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META-ANALYSIS

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Meta-analysis of blood parameters related to lipid and glucose metabolism between two subtypes of primary aldosteronism

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Abstract

It remains unclear whether metabolic profiles differ within the subtypes of primary aldosteronism (PA). This meta-analysis aimed to compare the blood parameters related to lipid and glucose metabolism at baseline between unilateral PA and bilateral PA. A search was performed using PubMed, Web of Science, and Sciencedirect databases, supplemented by hand-searching of related references. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for each parameter. Twenty-one studies involving 4197 patients with PA were included. Compared with bilateral PA groups, unilateral PA groups demonstrated significantly lower low-density lipoprotein cholesterol (LDL-C, SMD: −.14 mmol/L, 95% CI: −.20, −.07), total cholesterol (TC, SMD: −.16 mmol/L, 95% CI: −.23, −.09), triglyceride (TG, SMD: −.22 mmol/L, 95% CI: −.29, −.16), fasting blood glucose (FBG, SMD: −.11 mmol/L, 95% CI: −.18, −.04), hemoglobin A1c (HbA1c, SMD: −.21%, 95% CI: −.30, −.13), and homeostasis model assessment-insulin resistance (HOMA-IR, SMD: −.40, 95% CI: −.58, −.23). No significant difference was found in high-density lipoprotein cholesterol (HDL-C) level between the two groups (SMD: .40 mmol/L, 95% CI: −.02, .11). To sum up, comparison of several blood metabolic parameters between the two subtypes suggested that the bilateral PA may associate with a higher prevalence of impaired glucose and lipid metabolism than unilateral PA; however, results should be treated with caution. Additional well-designed studies are needed to prove the present results and better elucidate the link between metabolic abnormalities and etiologies of each PA subtype.

KEYWORDS
meta-analysis, metabolism, primary aldosteronism, subtype

1 | INTRODUCTION

Primary aldosteronism (PA) is a heterogeneous group of disorders characterized by autonomous aldosterone overproduction with renin activity suppression.[1] PA is considered a common cause of secondary hypertension, accounting for 5%–10% of the general population with hypertension, and an excess of aldosterone renders PA patients at an elevated risk of cardiovascular diseases (CVDs) relative to age and gender-matched patients with essential hypertensives (EHs).[2,3] Early diagnosis and proper management of PA is therefore crucial. The diagnosis of PA is a three-step process: case detection, case confirmation, and subtype classification.[1] The last step is essential for making a proper treatment option for this condition. PA has two main subtypes: unilateral PA (largely represented by aldosterone-producing

adenoma [APA]) and bilateral PA (usually idiopathic hyperaldosteronism [IHA]). Based on different etiologies, the former characterized by higher plasma aldosterone concentrations (PACs) and lower potassium levels requires an adrenalectomy treatment, while the latter can be treated with a medical therapy using mineralocorticoid receptor (MR) antagonists.[1,4]

There has been accumulating evidence linking PA with metabolic syndromes in general and with separate components, including hyperglycemia, dyslipidemia, and hypertension,[5–7] which may correlate with a higher prevalence of diabetes mellitus (DM) and contribute to an increased CVD risk.[8–10] However, whether or not aldosterone independently contributes to the development of metabolic abnormalities remains an unsolved issue. Some reports suggested that metabolic disorders such as hyperglycemia and dyslipidemia were not more prevalent in unilateral PA, which is theoretically associated with a higher prevalence of MetS based on higher PAC and lower potassium levels, compared with bilateral PA.[11–13] More importantly, so far there have been a limited number of studies analyzing the metabolic profiles according to the subtypes of PA. Hence, the present study conducted a meta-analysis with enough sample size through collating publications available which compared baseline blood parameters related to lipid and glucose metabolism between unilateral and bilateral PA, in order to investigate whether the different etiologies of PA subtypes would impact the metabolic profiles, which may help solve the aforementioned issue and better explain the elevated CVD risk in PA.

2 | METHODS

The present study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements.[14] All analyses were based on previous published studies; thus, no ethical approval and patient consent were required.

2.1 | Search strategy

Computerized searching of databases (PubMed, Web of Science, Science direct) was conducted for potential articles from January 1, 2000 to December 31, 2021, using the following searching terms with their synonyms as well as abbreviations in different combinations: "primary hyperaldosteronism," "subtype diagnosis," "unilateral hyperaldosteronism," "bilateral hyperaldosteronism," "aldosterone-producing adenoma," "idiopathic hyperaldosteronism," "lipid," "glucose," and "metabolism." Furthermore, we also obtained additional records by cross-checking the references of potentially relevant studies.

