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The value of the post-captopril aldosterone/renin ratio for the diagnosis of primary aldosteronism and the influential factors: A meta-analysis

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Abstract

Objective: The procedure for the captopril challenge test (CCT) in diagnosing primary aldosteronism (PA) is not standardized. We performed a meta-analysis to evaluate the controversial diagnostic value and influential factors of the post-captopril aldosterone/renin ratio (ARR).

Methods: We searched literature in databases for eligible studies (until October 1, 2020). We extracted information regarding study and patient characteristics, CCT methods, outcome data. We pooled studies using the random-effect model. We performed meta-regression and six pre-specified subgroup analyses to explore heterogeneity.

Results: Nineteen studies involving 4568 subjects were included. The pooled sensitivity and specificity were 0.825 (95% CI 0.804–0.844) and 0.919 (95% CI 0.908–0.928). The area under the summary receiver operating characteristic curve was 0.9487 (95% CI 0.9207–0.9767). Meta-regression revealed that heterogeneity might derive from time interval ($p = 0.0117$) and study population ($p = 0.0033$). Subgroup analyses showed significant differences between the subgroups stratified by the dose, posture, study region, time interval, cut-off value and study population for sensitivity and/or specificity ($p < 0.05$).

Conclusion: Post-captopril ARR is comparably valuable for diagnosing PA at cut-offs from 12.0 to 50.0. Conducting the CCT in the supine position with 25 mg of captopril may attain greater sensitivity. Conducting the CCT in the seated position with 50 mg of captopril may attain greater specificity. A 90-min time interval may perform best in both the sensitivity and specificity.

Keywords

Aldosteronism, aldosterone/renin ratio, captopril challenge test, meta-analysis

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Introduction

Primary aldosteronism (PA), one of the leading causes of secondary hypertension, is caused by idiopathic hyperaldosteronism (IHA) or an aldosterone-producing adenoma (APA), which leads to inappropriately high and partly autonomous aldosterone secretion[1–3]; PA has a prevalence of over 10% in the hypertensive population and is found in up to 17%–23% of patients with resistant hypertension.[4–6] Compared with blood-pressure-matched patients with essential hypertension (EH), PA patients have higher morbidity and mortality due to cardiovascular diseases,[7–9] which makes the early diagnosis of and intervention in PA very important.

The aldosterone/renin ratio (ARR), which is the plasma aldosterone concentration (PAC) divided by plasma renin activity (PRA), is recommended by clinical practice guidelines for PA screening[2,10,11] and is the most widely used screening tool in clinical practice. Inappropriate elevation of the ARR exceeding a certain threshold is defined as positive, and ARR-positive people are suspected of having PA, at which point additional tests are needed for confirmation. The captopril challenge test (CCT), first proposed by Lyons in 1983,[12] is now one of the four confirmatory tests recommended by the American Endocrine Society clinical practice guidelines published in 2016[2] and the Chinese Society of Endocrinology consensus released in 2016.[11] Compared with the saline infusion test, oral sodium loading test and fludrocortisone suppression test, the CCT has unique advantages in terms of improved security and feasibility, a lower incidence of sharp fluctuations in blood pressure, less time and expense, and not being affected by daily sodium intake.[11,13]

However, the interpretation of CCT results has not yet been standardized. The present recommendation in the guidelines is to interpret the results as the post-CCT suppression percentage of PAC.[2,10,11] Other studies also adopt the post-CCT absolute value of PAC for as the discriminatory standard.[10,12,14] Considering the screening value of baseline ARR and confirmatory value of CCT, we assume that a combination of both in the form of the post-CCT ARR may lead to more efficient PA diagnosis. However, few studies have investigated this less commonly used index, and their results are controversial in terms of the diagnostic value and optimal cut-off values, with a reported sensitivity of 59% to 100% and specificity of 82.76% to 99%.[12,13,15–29] Thus, a more precise evaluation of all the varying or even contradictory results of this index is needed.

Meanwhile, the procedure of the CCT has been vaguely described in some guidelines and has not yet been standardized across studies. According to the guidelines of the American Association of Clinical Endocrinologists, patients should receive 25–50 mg of captopril orally, and blood samples are drawn for the measurement of PRA, PAC, and cortisol at time 0 and at 60 or 120 min after the challenge, with the patient remaining seated during this period.[2] However, the guidelines of the Chinese Medical Association suggest using only 50 mg of captopril.[11] Indeed, the reported CCT procedure varies in many studies, with the different captopril doses defined as 25 or 50 mg; different intervals between captopril administration and blood sampling of 60, 90, or 120 min; and different postures (seated or supine position) during the blood draw.[12,13,15–29] More clearly defined CCT procedures with evidence-based superiority need to be established.

Hence, we performed a meta-analysis by systematically identifying and analyzing the available literature to evaluate the diagnostic value of post-captopril ARR and the factors influencing it, intending to explore the conditions under which to conduct CCT for optimal accuracy.

Methods

Literature search

We searched PubMed, EMBASE, the Cochrane Central Register of Controlled trials (CENTRAL), China National Knowledge Infrastructure (CNKI), and the Wanfang Database from the date of database inception to October 1, 2020, to identify relevant studies published in English and Chinese. We used various combinations of keywords including "captopril," "aldosteronism," and the corresponding synonyms to search for potentially eligible articles (the detailed search strategies were seen in Supplemental Table 1). We also reviewed reference lists of the included studies to identify additional relevant studies.

Inclusion and exclusion criteria

The inclusion criteria for eligible studies were as follows: (1) the study had a diagnostic cohort or case-control design; (2) the diagnostic standard for PA was consistent with the clinical practice guidelines of 2016 American Endocrine Society[2] or the 2016 consensus of the Chinese Society of Endocrinology[11]; (3) the study contained adequate information on the diagnostic efficacy of post-captopril ARR including the diagnostic cut-off value, study population, captopril dose, time interval between captopril administration and blood sampling, patient posture during blood measurement, and a four-fold table that could be converted with the true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values presented in or calculated from the text; (4) post-captopril ARR was defined as PAC divided by PRA; and (5) the full text of the article was available. Studies that did not meet the above criteria were excluded.

