Systematic Review and Meta-Analysis

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Cardiovascular risk in primary aldosteronism

A systematic review and meta-analysis

Xueyi Wu, MS[a,b], Jie Yu, MD[c], Haoming Tian, MS[a,*]

Abstract

Aim: This study aimed to evaluate whether the increased cardiovascular risk and the incidence of cerebrovascular (CCV) events in hypertensive patients were related to primary aldosteronism (PA).

Methods: The PubMed, EmBase, and the Cochrane Central Register of Controlled Trials were searched to evaluate the risk of CCV in PA patients and compared to essential hypertension (EH) patients. The mean differences (MD) and the risk ratios (RR) were calculated to assess the risk of main outcomes, such as stroke, coronary artery disease, left ventricular hypertrophy (LVH), levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, and urinary potassium.

Results: We identified 31 individual studies including 4546 patients in PA group and 52,284 patients in EH group. Our results revealed that PA was significantly associated with increased risk of stroke (RR=2.03, 95% CI=1.71–2.39, $P_{heterogeneity}=.331$, $I^2=12.7\%$), coronary artery disease (RR=1.67, 95% CI=1.23–2.25, $P_{heterogeneity}=.043$, $I^2=48.3\%$), and LVH (RR=1.54, 95% CI=1.29–1.83, $P_{heterogeneity}=.004$, $I^2=62.6\%$) when compared with those in the EH group. Moreover, PA group had significantly increased levels of SBP (WMD=4.14, 95% CI=2.60–5.68, $P_{heterogeneity}<.001$, $I^2=84.3\%$), DBP (WMD=2.65, 95% CI=1.83–3.47, $P_{heterogeneity}<.001$, $I^2=77.7\%$), and urinary potassium (SMD=0.04, 95% CI=-0.03–0.11, $P_{heterogeneity}=.827$, $I^2=0\%$) when compared to EH group. However, no significant difference was observed in the levels of blood glucose between the groups.

Conclusions: These findings suggested that PA significantly increased the risk of cardiac and cerebrovascular complications. In addition, patients with PA might benefit from a periodic assessment of CCV risk.

Abbreviations: APA = aldosterone-producing adenoma, CCV = cardiac and cerebrovascular, DBP = diastolic blood pressure, EH = essential hypertension, IHA = idiopathic (bilateral) hyperaldosteronism, LVH = left ventricular hypertrophy, MD = mean differences, MRA = mineralocorticoid receptor-antagonist, NOS = Newcastle–Ottawa Scale, PA = primary aldosteronism, RR = risk ratios, SBP = systolic blood pressure.

Keywords: cardiovascular risk, cerebrovascular events, meta-analysis, primary aldosteronism, systemic review

1. Introduction

Primary aldosteronism (PA) is one of the most common causes of curable arterial hypertension, accounting for approximately 7% to 10% in hypertensive patients and up to 20% in patients with resistant hypertension.[1,2] PA is caused by excessive aldosterone and is considered as one of the most common forms of secondary hypertension.[3] The main forms of PA include idiopathic (bilateral) hyperaldosteronism (IHA) and unilateral aldosterone-producing adenoma (APA). In addition, the other forms of PA are rare, and included unilateral adrenal hyperplasia and familial aldosteronism types I, II, and III.

Over the past 20 years, numerous studies have revealed the harmful effects of aldosterone on the cardiovascular system.[4] These studies have demonstrated that aldosterone independently effected the blood pressure levels, leading to increased cardiovascular damage, including left ventricular hypertrophy, fibrosis, vascular remodeling and arterial stiffening, in different animal models and humans.[5] Milliez et al in 2005[6] showed that the prevalence of stroke was high in 124 patients with PA when compared to 456 matched essential hypertension (EH) patients. Catena et al[7] compared 54 PA patients with 323 EH patients in a 7-year follow-up study. The results showed that PA patients demonstrated higher prevalence of stroke when compared to EH patients. Nevertheless, the results were inconsistent with other studies.[8,9] Hence, we conducted this systematic review and meta-analysis to assess the association between PA and cardiac and cerebrovascular adverse events, and the association of PA and EH with the incidence of cardiovascular events.

