Y, Zhang Y, Liu Y, Fu T, Zhang R, et al. Feasibility of screening primary aldosteronism by aldosterone-to-direct renin concentration ratio derived from chemiluminescent immunoassay measurement: diagnostic accuracy and cutoff value. Int J Hypertens 2019;2019:2195796. doi: 10.1155/2019/2195796.

15. Liu W, Li Y, Chen D, Yao Z, Xu H, Chen Y, et al. High efficiency and problems of chemiluminescence assay-detected aldosterone-to-renin ratio in practical primary aldosteronism screening. Int J Hypertens 2020;2020:3934212. doi: 10.1155/2020/3934212.

16. Corbin F, Douville P, Lelb M. Active renin mass concentration to determine aldosterone-to-renin ratio in screening for primary aldosteronism. Int J Nephrol Renovasc Dis 2011;4:115–120. doi: 10.2147/IJNRD.S22245.

17. Jansen PM, van den Born BJ, Frenkel WJ, de Bruijne ELE, Kerstens MN, et al. Exp Clin Characteristics of the aldosterone-to-renin ratio as a screening test for primary aldosteronism. J Hypertens 2014;32:115–126. doi: 10.1097/HJH.0b013e3283656b54.

18. Pilz S, Keppel MH, Trummer C, Theiler-Schwertz V, Pandis M, Borzan V, et al. Diagnostic accuracy of the aldosterone-to-active renin ratio for detecting primary aldosteronism. J Endocr Soc 2019;3:1748–1758. doi: 10.1210/js.2019-00145.

19. Perschel FH, Scherner R, Seiler L, Reinecke M, Deinum J, Maser-Gluth C, et al. Rapid screening test for primary hyperaldosteronism: ratio of plasma aldosterone to renin concentration determined by fully automated chemiluminescence immunoassays. Clin Chem 2004;50:1630–1635. doi: 10.1373/chlchem.2004.033159.

20. Teruyama K, Naruse M, Tsuki M, Kobayashi H. Novel chemiluminence immunoassay to measure plasma aldosterone and plasma active renin concentrations for the diagnosis of primary aldosteronism. J Hum Hypertens 2021. doi: 10.1038/s41371-020-00465-5.

21. Tzanela M, Effraimidis G, Vassiladi D, Szabo A, Gavalas N, Valatsoua S, et al. The aldosterone to renin ratio in the evaluation of patients with incidentally detected adrenal masses. Endocrine 2007;32:136–142. doi: 10.1007/s12020-007-9028-8.

22. Vorselaars WMCM, Valk GD, Vreens MR, Westerink J, Spiering W. Case detection in primary aldosteronism: high-diagnostic value of the aldosterone-to-renin ratio when performed under standardized conditions. J Hypertens 2018;36:1383–1391. doi: 10.1097/HJH.0000000000001718.

23. Willenberg HS, Kolentini C, Quinkler M, Capuisti K, Krausch M, Schott M, et al. The serum sodium to urinary sodium to (serum potassium)2 to urinary potassium (SUSPPUP) ratio in patients with primary aldosteronism. Clin Chem Lab Med 2008;46:2362–2368. doi: 10.1515/CCLM.2008.02060.x.

24. Mirfakhraee S, Rodriguez M, Ganji N, Auchen RJ, Hamidi O. A real saline challenge: diagnosing primary aldosteronism in the setting of chronic kidney disease. J Investig Med High Impact Case Rep 2021;9:5034337. doi: 10.1177/23247096211034337.

25. Catena C, Colussi G, Nadalini E, Chiuchi A, Baroselli S, Lapenna R, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med 2008;168:80–85. doi: 10.1001/archinternmed.2007.33.

26. Mulatero P, Monticone S, Bertello C, Viola A, Tizzani D, Iannaccone A, et al. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. J Clin Endocrinol Metab 2013;98:4826–4833. doi: 10.1210/jc.2013-2805.

27. Savard S, Amar L, Proulx PF, Steichen O. Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. Hypertension 2010;56:331–336. doi: 10.1161/HYPERTENSIONAHA.113.01060.

28. Qu YJ, Yang ZR, Sun F, Zhan SY. Risk on bias assessment: (6) a revised tool for the quality assessment on diagnostic accuracy studies (QUADAS-2) (in Chinese). Chin J Epidemiol 2018;39:524–531. doi: 10.3760/cma.j.issn.0254-6450.2018.04.028.

29. Morganti A. European study group for the validation of DiaSorin LDRA. A comparative study on inter and intralaboratory reproducibility of renin measurement with a conventional enzymatic method and a new chemiluminescent assay of immuno-reactive renin. J Hypertens 2010;28:1307–1312. doi: 10.1097/HJH.0b013e32833857ad.