Study screening and data collection

The literature search was completed by two investigators (XQ and WW) independently. These **t**wo investigators also independently screened the titles, abstracts and full texts for potentially eligible studies; assessed the risk of bias; and collected data from each eligible study, including

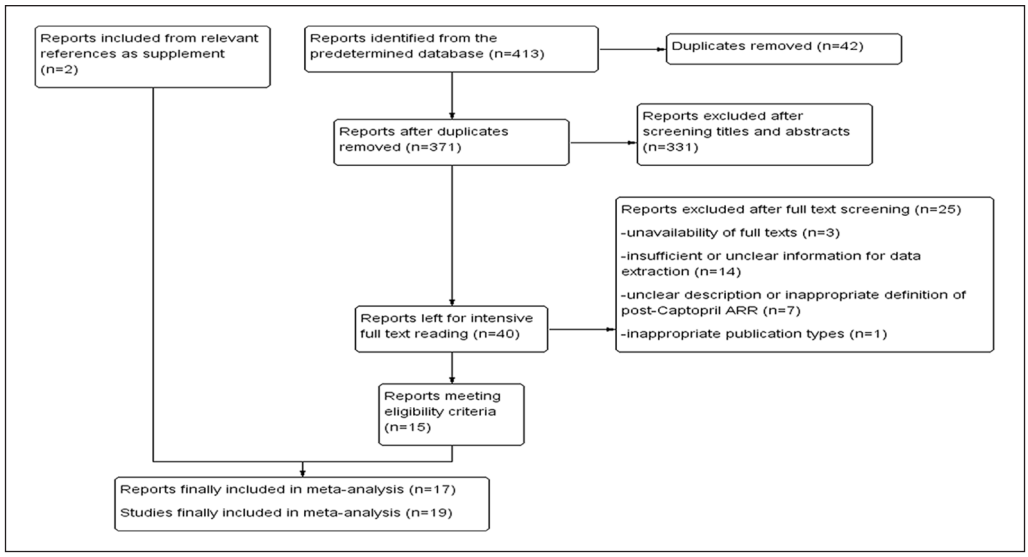

Figure 1. The procedure of study selection.
Two reports (Wang et al.[26] and Nakama et al.[25]) each involved two different studies so a total of 19 studies were obtained from 17 reports.

study characteristics (first author, year of publication, study region, sample size, study design), patient characteristics (sex, age, study population, diagnostic standard), CCT methods (captopril dose, time interval between captopril administration and blood sampling, patient posture during blood sampling, diagnostic cut-off value), and outcome data (TP, FP, FN, and TN). We converted the sensitivity and specificity to the TP, FP, FN, and TN values if the outcome data were unavailable. Disagreements were resolved through discussion or adjudication by another investigator (RY).

Quality assessment

We assessed the methodological quality of the included studies according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria,[30] which consist of four domains: patient selection, index test, reference standard, and flow and timing of cases. For the risk of bias, we rated each of the four domains as high, unclear, or low risk. For the clinical applicability concerns, we evaluated each of the first three domains as high, unclear, or low concern. Risk and concern were assessed to be unclear if there was inadequate information to formulate a judgment.

Statistical analysis

The threshold effect was assessed by the Spearman correlation coefficient between Logit (sensitivity) and Logit (1-specificity), and a strong positive correlation or a corresponding p value over 0.05 suggested a threshold effect. We examined statistical heterogeneity among studies using the I^2 statistic, and an I^2 of 0%, 25%, 50%, and 75% represented no, low, moderate, and high heterogeneity, respectively. We pooled the effect estimates sensitivity (Sen), specificity (Spe), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the corresponding 95% confidence intervals using the random-effect generic inverse variance method. To assess the diagnostic accuracy, a summary receiver operating characteristic (SROC) curve was constructed, and the relevant area under the curve and Q value were calculated. Choosing the captopril dose, posture used for blood sampling, study region, time interval between captopril administration and blood sampling, study population, diagnostic standard as variables, meta-regression was performed to investigate the potential covariates that might influence between-study inconsistency. Subgroup analyses by the dose, posture, study region, time interval, cut-off value, and study population were further conducted to explore heterogeneity. Differences among subgroups were determined through the Z-test of binomial distribution described by Altman and Bland.[31] We performed sensitivity analysis to evaluate the quality and consistency of results by sequentially excluding single study at a time. Potential publication bias was evaluated by visual inspection and the p value of Deeks' funnel plot.

All statistical analyses were carried out using Meta-Disc version 1.4 except publication bias, which was analyzed using Stata version 12.0. All statistical tests were two-sided, and p values equal to or less than 0.05 were considered statistically significant unless otherwise specified.

Results

Study selection and characteristics

A total of 413 reports were identified from the predetermined electronic databases. After careful selection, 17 reports involving 19 studies[12,13,15–29] were finally included in our meta-analysis (Figure 1). Of these, six were

diagnostic cohort studies,[12,18,20,22,23,29] and 13 were diagnostic case-control studies.[13,15–17,19,21,24–28] These 19 studies included 4568 subjects, of whom 1479 were patients with PA. Seven studies were carried out in mainland China,[13,24,26–29] four in Japan,[15,16,25] three in Italy,[18,20,21] two in the US,[12,19] two in Taiwan,[22,23] and one in England.[17]

Regarding the study population, 13 studies[16,19–28] enrolled subjects with PA and EH ("PA+EH" subgroup); four studies[13,15,17,18] enrolled subjects with PA, EH, and other forms of secondary hypertension (SH) except PA, such as renovascular hypertension, renoparenchymal hypertension, and pheochromocytoma ("PA+EH+SH" subgroup); and two studies[12,29] enrolled subjects with PA, EH, and normotension ("PA+EH+NMT" subgroup). In all the studies, CCT was conducted after the discontinuation of medications known to affect ARR levels despite slight differences in the specific types of medications or periods of withdrawal. In addition, PAC and PRA were determined by radioimmunoassay in all the studies. Captopril was orally administered at the dose of 25 mg in six studies[12,13,16,17,19,28] ("25 mg" subgroup) and 50 mg in 13 studies[15,18,20–27,29] ("50 mg" subgroup). The intervals between captopril administration and blood sampling were set at 60 ("60 min" subgroup), 90 ("90 min" subgroup), and 120 min ("120 min" subgroup) in six,[17,20,22,25–27] four,[15,18,23,25] and nine studies,[12,13,16,19,21,24,26,28,29] respectively. Blood for post-ARR detection was sampled in the seated position in 11 studies[12,18–24,27–29] ("seated" subgroup) and in the supine position in eight studies[13,15–17,25,26] ("supine" subgroup). The diagnostic cut-off values varied from 12.0[19] to 50.0[12,17] ng/dL per ng/mL/h across studies. The characteristics of the included studies are summarized in Table 1 (the diagnostic standards of the included studies are listed in Supplemental Table 2).

Quality assessment

Table 2 displays a summary of the methodological quality of the included studies. In terms of the risk of bias, all the studies had low risk associated with the reference standard and flow and timing. With respect to the index test, 13 studies (13/19) had a high risk of bias due to the lack of a pre-specified threshold, and three studies[12,15,17] (3/19) had high risk of bias in the domain of patient selection. Regarding applicability concerns, 16 studies (16/19) had low levels of concern in all three domains, but three studies[12,15] (3/19) had high levels of applicability concerns. Of these three studies, two[12,29] enrolled both EH and normotensive subjects as controls, which could potentially exaggerate the diagnostic efficacy; the other[15] only enrolled APA subjects as patients, both of which led to high levels of applicability concerns with regard to patient selection.