2.2 | Eligibility criteria

All retrieved articles were scrutinized for eligibility by two reviewers independently. Candidate studies were kept in the meta-analysis if they met the following selection criteria: (i) adult patients (age > 18 years) with PA; (ii) comparing baseline (pre-treatment) biochemical parameters between unilateral PA versus bilateral PA, or between APA (the main type of unilateral PA) versus IHA; (iii) containing at least one of the following related outcomes: blood levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), homeostasis model assessment-insulin resistance (HOMA-IR), and HOMA for β cell function (HOMA-β); and (iv) original observational studies, prospective or retrospective, in English.

In face of overlapped samples in multiple studies, only the one with the most sufficient data was incorporated into the analysis. We ruled out the following types of publications: grey literature, reviews, letters, editorials, conference abstracts, case reports, basic experiments, or animal studies. Reviewers initially browsed the titles and abstracts of search results and selected potentially relevant articles for additional full-text assessment. Any divergence was resolved by discussion.

2.3 | Data extraction and quality assessment

The following data were extracted and tabulated into the pre-defined Microsoft Excel spreadsheet: the first author, year of publication, location, study design, characteristics of unilateral/bilateral PA (number, mean/median age, gender, and BMI), methods of subtype classification, and outcomes of interest. The literature quality evaluation was performed by two reviewers independently using the JBI critical appraisal tool for observational studies.[15] Each study was judged as having a high, moderate, or low risk of bias.

2.4 | Data analysis

Data synthesis was performed using Stata Version 15.1 (Stata Corp.). Standardized mean differences (SMDs) with their corresponding 95% confidence intervals (CIs) were calculated for continuous data given the fact that there was no standardized method used for measuring these outcomes in included studies. Statistical heterogeneity was quantified by the *I*-squared (*I*2) statistics. If the significant heterogeneity was present ($I^2 > 50\%$), a random-effect model was adopted for data-pooling; conversely, its absence called for a fix-effect model. Sensitivity analysis was done by omitting each study one time to explore the potential source of heterogeneity; if one study was identified as a significant heterogeneity-contributor it would be removed from the analysis and the overall results would be re-calculated. The study with the largest sample size would be omitted to examine the robustness of overall results. In addition, subgroup analysis was performed based on ethnicity (Asian or non-Asian) and enrolled subjects (whether studies focused on "APA vs. IHA" or not) if each subgroup included at least two independent studies. A p value less than .05 was considered statically significant and a significant SMD > 0 indicated that the unilateral PA group had a higher blood level of interest. If there are at least 10 studies, publication bias was evaluated using a funnel plot and the Egger's test, with a $p < .05$ confirming the existence of publication bias.[16]