2. Materials and methods

All analyses were conducted based on previously published studies, and so no ethical approval and patient consent are required.

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XW and JY contributed equally to this study, co-first author.

The authors have no conflicts of interest to disclose.

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The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[10] in order to evaluate the association of the increased risk of cardiovascular events and the incidence of cardiovascular events in patients affected by PA.

2.1. Search strategy

The PubMed, EmBase, and the Cochrane Central Register of Controlled Trials online databases were searched from inception till June 1, 2018. The following terms and their combinations were used for searching the articles: "primary aldosteronism" and "hyperaldosteronism" and "left ventricular hypertrophy," "stroke," "coronary artery disease," "left ventricular mass index," "systolic blood pressure," "diastolic blood pressure," "blood glucose," and "urinary potassium." The retrieved abstracts, reports, and citations were evaluated for relevance. In addition, the reference lists of the obtained articles were manually searched to find any eligible studies.

2.2. Selection criteria

The inclusion criteria of the literature were as follows: adult patients with PA; comparison of PA patients and EH patients; and primary outcomes included the incidence of stroke, coronary artery disease, left ventricular hypertrophy, blood pressure, blood glucose and urinary potassium change. The exclusion criteria were as follows: studies on animal models; and literature types such as abstracts, letters, reviews, and meta-analysis. Additionally, if more than 1 article was published with the same case series, the study with the largest sample size was selected.

2.3. Data extraction and quality assessment

Two investigators independently extracted relevant data, and any disagreements between them were resolved by reaching a consensus. For each study, the following information was collected: the name of the first author, publication year, country, sample size, mean age, group, study type, and primary assessed outcomes. A 9-star system by Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies. Among these studies, high-quality was defined as a study with ≥7 stars.[11]

2.4. Statistical analysis

The mean differences (MD) for continuous data, and the risk ratios (RR) for dichotomous data were determined to assess the

Table 1

Characteristics of studies included in this meta-analysis.

Authors/year of publication	Country	Sample size	Mean age, years (PA, EH)	Group		Type of study	Outcomes assessed
				PA	EH		
Takeda/1995	Japan	448	49	224	224	Retrospective	Stroke, coronary artery disease, SBP, DBP
Tanabe/1997	Japan	67	42, 47	20	47	NA	SBP, DBP
Rizzoni/1998	Italy	32	52, 55	14	18	NA	SBP, DBP,LVH
Widimsky/2001	Czech	57	52, 53	36	21	NA	SBP, DBP
Goldkorn/2002	USA	70	52, 52	35	35	NA	SBP, DBP
Muiesan/2002	Italy	37	48, 57	12	25	Retrospective	SBP, DBP, blood glucose,LVH
Kozakova/2003	Italy	35	47,51	14	21	NA	SBP, DBP
Milliez/2005	France	589	52	124	465	Retrospective	Stroke, coronary artery disease,SBP, DBP, blood glucose, urinary potassium,LVH
Fallo/2006	Italy	466	55,53	85	381	Retrospective	SBP, DBP, blood glucose,LVH
Matsumura/2006	Japan	54	47,53	25	29	NA	SBP, DBP,LVH
Maule/2006	Italy	144	51,47	27	117	Prospective	SBP, DBP
Catena/2007	Italy	328	53	54	274	Prospective	SBP, DBP, blood glucose, urinary potassium
Catena/2008	Italy	377	53,52	54	323	Prospective	Stroke, coronary artery disease
Muiesan/2008	Italy	250	50,51	125	125	Retrospective	SBP, DBP,LVH
Matrozova/2009	France	1823	51,52	460	1363	Retrospective	SBP, DBP
Omlov/2010	Czech	190	50	100	90	Retrospective	SBP, DBP, blood glucose
Reincke/2010	Germany	1535	55,66	638	897	Retrospective	SBP, DBP
Pimenta/2011	Australia	42	56	21	21	NA	SBP, DBP
Indra/2012	Czech	88	55,51	44	44	NA	SBP, DBP
Reincke/2012	Germany	900	50	300	600	Retrospective	Coronary artery disease, SBP, DBP
Fischer/2013	Germany	33	52,57	22	11	Prospective	SBP, DBP
Hung/2013	China	84	51	53	31	Prospective	SBP, DBP,LVH
Mulatero/2013	Italy	1080	44	270	810	Retrospective	Stroke, coronary artery disease,SBP, DBP, blood glucose
Rossi/2013	Italy	323	51,52	180	143	Retrospective	SBP, DBP,LVH
Savard/2013	France	1749	51	459	1290	Retrospective	Coronary artery disease, SBP, DBP, blood glucose,LVH
Curione/2014	Italy	61	55,54	30	31	Prospective	SBP, DBP
Iacobellis/2016	Italy	50	51,52	20	30	Prospective	SBP, DBP
Monticone/2017	Italy	1672	49,46	99	1573	Prospective	Stroke, coronary artery disease,SBP, DBP,LVH
Murata/2017	Japan	790	63,62	292	498	Retrospective	Stroke, coronary artery disease,SBP, DBP
Hundemer/2018	USA	42455	58,57	602	41853	Retrospective	Stroke, coronary artery disease,SBP, DBP
Rossi/2018	Italy	1001	50,46	107	894	Prospective	Stroke, coronary artery disease,SBP, DBP