Overall meta-analysis

No threshold effect was revealed by analyzing the Spearman correlation coefficient between Logit (Sen) and Logit (1-Spe) ($r_s = 0.280$, $p = 0.246$). The pooled effect estimates showed moderate to high levels of heterogeneity indicated by the I^2 for the Sen (85.9%), Spe (78.0%), PLR (71.2%), NLR (82.1%), and DOR (73.8%) (Figure 2(a)–(e)), which showed unignorable inconsistencies caused by covariates other than the threshold setting.

The meta-analysis using the random-effect model showed that the pooled Sen was 0.825 (95% CI 0.804–0.844), the Spe was 0.919 (95% CI 0.908–0.928), the PLR was 8.575 (95% CI 6.258–11.749), the NLR was 0.194 (95% CI 0.142–0.264), and the DOR was 62.762 (95% CI 34.608–113.82) (Figure 2(a)–(e)).

The symmetric area under the curve (SAUC) using the random-effect model was 0.9487 (95% CI 0.9207–0.9767), and the Q value was 0.8887 (Figure 2(f)).

Meta-regression

The meta-regression analysis indicated that time interval ($p = 0.0117$) and study population ($p = 0.0033$) might have a significant influence on the between-study inconsistency, while dose, posture, study region or diagnostic standard did not account for such heterogeneity.

Subgroup analysis

The SAUCs were not significantly different between each pair of subgroups ($p = 0.700$ between "25 mg" and "50 mg"; 0.339 between "supine" and "seated"; 0.487 between "Asian" and "non-Asian"; 0.314 between "60 min" and "90 min"; 0.171 between "60 min" and "120 min"; 0.948 between "90 min" and "120 min"; 0.613 between "low" and "high" cut-off; and 0.727 between "PA+EH" and "PA+EH+SH.")

The subgroup analysis regarding the captopril dose showed that the Sen for the "25 mg" and "50 mg" subgroups were 0.880 (95% CI 0.850–0.906, $I^2 = 67.4\%$) and 0.792 (95% CI 0.765–0.818, $I^2 = 87.1\%$), respectively ($p = 0.000$), while the Spe for the "25 mg" and "50 mg" subgroups were 0.867 (95% CI 0.830–0.899, $I^2 = 50.9\%$) and 0.926 (95% CI 0.916–0.936, $I^2 = 79.0\%$), respectively ($p = 0.002$). Compared with the overall results, the levels of heterogeneity for all the effect estimates in the "25 mg" subgroup were lower, as indicated by the I^2 statistics for Sen (67.4%), Spe (50.9%), PLR (0), NLR (33.9%), and DOR (0) (Figure 3, Table 3).

In terms of the posture used for blood sampling, the Sen for the "supine" and "seated" subgroups were 0.864 (95% CI 0.837–0.888, $I^2 = 71.8\%$) and 0.788 (95% CI 0.758–0.817, $I^2 = 88.6\%$), respectively ($p = 0.000$), while the Spe for the "supine" and "seated" subgroups were 0.867 (95% CI 0.833–0.897, $I^2 = 49.1\%$) and 0.928 (95% CI 0.917–0.937, $I^2 = 80.5\%$), respectively ($p = 0.001$). The PLR for the "supine" and "seated" subgroups were 6.025 (95% CI 4.789–7.578, $I^2 = 0$) and 11.231 (95% CI 6.973–18.087, $I^2 = 79.9\%$), respectively ($p = 0.021$). Furthermore, the levels

Table 1. Characteristics of the included studies.

Study (author)	Study characteristics			Patient characteristics			CCT methods			
	Study region	Sample size	Study design	Female proportion	Age, years (mean ± SD)	Study population	Cut-off (ng/dL per ng/mL/h)	Dose (mg)	Time interval (min)	Posture
Lyons et al.[12]	USA	31	Cohort	41.90%	NA	PA, EH+NMT	50	25	120	Seated
Naomi et al.[15]	Japan	31	Case-control	45.16%	45.2 ± 10.7	PA, EH+RH+RVH	20	50	90	Supine
Muratani et al.[16]	Japan	91	Case-control	NA	NA	PA, EH	12.6	25	120	Supine
Hambling et al.[17]	England	22	Case-control	NA	NA	PA, EH+SH	50	25	60	Supine
Rossi et al.[18]	Italy	1046	Cohort	49.20%	49.5 ± 11.9	PA, EH+RH+RVH+PC	35	50	90	Seated
Castro et al.[19]	USA	7	Case-control	100%	52.14 ± 9.70	PA, EH	12	25	120	Seated
Rossi et al.[20]	Italy	1125	Cohort	43.60%	PA: 49.7 ± 12.2 EH: 45.9 ± 12.0	PA, EH	30	50	60	Seated
Giacchetti et al.[21]	Italy	82	Case-control	NA	NA	PA, EH	30	50	120	Seated
Wu et al.[22]	Taiwan	135	Cohort	48.90%	47.9 ± 1.5	PA, EH	34.6	50	60	Seated
Wu et al.[23]	Taiwan	114	Cohort	52.63%	48.7 ± 15.2	PA, EH	30.5	50	90	Seated
Hao et al.[24]	Mainland China	199	Case-control	47.20%	NA	PA, EH	30	50	120	Seated
Nakama et al.[25*]	Japan	35	Case-control	NA	PA: 46.8 ± 10.7 EH: 50.0 ± 11.5	PA, EH	19.8	50	60	Supine
Nakama et al.[25*]	Japan	35	Case-control	NA	PA: 46.8 ± 10.7 EH: 50.0 ± 11.5	PA, EH	21.3	50	90	Supine
Wang et al.[26#]	Mainland China	141	Case-control	55.30%	NA	PA, EH	34.6	50	60	Supine
Wang et al.[26#]	Mainland China	141	Case-control	55.30%	NA	PA, EH	42.2	50	120	Supine
Chen et al.[13]	Mainland China	674	Case-control	49.40%	45.0 ± 13.7	PA, EH + PC	46.2	25	120	Supine
Zhao et al.[27]	Mainland China	222	Case-control	42.30%	NA	PA, EH	22.7	50	60	Seated
Wei[28]	Mainland China	124	Case-control	NA	NA	PA, EH	26.5	25	120	Seated
Zhu et al.[29]	Mainland China	313	Cohort	46.96%	NA	PA, EH + NMT	20	50	120	Seated

Dose: the dose of captopril administered; Time interval: the time interval between captopril administration and blood sampling; Posture: the posture used for blood sampling; PA: primary aldosteronism; EH: essential hypertension; RH: renoparenchymal hypertension; RVH: renovascular hypertension; PC: pheochromocytoma; NMT: normotension; SH: other forms of secondary hypertension except PA; NA: not available.

The diagnostic standards of the included studies are listed in Supplemental Table 2.

*Two different studies were involved in the same article (Nakama et al.[25]), distinguished by a, b.

#Two different studies were involved in the same article (Wang et al.[26]), distinguished by a, b.

Table 2. Methodological quality summary of the included studies.