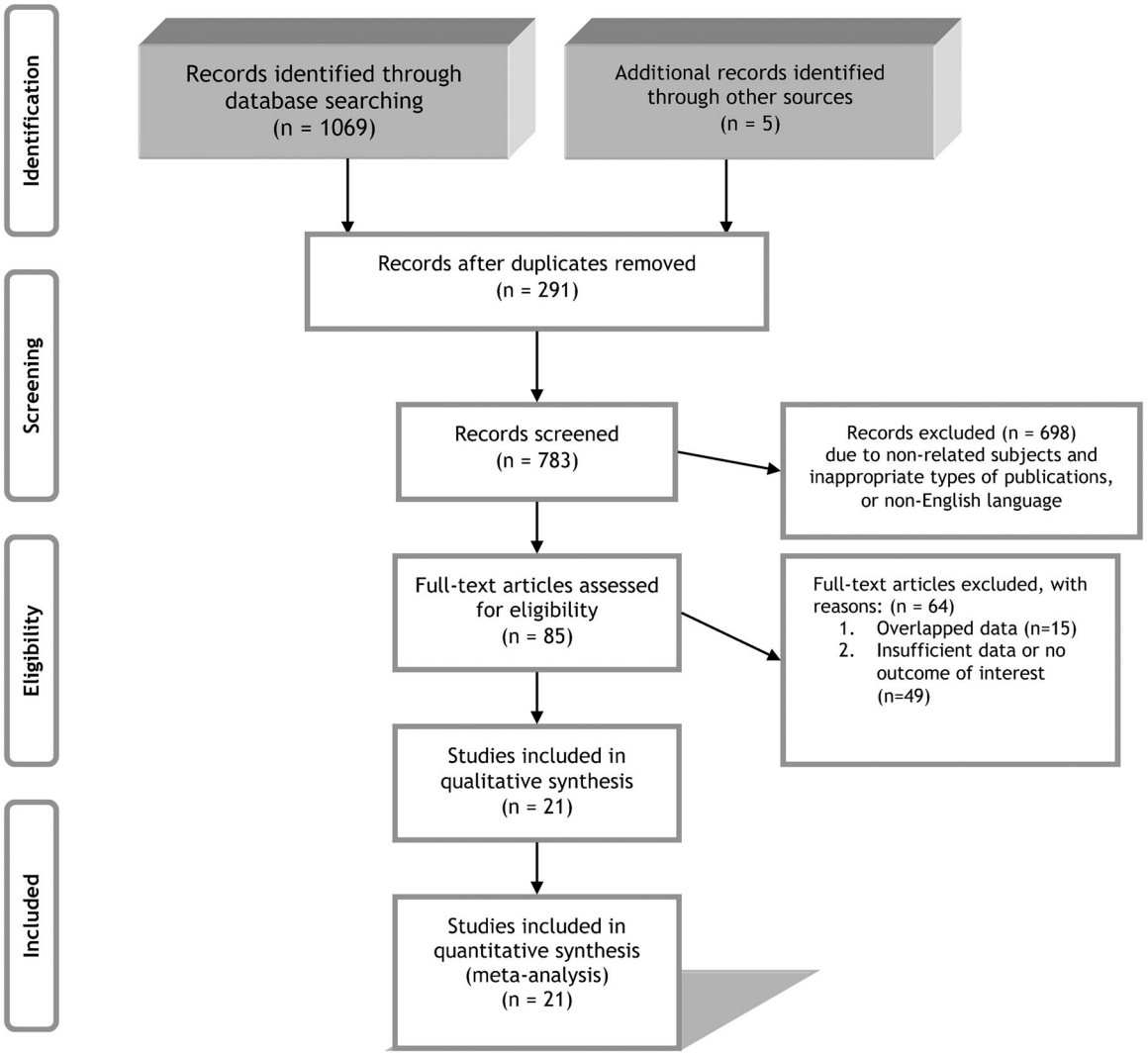

FIGURE 1 A flow chart of study selection

3 | RESULTS

3.1 | Study selection

A total of 1074 potential citations were identified for inclusion via initial searching, 291 of which were subsequently removed due to duplication. The remaining 783 records were screened further in titles and abstracts and 85 candidates were subsequently examined in full text for eligibility. After exclusion of studies using overlapped samples or lacking sufficient data, 21 articles[13,17–36] remained eligible and successfully incorporated into the meta-analysis. A detailed flow chart of study selection is displayed in Figure 1.

3.2 | Basic characteristics and quality evaluation

Twenty-one studies enrolled a total of 4197 PA cases, with 1796 patients classified into unilateral PA (APA accounting for 82.3%) and 2401 subjects diagnosed as bilateral PA (IHA accounting for 78.3%). More than half of the included articles were conducted in Asia regions (13 studies), followed by Europe (eight studies). All the enrolled subjects were reported to receive confirmatory tests to confirm the diagnosis of PA, except for patients in the study of Matrozova et al.[25] For unilateral PA groups, the median/mean age ranged from 46 to 53; for bilateral PA groups, the median/mean age ranged from 47.9 to 60.2. The mean/median BMI of unilateral PA groups (24.2–28.2 kg/m2) was overall lower than that of bilateral PA groups (24.5–30.16 kg/m2). Unilateral PA groups were reported to have significantly higher aldosterone concentration in blood than bilateral PA groups ($p < .05$) in 15 studies, with three studies[20,31,36] reporting no differences (three studies[21–23] no measured). Likewise, 15 studies reported markedly lower serum potassium levels in unilateral PA groups ($p < .05$), with four studies[17,21,26,35] reporting no differences (two studies no measured). More detailed information regarding the included publications is displayed in Table 1.

A majority of the studies had a retrospective cross-sectional design and the rest were case–control or cohort studies.[17,18,21,22,29] Overall, the included studies were considered to have a moderate or low