DBP = diastolic blood pressure, EH = essential hypertension, LVH = left ventricular hypertrophy, PA = primary aldosteronism, SBP = systolic blood pressure, USA = United States of America.

risk of the main outcomes, such as stroke, coronary artery disease, left ventricular hypertrophy (LVH), systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, and urinary potassium. If the P value for heterogeneity was $>.1$ and $I^2>50\%$, then no heterogeneity was found among these studies, and used a fixed-effects model (the Mantel–Haenszel method). Conversely, if either the P value for heterogeneity was $<.1$ or I^2 was $<50\%$, then a more appropriate random-effects model (the DerSimonian and Laird method) was used to indicate heterogeneity among the studies. In addition, sensitivity analyses were performed to evaluate the stability of the results. Besides, funnel plots and Egger linear regression test were used to diagnose for any potential publication bias, and $P>.05$ was used to indicate a possible publication bias. All analyses were performed using Stata software and P values were based on 2-sided tests.

3. Results

3.1. Features of the included reports

The initial search yielded a total of 602 studies (598 from database search and 4 by manual retrieval). Of these, 110 were excluded due to duplications. Subsequently, 426 irrelevant studies were excluded after screening the abstracts, and 20 studies were excluded due to different publication types (letters, reviews, or meta-analysis). After reading the full texts, 15 articles were deemed unsuitable and therefore excluded. Following these exclusions, 31 individual studies with a total of 4546 patients in PA group and 52,284 patients in EH group were found suitable for inclusion in our meta-analysis. The detailed literature search process was listed in Table 1 and Figure 1. These studies were published between 1995 and 2018, and all the 31 included studies were conducted in different countries of Italy,[7–9,12–22]