Study (author)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Lyons et al.[12]	−	−	+	+	−	+	+
Naomi et al.[15]	−	−	+	+	−	+	+
Muratani et al.[16]	?	−	+	+	+	+	+
Hambling et al.[17]	−	?	+	+	+	+	+
Rossi et al.[18]	+	+	+	+	+	+	+
Castro et al.[19]	?	+	+	+	+	+	+
Rossi et al.[20]	+	+	+	+	+	+	+
Giacchetti et al.[21]	+	−	+	+	+	+	+
Wu et al.[22]	+	−	+	+	+	+	+
Wu et al.[23]	+	−	+	+	+	+	+
Hao et al.[24]	+	+	+	+	+	+	+
Nakama et al.[25*]	+	−	+	+	+	+	+
Nakama et al.[25*]	+	−	+	+	+	+	+
Wang et al.[26#]	?	−	+	+	+	+	+
Wang et al.[26#]	?	−	+	+	+	+	+
Chen et al.[13]	+	−	+	+	+	+	+
Zhao et al.[27]	?	−	+	+	+	+	+
Wei[28]	?	−	+	+	+	+	+
Zhu et al.[29]	?	?	+	+	−	+	+

"+," "?," and "−" indicate low, unclear, and high risk of bias or applicability concerns, respectively.
*2 different studies were involved in the same article (Nakama, C. 2014), distinguished by a, b.
#2 different studies were involved in the same article (Wang, L.X. 2016), distinguished by a, b.

of heterogeneity for all the effect estimates in the "supine" subgroup were lower than those for the overall results, as indicated by I^2 statistics for Sen (71.8%), Spe (49.1%), PLR (0), NLR (53.8%), and DOR (0) (Figure 4, Table 3).

With regard to the study region, seven mainland Chinese, four Japanese, and two Taiwanese studies formed the "Asian" subgroup, while the rest formed the "non-Asian" subgroup. The Sen for the "Asian" and "non-Asian" subgroups were 0.842 (95% CI 0.820–0.862, $I^2 = 75.0\%$) and 0.746 (95% CI 0.689–0.797, $I^2 = 92.5\%$), respectively ($p = 0.002$). Compared with the overall analysis results, the I^2 statistic was lower for Sen (75.0%), PLR (65.8%), NLR (68.6%), and DOR (63.9%) in the "Asian" subgroup and Spe (47.1%) in the "non-Asian" subgroup (Supplemental Figure 1, Table 3).

Regarding the time interval, the Sen was 0.740 (95% CI 0.698–0.779, $I^2 = 84.6\%$) for the "60 min" subgroup, 0.908 (95% CI 0.851–0.949, $I^2 = 85.4\%$) for the "90 min" subgroup and 0.856 (95% CI 0.830–0.878, $I^2 = 79.5\%$) for the "120 min" subgroup ($p = 0.000$ between "60 min" and "90 min"; 0.000 between "60 min" and "120 min"; 0.059 between "90 min" and "120 min"). The Spe was 0.904 (95% CI 0.886–0.920, $I^2 = 0$) for the "60 min" subgroup, 0.928 (95% CI 0.911–0.942, $I^2 = 59.5\%$) for the "90 min" subgroup and 0.929 (95% CI 0.909–0.946, $I^2 = 87.5\%$) for the "120 min" subgroup ($p = 0.042$ between "60 min" and "90 min"; 0.051 between "60 min" and "120 min"). The PLR was 6.312 (95% CI 5.163–7.716, $I^2 = 0$) for the "60 min" subgroup and 16.315 (95% CI 7.467–35.647, $I^2 = 78.0\%$) for the "120 min" subgroup ($p = 0.021$), while the DOR for the "60 min" and "120 min" subgroups were 18.613 (95% CI 13.534–25.599, $I^2 = 0$) and 143.29 (95% CI 52.681–389.75, $I^2 = 65.7\%$), respectively ($p = 0.000$). Compared with the overall analysis results, the I^2 statistic was lower for the Sen (84.6%), Spe (0), PLR (0), NLR (75.7%), and DOR (0) in the "60 min" subgroup; for the Sen (85.4%), Spe (59.5%) in the "90 min" subgroup; and for the Sen (79.5%), NLR (75.3%), and DOR (65.7%) in the "120 min" subgroup (Supplemental Figure 2, Table 3).

Because 30 was both the mode and median of all the cut-off values in the 19 included studies and was close to the mean cut-off of 29.9, we divided our studies into the "low" (<30) and "high" ($\geqslant 30$) cut-off subgroups. The Sen for the "low" and "high" subgroups were 0.869 (95% CI 0.832–0.900, $I^2 = 70.8\%$) and 0.808 (95% CI 0.783–0.831, $I^2 = 89.5\%$), respectively ($p = 0.004$). However, no significant differences were found between the "low" and "high" cut-off subgroups with regard to the Spe, PLR, NLR, or DOR ($p = 0.133$, 0.874, 0.097, or 0.318, respectively) (Table 3). Compared with the overall analysis results, the I^2 statistic was lower for the Sen (70.8%), NLR (64.9%), and