TABLE 1 Characteristics of included papers

				Unilateral PA				Bilateral PA					
First author	Year	Ethnicity	Design	No.	Age[a]	Fe (%)	BMI[a]	No.	Age[a]	Fe (%)	BMI[a]	Subtype diagnosis	JBI[b]
Adolf[17]	2016	Non-Asian	Pro, MC	142	/	/	27.9	71	/	/	28.7	Imaging + AVS	M
Adolf[18]	2020	Non-Asian	Pro, SC	66	52	36.4%	28.2	82	51	39.0%	27	CT + AVS	M
Berge[19]	2015	Non-Asian	Retro, MC	35	50.2	48.6%[c]	24.9[d]	57	54.9	24.6%	28.4	CT + AVS + pathology + postsurgical outcomes	H
Chen[20]	2015	Asian	Retro, MC	41	46.7	61.0%	/	20	49	60.0%	/	CT + AVS + pathology	M
Giacchetti[21]	2007	Non-Asian	Pro, SC	25	50.5	52.0%[c]	27	36	51.2	33.3%	28.3	CT/MRI ± AVS	M
Huang[22]	2021	Asian	Retro, SC	111	/	/	26.31	63	/	/	25.35	CT, AVS	L
Iacobellis[23]	2016	Non-Asian	Retro, SC	20	50.8	50.0%	28	59	47.9	59.3%	27.9	CT/MRI and/or AVS	L
Kaneko[24]	2021	Asian	Retro, SC	91	53	/	24.5	138	54	/	24.7	AVS	M
Kishimoto[13]	2018	Asian	Retro, SC	53	49	34.0%	25.5	52	53	42.3%	26.3	AVS	L
Matrozova[25]	2009	Non-Asian	Retro, SC	103	46	38.8%	27	150	49	28.7%	28.3	AVS	M
Monticone[26]	2017	Non-Asian	Pro, MC	27	49	55.5%[c]	26.4	64	49	32.8%	27.5	AVS	L
Moon[27]	2021	Asian	Retro, SC	49	51.1	59.2%[c]	25	34	52.8	35.3%	25.4	AVS	L
Ohno[28]	2018	Asian	Retro, MC	516	52	58.5%	24.3[d]	1015	52.9	44.8%	25	AVS	L
Okazaki-Hada[29]	2020	Asian	Retro, SC	28	48.1[e]	42.9%[c]	24.9	88	53.5	67.0%	24.9	AVS	L
Puar[30]	2020	Asian	Retro, MC	70	50[e]	37.1%	26.4	33	60.2	36.4%	26.2	AVS, treatment outcomes	M
Sang[31]	2021	Asian	Retro, SC	22	52.09	54.5%	25.67	14	52	42.9%	25.94	CT + AVS	M
Shibayama[32]	2020	Asian	Retro, SC	33	48.9	51.5%	24.7	56	49.6	66.1%	24.5	AVS	M
Somloova[33]	2010	Non-Asian	Retro, SC	50	49.46	42.0%[c]	27.27[d]	50	50.52	72.0%	30.16	CT ± AVS	H
Watanabe[34]	2021	Asian	Retro, SC	42	51	52.4%	24.2	37	54	56.8%	25.3	AVS	L
Wu[35]	2021	Asian	Retro, SC	187	50	57.2%[c]	24.6	198	51	34.3%	25.5	CT and/or AVS	M
Zhang[36]	2021	Asian	Retro, SC	85	48.79	45.9%	25.57[d]	84	48.44	41.7%	27.55	AVS	L

Fe, female; no, number; pro, prospective; retro, retrospective. AVS, adrenal vein sampling; CT, computed tomography; MC, multi-center; ; SC, single-center.
[a]Values in mean or median.
[b]JBI critical appraisal tools for the observational study were used for quality assessment, where each study was judged as having a high (H), moderate (M), or low (L) risk of bias in overall.
[c]The difference in the proportion of females between the two groups was >15%.
[d]Two groups were significantly different in BMI ($p < .05$), as reported by included studies.
[e]Two groups were significantly different in age ($p < .05$), as reported by included studies.

risk of bias in terms of methodological quality. Distributions of quality assessment for each study are summarized in Table S1.

3.3 | Blood metabolic parameters between PA subtypes

Meta-analyses were done for the following metabolic parameters at baseline: HDL-C (18 studies), LDL-C (17 studies), TC (17 studies), TG (17 studies), FBG (15 studies), HbA1c (10 studies), and HOMA-IR (six studies). Except for the analysis of FBG, pooled results for the aforementioned parameters were shown without including the study of Okazaki-Hada et al.[29] as sensitivity analyses identified it as the potential cause of heterogeneity (omitting it made the I^2 drop below 50% yet did not affect the general outcome). The reason might be that only in this study patients with two subtypes of PA were significantly different from each other regarding age and sex at baseline.

Regarding lipid metabolic parameters (in mmol/L), bilateral PA groups exhibited significantly elevated levels of LDL-C (SMD: −.14, 95% CI: −.20 to −.07, $p < .001$; I^2: 0%; Figure 2B), TC (SMD: −.16, 95% CI: −.23 to −.09, $p < .001$; I^2: 4.1%; Figure 2C), and TG (SMD: −.22, 95% CI: −.29 to −.16, $p < .001$; I^2: 0%; Figure 2D) than unilateral PA groups. Nevertheless, no remarkable differences were noted between two groups as far as the HDL-C level was concerned, despite a general trend of higher HDL-C toward unilateral PA (SMD: .04, 95% CI: −.02 to .11, $p = .19$; I^2: 40.1%; Figure 2A).