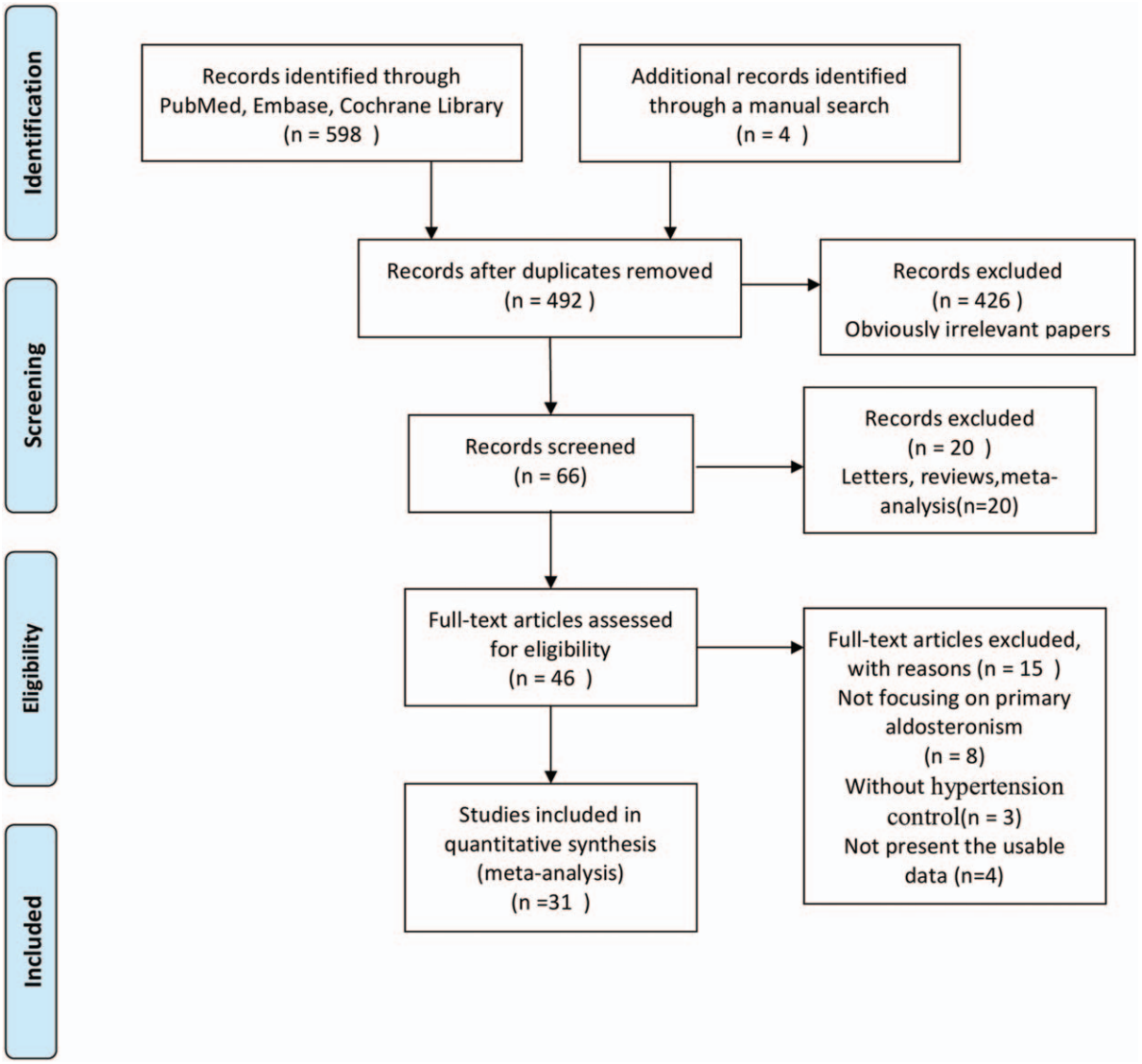

Figure 1. Flow diagram of identification of studies.

Japan,[23–26] Czech,[27–29] France,[6,30,31] Germany,[32–34] USA,[35,36] Australia,[37] and China[38] (Table 1). The quality of the studies included in this meta-analysis was generally high, where 11 studies had 8 stars, and 20 studies had 7 stars (Table 2).

3.2. Quantitative synthesis

Stroke: Eight studies explored the association of risk of stroke with PA. Pooled analysis was performed with the available data on the correlation. The results showed a significantly increased risk of stroke by comparing the PA group with the EH group (RR = 2.03, 95% CI = 1.71–2.39, $P_{\text{heterogeneity}} = .331$, $I^2 = 12.7\%$) (Fig. 2A).