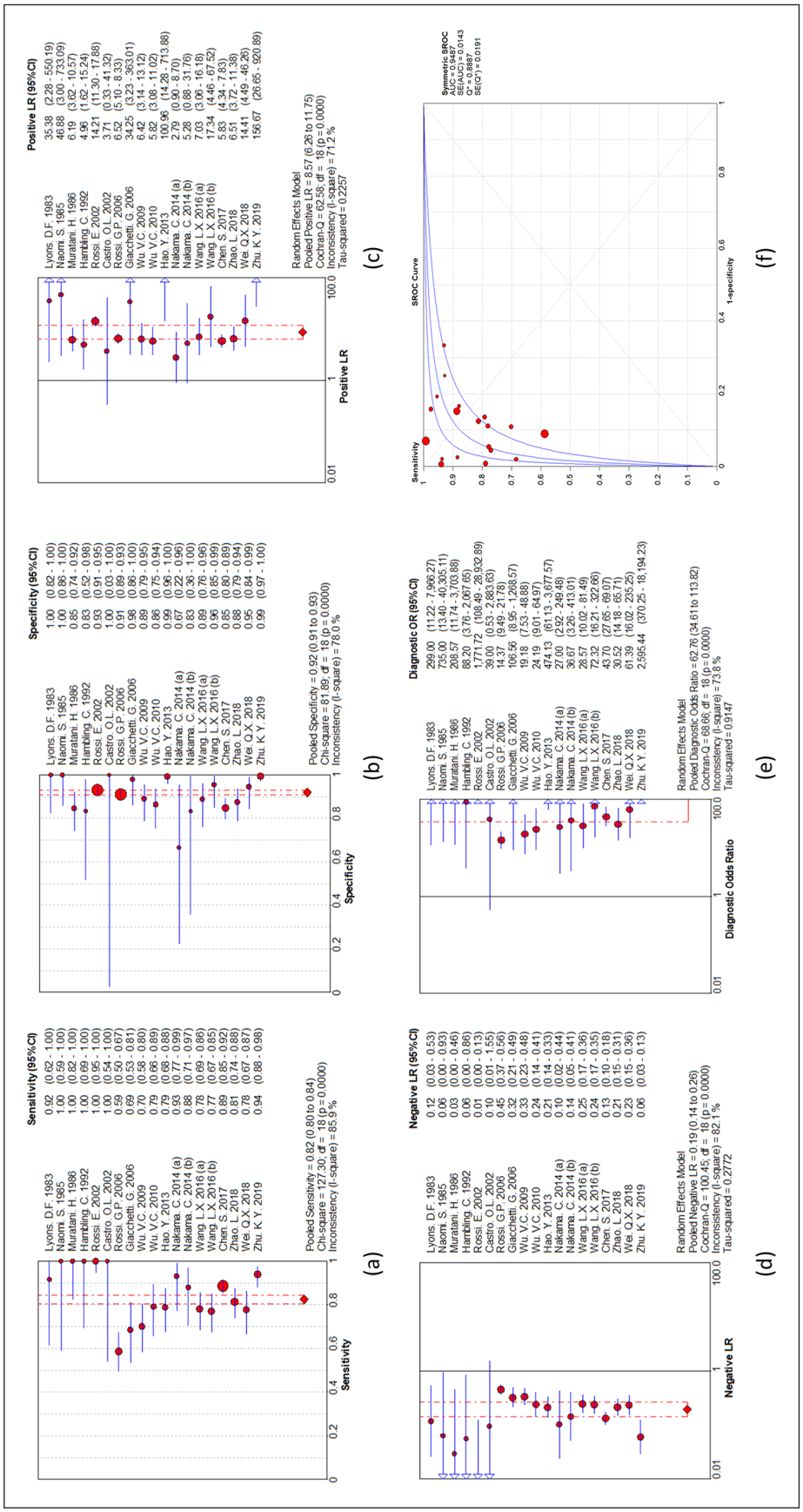

Figure 2. Overall meta-analysis results of the included 19 studies: the forest plots of the pooled: (a) Sen, (b) Spe, (c) PLR, (d) NLR, (e) DOR, and (f) the summary receiver operating characteristic (SROC) curve for the accuracy of diagnosing primary aldosteronism.
CI: confidence interval; AUC: area under the curve; SE: standard error.

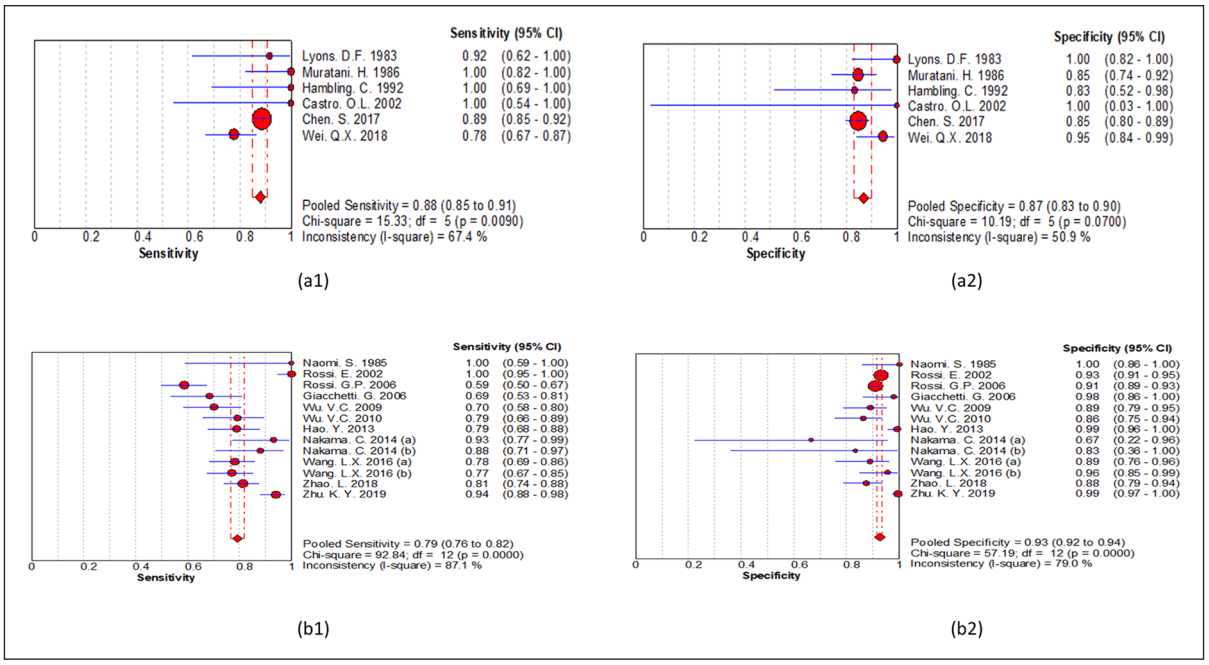

Figure 3. (a) The forest plots of Sen (a1) and Spe (a2) of the six studies in the "25 mg" subgroup, and (b) the forest plots of Sen (b1) and Spe (b2) of the 13 studies in the "50 mg" subgroup.
CI: confidence interval.

DOR (67.3%) in the "low" subgroup; for the Spe (76.1%) in the "high" subgroup (Supplemental Figure 3, Table 3).

With regard to the study population, the Sen for the "PA+EH" and "PA+EH+SH" subgroups were 0.760 (95% CI 0.730–0.789, I^2=74.2%) and 0.905 (95% CI 0.876–0.929, I^2=83.4%), respectively (p=0.000). Compared with the overall analysis results, the I^2 was lower for the Sen (74.2%), Spe (62.0%), PLR (41.9%), NLR (63.4%), and DOR (52.1%) in the "PA+EH" subgroup and the Sen (83.4%), NLR (69.7%), and (69.9%) in the "PA+EH+SH" subgroup. (Supplemental Figure 4, Table 3). The "PA+EH+NMT" subgroup was not involved in the subgroup analysis due to the limited number of the relevant studies included (n=2).

Sensitivity analysis

The results showed that the stability of results did not significantly change after omitting one study at a time (Supplemental Figure 5, Supplemental Table 3), which provided greater robustness on the pooled effect.

Publication bias

As shown in Figure 5, no obvious publication bias was observed, with a visually symmetric distribution of Deeks' funnel plot (p=0.815).

Discussion

The overall pooled results favored the clinical application of post-captopril ARR with a moderate Sen (82.5%) and a relatively high Spe (91.9%), probably suggesting that it is better used to minimize misdiagnoses than missed diagnoses. The SAUC (0.9487) also showed a high diagnostic value, and a DOR of 62.762, calculated by the ratio of the PLR and NLR, indicated the ideal discriminatory effect of post-captopril ARR due to its significant correlation with the status of PA. Therefore, ARR after CCT should be taken into consideration and generalized for PA diagnosis. The quality assessment revealed that although 13/19 studies had a high risk of bias in the domain of the index test, the overall quality was acceptable regarding the relevant domains of risk of bias and applicability concerns, which ensured the validity of our quantitative synthesis.