With respect to glucose metabolic parameters, bilateral PA groups had significantly higher FBG levels (in mmol/L), as compared to unilateral PA groups (SMD: −.11, 95% CI: −.18 to −.04, $p = .003$; I^2: 8.6%; Figure 3A). Likewise, bilateral PA was significantly higher than unilateral PA in terms of HbA1c (%) (SMD: −.21, 95% CI: −.30 to −.13, $p < .001$; I^2: 0%; Figure 3B) and HOMA-IR (SMD: −.40, 95% CI: −.58 to −.23, $p < .001$; I^2: 0%; Figure 3C). Due to a limited number of studies and high heterogeneity, we narratively reported the results for

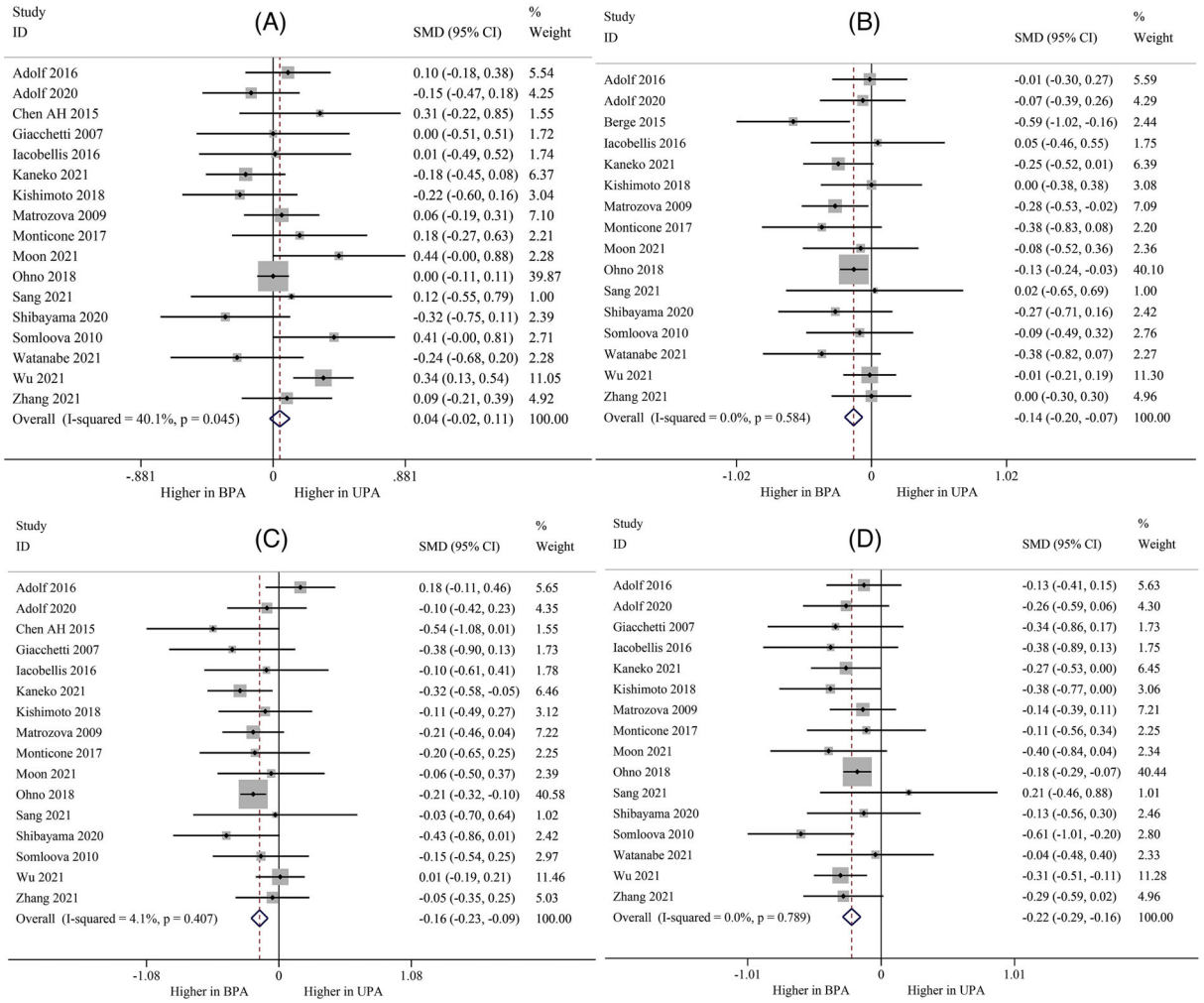

FIGURE 2 Forest plot of (A) HDL-C, (B) LDL-C, (C) TC, and (D) TG. BPA, bilateral primary aldosteronism; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SMD, standardized mean difference; TC, total cholesterol; TG, triglyceride; UPA, unilateral primary aldosteronism

HOMB-β. Three studies showed the HOMB-β index between the two subtypes: 1 study[21] reporting high HOMB-β in unilateral PA, 1 study[22] favoring bilateral PA, and 1 study[29] reporting no difference between groups.