However, we could not neglect the moderate to high heterogeneity for the overall pooled diagnostic effect estimates, with the I^2 ranging from 71.2% to 85.9%. The heterogeneity might be the result of the inherent inconsistency of the included subjects, with differences in age, sex, serum potassium concentration, PA subtype, predisposition to PA, study region, varying criteria for the study population and confirmatory diagnosis, and different CCT methods involving various captopril doses, time intervals between captopril administration and blood sampling, and postures adopted during blood sampling. The varying diagnostic cut-offs between 12.0[19] and 50.0 (12, 17) ng/dL per ng/mL/h might also be attributed to such causes, but no threshold effect was shown for the overall explanation.

Our subgroup analysis stratified by the dose favored choosing 25 mg of captopril for the CCT to reduce the

Table 3. Overall and subgroup analyses for diagnostic effect estimates of post-captopril ARR and the corresponding I^2 or Q value.

Overall and subgroup analysis	Diagnostic effect estimates Mean (95% CI; I^2 or Q value)					
	Sen	Spe	PLR	NLR	DOR	SAUC
Pooled analysis	0.825 (0.804–0.844; I^2 = 85.9%)	0.919 (0.908–0.928; I^2 = 78.0%)	8.575 (6.258–11.749; I^2 = 71.2%)	0.194 (0.142–0.264; I^2 = 82.1%)	62.762 (34.608–113.82; I^2 = 73.8%)	0.9487 (0.9207–0.9767; Q = 0.8887)
Captopril dose						
25 mg	0.880 (0.850–0.906; I^2 = 67.4%)	0.867 (0.830–0.899; I^2 = 50.9%)	6.156 (4.824–7.855; I^2 = 0.0%)	0.154 (0.101–0.234; I^2 = 33.9%)	48.728 (32.049–74.086; I^2 = 0.0%)	0.9385 (0.9197–0.9573; Q = 0.8755)
50 mg	0.792 (0.765–0.818; I^2 = 87.1%)	0.926 (0.916–0.936; I^2 = 79.0%)	9.776 (6.385–14.970; I^2 = 77.4%)	0.214 (0.153–0.300; I^2 = 82.4%)	66.572 (29.423–150.63; I^2 = 80.9%)	0.9477 (0.9048–0.9906; Q = 0.8873)
p	0.000*	0.002*	0.065	0.231	0.505	0.700
Posture						
Supine	0.864 (0.837–0.888; I^2 = 71.8%)	0.867 (0.833–0.897; I^2 = 49.1%)	6.025 (4.789–7.578; I^2 = 0.0%)	0.169 (0.116–0.247; I^2 = 53.8%)	44.655 (30.421–65.547; I^2 = 0.0%)	0.9339 (0.9159–0.9519; Q = 0.8699)
Seated	0.788 (0.758–0.817; I^2 = 88.6%)	0.928 (0.917–0.937; I^2 = 80.5%)	11.231 (6.973–18.087; I^2 = 79.9%)	0.215 (0.144–0.320; I^2 = 84.8%)	82.122 (31.204–216.12; I^2 = 84.1%)	0.9583 (0.9117–1.0049; Q = 0.9021)
p	0.000*	0.001*	0.021*	0.391	0.251	0.339
Study region						
Asian	0.842 (0.820–0.862; I^2 = 75.0%)	0.913 (0.895–0.930; I^2 = 83.3%)	8.504 (5.665–12.767; I^2 = 65.8%)	0.191 (0.147–0.249; I^2 = 68.6%)	57.128 (31.494–103.63; I^2 = 63.9%)	0.9302 (0.8951–0.9653; Q = 0.8654)
Non-Asian	0.746 (0.689–0.797; I^2 = 92.5%)	0.921 (0.909–0.933; I^2 = 47.1%)	9.336 (5.091–17.118; I^2 = 79.9%)	0.183 (0.076–0.438; I^2 = 83.5%)	108.16 (12.427–941.43; I^2 = 80.5%)	0.9480 (0.9121–0.9839; Q = 0.8878)
p	0.002*	0.461	0.802	0.927	0.577	0.487
Time interval						
60 min	0.740 (0.698–0.779; I^2 = 84.6%)	0.904 (0.886–0.920; I^2 = 0.0%)	6.312 (5.163–7.716; I^2 = 0.0%)	0.277 (0.189–0.407; I^2 = 75.7%)	18.613 (13.534–25.599; I^2 = 0.0%)	0.9163 (0.8810–0.9516; Q = 0.8492)
90 min	0.908 (0.851–0.949; I^2 = 85.4%)	0.928 (0.911–0.942; I^2 = 59.5%)	9.867 (4.102–23.733; I^2 = 75.5%)	0.086 (0.015–0.498; I^2 = 85.1%)	136.56 (12.222–1525.9; I^2 = 76.8%)	0.9421 (0.9064–0.9778; Q = 0.8802)
120 min	0.856 (0.830–0.878; I^2 = 79.5%)	0.929 (0.909–0.946; I^2 = 87.5%)	16.315 (7.467–35.647; I^2 = 78.0%)	0.174 (0.118–0.256; I^2 = 75.3%)	143.29 (52.681–389.75; I^2 = 65.7%)	0.9434 (0.9273–0.9595; Q = 0.8817)
p	0.000* (60 vs 90 min) 0.000* (60 vs 120 min) 0.059 (90 vs 120 min)	0.042* (60 vs 90 min) 0.051 (60 vs 120 min) 0.935 (90 vs 120 min)	0.331 (60 vs 90 min) 0.021* (60 vs 120 min) 0.402 (90 vs 120 min)	0.201 (60 vs 90 min) 0.095 (60 vs 120 min) 0.441 (90 vs 120 min)	0.109 (60 vs 90 min) 0.000* (60 vs 120 min) 0.971 (90 vs 120 min)	0.314 (60 vs 90 min) 0.171 (60 vs 120 min) 0.948 (90 vs 120 min)
Cut-off						
Low	0.869 (0.832–0.900; I^2 = 70.8%)	0.936 (0.909–0.957; I^2 = 81.5%)	9.338 (4.234–20.595; I^2 = 73.7%)	0.132 (0.076–0.232; I^2 = 64.9%)	100.04 (28.847–346.93; I^2 = 67.3%)	0.9588 (0.9227–0.9949; Q = 0.9027)
High	0.808 (0.783–0.831; I^2 = 89.5%)	0.916 (0.905–0.926; I^2 = 76.1%)	8.699 (5.950–12.720; I^2 = 77.0%)	0.232 (0.161–0.334; I^2 = 85.7%)	48.537 (24.541–95.997; I^2 = 75.3%)	0.9454 (0.9080–0.9828; Q = 0.8844)
p	0.004*	0.133	0.874	0.097	0.318	0.613
Study population						
PA+EH	0.760 (0.730–0.789; I^2 = 74.2%)	0.911 (0.896–0.925; I^2 = 62.0%)	7.142 (5.277–9.666; I^2 = 41.9%)	0.258 (0.206–0.323; I^2 = 63.4%)	35.094 (20.923–58.863; I^2 = 52.1%)	0.9128 (0.8734–0.9522; Q = 0.8453)
PA+EH+SH	0.905 (0.876–0.929; I^2 = 83.4%)	0.915 (0.898–0.929; I^2 = 85.2%)	9.076 (3.731–22.079; I^2 = 92.1%)	0.054 (0.009–0.334; I^2 = 69.7%)	196.88 (21.987–1762.9; I^2 = 69.9%)	0.9220 (0.8885–0.9555; Q = 0.8557)
p	0.000*	0.712	0.617	0.092	0.133	0.727

CI: confidence interval; Sen: sensitivity; Spe: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; SAUC: symmetric area under the curve; PA: primary aldosteronism; EH: essential hypertension; SH: other forms of secondary hypertension except PA.
*Indicates statistically significant differences.

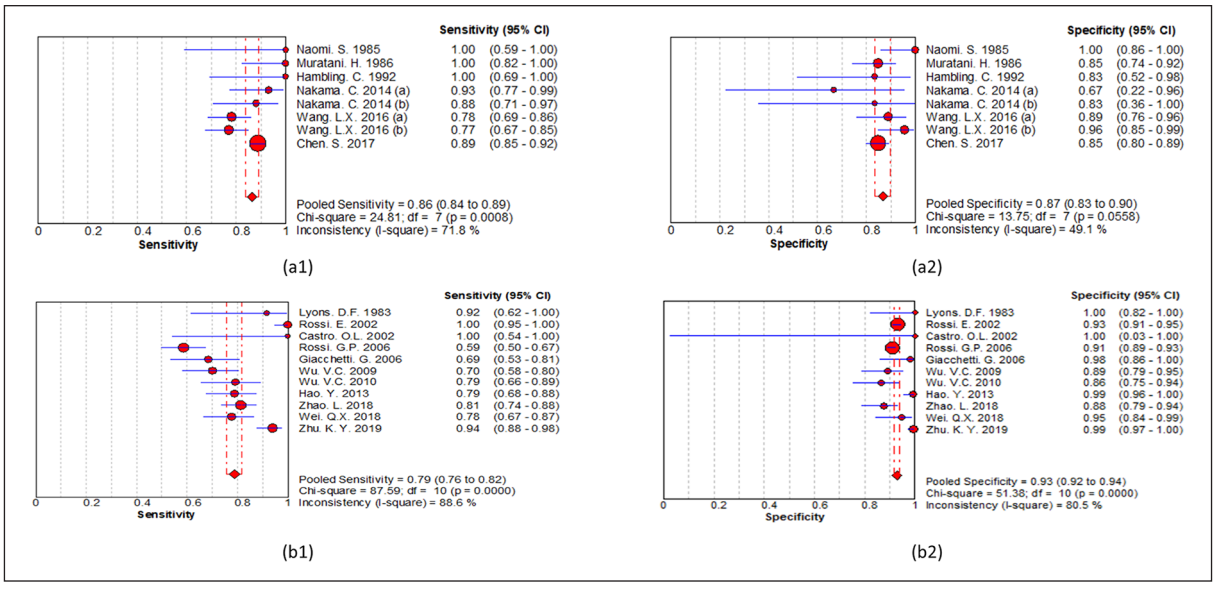

Figure 4. (a) The forest plots of Sen (a1) and Spe (a2) of the eight studies in the "supine" subgroup, (b) the forest plots of Sen (b1) and Spe (b2) of the 11 studies in the "seated" subgroup.
CI: confidence interval.

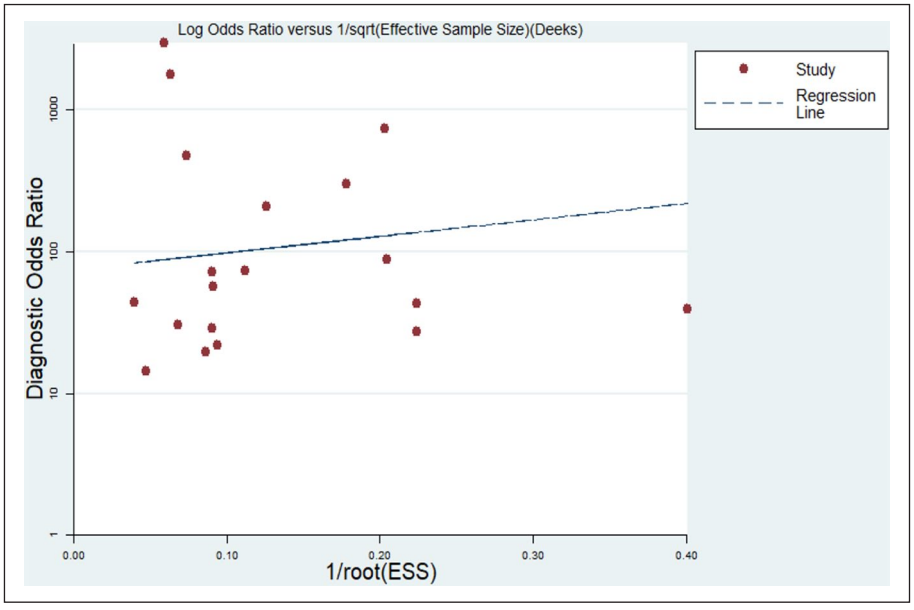

Figure 5. Deeks' funnel plot of publication bias in the included 19 studies.
ESS: effective sample size.

number of missed diagnoses. However, 50 mg of captopril might be a better choice for reducing the number of false positives or misdiagnoses. This is consistent with the pharmacological perspective that the blood concentration of drugs has a positive correlation with the administration dose within a certain range[32] so that the suppressive effect of captopril on RAAS should be stronger with larger doses.

The analysis stratified by the posture favored the seated position during blood sampling for the CCT when the focus was to avoid unnecessary subsequent diagnostic procedures and overtreatment by minimizing misdiagnoses. Using the seated position made this test more flexible, regardless of the site. However, adopting the supine position might have more advantages if it is more important to reduce missed diagnoses and confirm the possible diagnosis of PA in a timely manner. However, we did not discuss APA and IHA separately, in which the influence of the posture might differ,[33] because most of

the included studies did not have clear information about the PA subtype.

The analysis stratified by the study region suggested that post-captopril ARR may perform better for reducing missed diagnoses of PA in Asian populations than non-Asian populations. The disparity might be the result of ethnic, regional or dietary differences, which could be explained by the fact that the optimal cut-offs for the post-captopril ARR in Chinese studies were generally higher than those in studies performed in other countries,[12,13,15–29] perhaps due to the high dietary salt intake of Chinese people, which could lead to a high false positive rate.[34] However, we roughly divided the study regions into Asian and non-Asian countries without a standard stratification based on race due to an inadequate number of studies for subdivision.