Among the included studies, the study of Ohno et al.[28] contributed data of the largest sample size and removing this study did not significantly change the overall results and heterogeneity, thus supporting the robustness of study (Table 2). Additional subgroup analyses were performed when there were at least two studies in each subgroup and the results are summarized in Table 3. Notably, among non-Asian subjects, there was no significant difference between unilateral and bilateral PA groups pertaining to TC and FBG levels ($p > .05$).

3.4 | Evaluation of publication bias

Funnel's plot and Egger's test were done for analyses containing at least 10 studies. Results revealed that there was no potential publication bias: HDL-C ($p = .81$), LDL-C ($p = .59$), TC ($p = .95$), TG ($p = .46$), and FBG ($p = .61$). Their funnel plots are summarized in Figures S1–S5.

4 | DISCUSSION

To our best knowledge, this is the first meta-analysis to compare blood parameters related to lipid and glucose metabolism, based on 21 original articles involving 1796 patients with unilateral PA and 2401 patients with bilateral PA. In terms of blood lipid profiles, levels of TC, LDL-C, and TG were higher in bilateral PA groups than in unilateral PA groups with statistical significance, but no difference existed between the two subtypes in HDL-C levels. Regarding glucose metabolism, bilateral PA had higher levels of FBG and HbA1c with higher HOMA-IR, compared with unilateral PA. Overall results indicated a possibility that the bilateral subtype of PA might associate with a higher prevalence of lipid and glucose abnormalities relative to the unilateral PA subtype.

Hyperaldosteronism has been considered to promote abnormalities in glucose metabolism in a multifactorial manner. Aldosterone-induced hypokalemia may contribute to impaired insulin secretion and sensitivity.[37–39] Furthermore, aldosterone itself exerts a detrimental effect on β-cell function and results in an impaired insulin release,

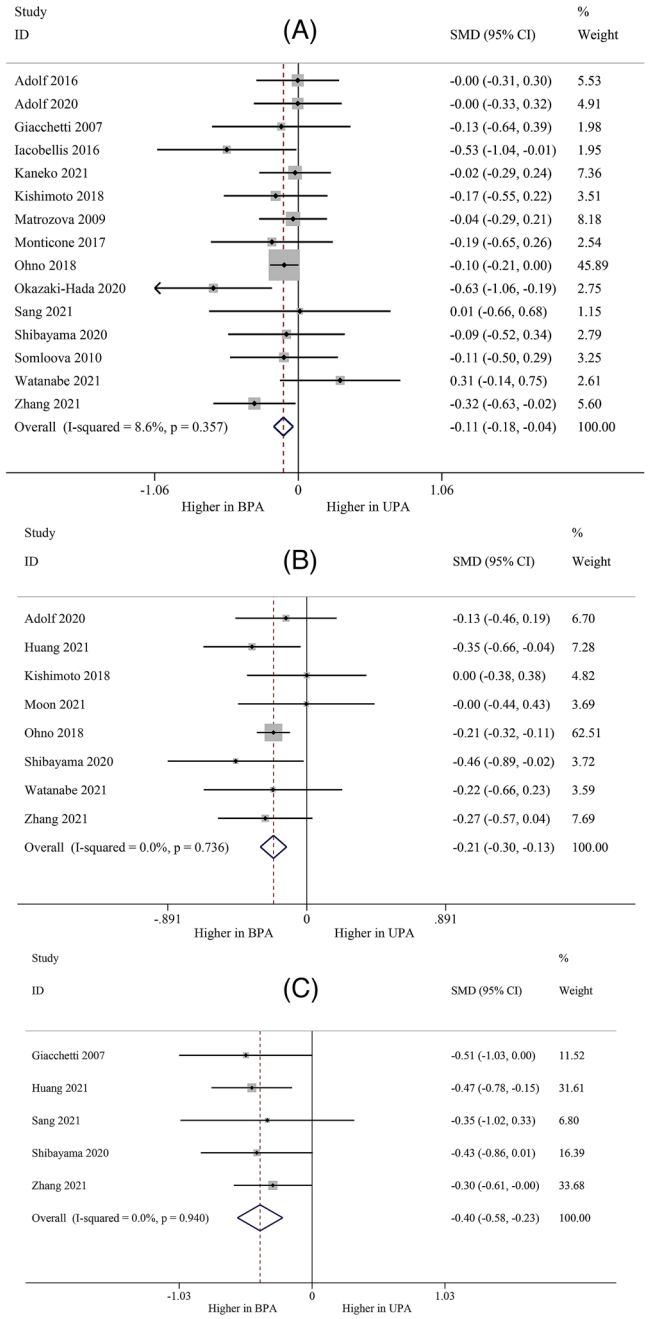

FIGURE 3 Forest plot of (A) FBG, (B) HbA1c, (C) HOMA-IR. BPA, bilateral primary aldosteronism; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment-insulin resistance; SMD, standardized mean difference; UPA, unilateral primary aldosteronism