Regarding the time interval, the Sen of the post-captopril ARR was the highest in the "90 min" subgroup, moderate in the "120 min" subgroup and the worst in the "60 min" subgroup, although the difference between "90 min" and "120 min" tended to reach statistical significance. Besides, the Spe in the "90 min" subgroup was significantly higher than that in the "60 min" subgroup and similar to that in the "120 min" subgroup. This could provide a new way to conduct the CCT with the time interval defined as 90 min to generally attain the best accuracy with high Sen and Spe; this seems to challenge our traditional practice of drawing blood both 60 min and 120 min after taking captopril.[11] Regarding the pharmacological explanation, captopril takes effect 15 min after administration, reaches the plateau of action at 60 to 90 min, after which it is eliminated quickly, with a half-life of 180 min.[35] Therefore, 60 min may be too early for the drug action to peak, while 120 min may be a too late, and drug elimination may have already begun. Thus, choosing 90 min as a compromise seems reasonable to detect an obvious effect on RAAS suppression.

Due to the limited number of included studies and various cut-off values, we were not able to perform a subgroup analysis based on every individual cut-off value. The diagnostic cut-off values varied from 12.0[19] to 50.0[12,17] ng/dL across the 19 studies and obeyed a normal distribution. Because 30 was both the mode and median of all the cut-off values in the included studies and was close to the mean cut-off value of 29.9, we chose 30 as the split-point to perform a preliminary subgroup analysis. No significant differences were found between the "low" (<30) and "high" ($\geqslant 30$) cut-off value subgroups for all the effect estimates except Sen, which was consistent with the absence of a threshold effect in our meta-analysis. However, lower cut-off values showed a higher sensitivity in our analysis and might logically attain a lower specificity than higher cut-off values. Our meta-analysis might not have enough power to detect the statistical significance due to the limited number of studies.

Meanwhile, the Sen of the post-captopril ARR was higher in the "PA + EH + SH" subgroup than in the "PA + EH" subgroup. This finding indicated that the levels of the post-captopril ARR of PA may overlap more with that of EH, which made it harder to distinguish PA from EH than from other forms of secondary hypertension, such as renovascular hypertension, renoparenchymal hypertension, and pheochromocytoma. It is reasonable because PA and low-renin essential hypertension (LREH) can both manifest as low PRA and high PAC,[36] while secondary hypertension, except PA, is usually associated with the inappropriate activation of RAAS, leading to high levels of both PRA and PAC.[37]To the best of our knowledge, this is the first meta-analysis to combine the results of previous eligible studies to reach a summary conclusion about the diagnostic efficacy of post-captopril ARR and explore the factors influencing that efficacy, providing a comprehensive understanding of the topic and compensating for the shortcomings of individual studies, such as small sample sizes, non-ideal study designs, or restricted study regions, so that more valid results could be obtained. In both the overall and subgroup analyses, we analyzed and compared important diagnostic effect estimates, including the Sen, Spe, PLR, NLR, DOR, and SAUC, each of which focused on different diagnostic aspects. This may give us references for flexibly determining the details of CCT, including the captopril dose or the posture, so that it can be adapted to specific circumstances when different diagnostic aspects are of greater importance, such as reducing misdiagnoses or missed diagnoses. In addition, in all the included studies, the CCT was conducted with the prior discontinuation of medications known to affect the ARR level, which avoided interference with testing results; the radioimmunoassay, which was commonly recommended by the guidelines, was adopted for the measurement of PAC and PRA. This standardization helped assure the validity of the conclusion.

However, there were also some limitations in our meta-analysis that should be taken into account. First, the pooled effect estimates showed moderate to high levels of heterogeneity. However, our meta-regression analysis owed the main source of between-study inconsistency to the time interval and study population, which was also verified in the corresponding subgroup analysis with decreased heterogeneity; besides, meta-regression and sensitivity analysis results partially supported that varying diagnostic criteria did not influence the final results. Second, not all the included studies had ideal quality, and flaws existed in the study designs to varying degrees. Most of the included studies were retrospective, which made it difficult to avoid a case-control design or interpret test results without the knowledge of the reference standards. Only a few studies[18–20,24] specified the cut-off values beforehand; thus, a high risk of bias in the domain of the

index test was identified. Three studies[12,17,38] (3/19) enrolled patients from a non-consecutive sample or made inappropriate exclusions that caused a high risk of bias in the domain of patient selection; two studies[12,29] enrolled both EH and normotensive subjects as controls, and another study[38] only enrolled APA subjects as patients, leading to high levels of applicability concerns in the domain of patient selection. Third, although some variables were involved in meta-regression and subgroup analyses to explore heterogeneity, the results of our quantitative synthesis were still based on estimates and were not adjusted for other confounders or potential sources of heterogeneity, including age, sex, serum potassium level, PA subtype, and predisposition to PA, which might have reduced the efficacy of our analysis. However, sensitivity analysis at least revealed that the robustness of overall results was not driven by a single study. Fourth, we could only obtain an overview of the diagnostic value with the pooled diagnostic effect estimates but could not obtain a pooled optimal cut-off value due to the inherent limitation in the statistical methodology of diagnostic meta-analysis, which would lead to some difficulties in explanation and application. However, no threshold effect was revealed in our meta-analysis, indicating comparable diagnostic value at different cut-off values ranging from 12.0 to 50.0 ng/dL. Fifth, we were not able to compare the diagnostic value of post-captopril ARR with the post-captopril absolute value or suppression percentage of aldosterone because not all the included studies contained adequate information on every diagnostic index; this indicates the need for prospective studies with good designs and large sample sizes to further clarify which one is superior. A meta-analysis by Wu et al.[39] may serve as a supplement by revealing no significant differences in diagnostic accuracy between post-captopril PAC and post-captopril ARR. However, that meta-analysis included fewer eligible studies than ours and did not exclude those studies which used direct renin concentration to define ARR; besides, we focused not only on diagnostic value of post-captopril ARR but also on the factors influencing it. In a word, despite these limitations, our meta-analysis still has a certain value as a reference showing that post-captopril ARR is a good index for PA diagnosis, and it sheds light on the best conditions under which to conduct the CCT.

Conclusion

Our meta-analysis suggests that post-captopril ARR is considerably valuable for the diagnosis of PA; it is probably more sensitive in Asian populations. In addition, we suggest conducting the CCT in the supine posture with a captopril dose of 25 mg to attain greater sensitivity and reduce missed diagnoses, while we suggest conducting the CCT in the seated posture with a captopril dose of 50 mg to attain greater specificity and reduce misdiagnoses. A 90-min interval between captopril administration and blood sampling may perform the best in terms of both sensitivity and specificity. Lower cut-off values (<30) can lead to a higher sensitivity and a logically lower specificity than higher cut-off values ($\geqslant 30$). The diagnostic value is suggested to be comparable at different cut-off values ranging from 12.0 to 50.0 ng/dL per ng/mL/h. More evidence from prospective clinical studies with good designs and large sample sizes is expected to result in a more robust conclusion.

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Supplemental material

Supplemental material for this article is available online.

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