with clinical data suggesting reduced first-phase insulin reaction, lower HOMA-βF index, and C-peptide levels in PA patients.[40,41] Based on abovementioned mechanisms, unilateral PA, which has been shown to have higher PAC and lower serum potassium level, may theoretically have a worse glucose metabolic status than bilateral PA. Our analysis, however, revealed higher blood glucose levels and insulin resistance in bilateral disease, implying that hypokalemia and aldosterone are not the only contributors to impaired glucose metabolism. The two PA subtypes are different in the pathogenesis and the results suggested the unique metabolic cause of bilateral PA, although the underlying mechanism remains unclear, requiring further investigation. Notably enough, obesity may serve as a key factor underlying bilateral PA, which has been shown to cause hyperaldosteronism through the action of adipocytokines and activation of sympathetic nervous system.[28]

Likewise, there remains a lack of evidence that aldosterone is directly involved in the lipid metabolism and conflicting results have also been observed in a few studies analyzing lipid profiles according to the type of PA.[24,25,27,33] Our analysis showed that blood lipid levels (LDL-C, TC, and TG) were markedly higher in bilateral PA despite less active PA profiles (higher PAC and lower potassium level), implying that additional mechanism such as the unique etiology of bilateral disease, other than aldosterone excess, may involve in lipid metabolism in PA and warrants further investigation.

Of note, we found that ethnicity might affect the overall results based on subgroup analyses. No differences existed between the two subtypes in terms of TC and FBG levels among non-Asian patients with PA. We supposed the different lifestyles play an important part. In addition, KCNJ5 mutation, prevalent in APA patients of Asian ethnicity,[42] might matter. According to Chen et al.,[42] IHA patients exhibited significantly higher TG levels than APA patients with KCNJ5 mutations but showed no difference compared with those without KCNJ5 mutations, which is in accordance with our results. Given the relatively small number of studies included in each subgroup, additional research should be conducted to validate it.

Results should be interpreted with the consideration of two significant factors, which may pave the way for future studies. Firstly, the effects of drugs potentially affecting the glucose and lipid profiles, including antihypertensive drugs as well as glucose- and lipid-lowering agents, cannot be ignored. PA serves as a frequent cause of hypertension. Antihypertensive medications that interfere with the renin–angiotensin–aldosterone system were discontinued for at least 2 weeks before PA diagnosis. However, in several included studies, calcium channel blockers or alpha-adrenergic blockers were allowed as appropriate. Calcium channel blockers are considered metabolically neutral, while alpha-adrenergic blockers may exert beneficial effects on lipids and glucose, including reduced TC, TG, LDL-C, and FBG.[43] According to Somloova et al.,[33] no significant differences existed between two subtypes in the prevalence of DM, blood glucose level, and the use of antidiabetic therapy; more patients having abnormal lipid profiles and using lipid-lowering drugs were noted in IHA group rather than in APA group. Whether or not glucose- and lipid-lowering agents might impact the glucose and lipid profiles of PA patients remains unknown. No safe conclusion can be drawn from the present analysis, as most of our included papers failed to eliminate the effect of these concomitant drugs during selection process (e.g., excluding patients using these agents) or they did not provide detailed information in their papers. Besides, inconsistent AVS methods and criteria for PA subtyping should be noted. AVS remains the gold standard for differentiation of unilateral from bilateral adrenal disease in patients with PA. A majority of includes studies adopted AVS with or without adrenocorticotropic hormone (ACTH) stimulation, leading to different

TABLE 2 Overall results after removing the study with the largest sample size

Parameters	Study (n.)	SMD (95% CI)	*p*	I^2 (%)
HDL-C (mmol/L)	17	.04 (−.02, .11)	.19	40.1
Excluding Ohno et al.	16	.07 (−.01, .16)	.09	41.4
LDL-C (mmol/L)	16	−.14 (−.20, −.07)	<**.001**	0
Excluding Ohno et al.	15	−.14 (−.22, −.05)	**.0021**	0
TC (mmol/L)	16	−.16 (−.23, −.09)	<**.001**	8.5
Excluding Ohno et al.	15	−.12 (−.21, −.03)	**.006**	.6
TG (mmol/L)	16	−.22 (−.29, −.15)	<**.001**	0
Excluding Ohno et al.	15	−.25 (−.34, −.16)	<**.001**	0
FPG (mmol/L)	15	−.11 (−.18, −.04)	**.003**	8.6
Excluding Ohno et al.	14	−.11 (−.21, −.02)	**.022**	15
HbA1c (mmol/L)	9	−.21 (−.30, −.13)	<**.001**	0
Excluding Ohno et al.	8	−.20 (−.34, −.07)	**.003**	0

Note: A significant SMD > 0 indicated that the unilateral PA group had a higher blood level. CI, confidence interval; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PA, primary aldosteronism; SMD, standardized mean differences; TC, total cholesterol; TG, triglyceride.

TABLE 3 Results of subgroup analysis

Parameters	Study (n.)	SMD	95% CI	*p*	I^2 (%)
HDL-C (mmol/L)	17	.04			
Asian	10	.03	−.04, .11	.37	58.6
Non-Asian	7	.07	−.06, .20	.28	0
APA vs. IHA[a]	12	.06	−.02, .14	.14	42.9
LDL-C (mmol/L)					
Asian	9	−.12	−.20, −.04	**.003**	0
Non-Asian	7	−.18	−.31, −.05	**.007**	20.7
APA vs. IHA[a]	11	−.13	−.20, −.05	**.001**	2.7
TC (mmol/L)					
Asian	9	−.18	−.26, −.10	<**.001**	11.4
Non-Asian	7	−.1	−.24, .03	.13	0
APA vs. IHA[a]	10	−.15	−.23, −.07	<**.001**	24.8
TG (mmol/L)					
Asian	9	−.22	−.30, −.14	<**.001**	0
Non-Asian	7	−.24	−.37, −.10	<**.001**	0
APA vs. IHA[a]	10	−.21	−.30, −.14	<**.001**	0
FBG (mmol/L)					
Asian	8	−.12	−.20, −.03	**.006**	38.7
Non-Asian	7	−.09	−.22, .05	.21	0
APA vs. IHA[a]	11	−.12	−.20, −.03	**.006**	18.4
HbA1c (%)					
APA vs. IHA[a]	6	−.22	−.31, −.13	<**.001**	0

Note: A significant SMD > 0 indicated that the unilateral PA group had a higher blood level. APA, aldosterone-producing adenoma; CI, confidence interval; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IHA, idiopathic hyperaldosteronism; LDL-C, low-density lipoprotein cholesterol; PA, primary aldosteronism; SMD, standardized mean differences; TC, total cholesterol; TG, triglyceride.

[a]Only including studies focusing on the comparison between APA and IHA.

criteria for determining lateralization[1]; moreover, whether AVS with ACTH stimulation is more effective than AVS without ACTH stimulation remains controversial. Therefore, this is a potential founder that needs to be considered when interpreting the results.

Subtype diagnosis is crucial for the therapeutic management of PA. Given that AVS is limited by its invasiveness and technical difficulty, prediction models using easy-to-obtain clinical and biochemical data are increasingly developed. Therefore, there is a strength of this meta-analysis, of which results showed that these blood lipid and glucose parameters might be useful for subtype diagnosis in patients with PA, demonstrating their potential for being included in the prediction models in the future.

Some limitations in this meta-analysis need to be noted. A majority of the included papers processed a retrospective cross-sectional design, possibly resulting in selection bias. Likewise, all the outcome data used in the analysis were acquired from baseline characteristics and some potential confounders such as sex, age, BMI, and duration of hypertension were not matched between the two groups prior to the analysis in some included studies. The present analysis conducted a univariate comparison with not well-adjusted effect sizes based on several parameters that did not always correctly reflect the glucose and lipid profiles. Furthermore, there were discrepancies in the criteria for subtype diagnosis and laboratory methods for measuring these blood parameters as they were conducted in various centers, which might correlate with the heterogeneity among studies. Despite 21 included papers, our study was limited by the number of the included studies for some parameters, mainly due to quite a few potential studies using overlapped samples, and meanwhile, we did not have sufficient data to meta-analyze several metabolic parameters such as HOMA-β. Thus, more prospective, well-designed trials comparing metabolic profiles between the two subtypes of PA are needed to further verify our results and investigate the underlying mechanisms of metabolic abnormalities in each PA subtype with different etiologies.

5 | CONCLUSIONS

To conclude, this study compared the blood parameters related to lipid and glucose parameters between the two subtypes of PA using a meta-analysis. Overall results suggested that bilateral PA may be associated with a higher prevalence of impaired glucose as well as lipid metabolism than unilateral PA, possibly due to distinct pathophysiology of the different PA subtypes. Results should be treated with caution, and drug effects and the differences in the methods of subtype diagnosis should be taken into consideration. Additional well-designed studies are needed to prove the present results and better investigate the link between metabolic abnormalities and the etiology of each PA subtype.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

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SUPPORTING INFORMATION

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