Coronary artery disease: A total of 10 studies explored the risk of coronary artery disease. Pooled analysis was performed with the available data on the correlation between PA and the risk of coronary artery disease. Results showed a significantly increased risk of coronary artery disease by comparing the PA group with the EH group (RR = 1.67, 95% CI = 1.23–2.25, $P_{\text{heterogeneity}} = .043$, $I^2 = 48.3\%$) (Fig. 2B).

Left ventricular hypertrophy (LVH): Ten studies discussed the risk of LVH. Pooled analysis was performed with the available data regarding the relationship between PA and LVH. The results revealed a significantly increased risk of LVH when both PA and EH groups were compared (RR = 1.54, 95% CI = 1.29–1.83, $P_{\text{heterogeneity}} = .004$, $I^2 = 62.6\%$) (Fig. 2C).

Systolic blood pressure (SBP): Pooled analysis was performed with the available data on the correlation between PA and the SBP in 30 studies to explore the risk of SBP. Compared with the EH group, a significantly higher SBP was found in the PA group (WMD = 4.14, 95% CI = 2.60–5.68, $P_{\text{heterogeneity}} < .001$, $I^2 = 84.3\%$) (Fig. 3A).

Diastolic blood pressure (SBP): Pooled analysis of 30 studies was performed to assess the correlation between PA and the DBP was performed. The results showed a significantly higher DBP in the PA group when compared with the EH group (WMD = 2.65, 95% CI = 1.83–3.47, $P_{\text{heterogeneity}} < .001$, $I^2 = 77.7\%$) (Fig. 3B).

Blood glucose: Pooled analysis of 8 studies regarding the association of blood glucose levels and PA was performed with the available data. The pooled results showed no significant differences in the levels of blood glucose between the 2 groups (SMD = 0.04, 95% CI = −0.03–0.11, $P_{\text{heterogeneity}} = .827$, $I^2 = 0\%$) (Fig. 3C).

Urinary potassium: Pooled analysis was performed with the available data on the correlation between PA and urinary potassium. The pooled results showed a significantly higher urinary potassium levels in the PA group when compared with

Table 2

Methodological quality of observational studies included in the meta-analysis*.

First author	Representativeness of the cases	Selection of the controls	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Same method of ascertainment for cases and controls	Same nonresponse for both groups	Total quality scores
Takeda/1995	☆	☆	☆	☆	☆	☆	☆	—	7
Tanabe/1997	☆	☆	☆	☆	☆	☆	☆	—	7
Rizzoni/1998	☆	☆	☆	☆	☆	☆	☆	—	7
Widimsky/2001	☆	☆	☆	☆	☆	☆	☆	—	7
Goldkorn/2002	☆	☆	☆	☆	☆	☆	☆	—	7
Muiesan/2002	☆	☆	☆	☆	☆	☆	☆	—	7
Kozakova/2003	☆	☆	☆	☆	☆	☆	☆	—	7
Milliez/2005	☆	☆	☆	☆	☆	☆	☆	—	7
Fallo/2006	☆	☆	☆	☆	☆	☆	☆	—	7
Matsumura/2006	☆	☆	☆	☆	☆	☆	☆	—	7
Maule/2006	☆	☆	☆	☆	☆	☆	☆	☆	8
Catena/2007	☆	☆	☆	☆	☆	☆	☆	☆	8
Catena/2008	☆	☆	☆	☆	☆	☆	☆	☆	8
Muiesan/2008	☆	☆	☆	☆	☆	☆	☆	—	7
Matrozova/2009	☆	☆	☆	☆	☆	☆	☆	☆	8
Omlov/2010	☆	☆	☆	☆	☆	☆	☆	☆	8
Reincke/2010	☆	☆	☆	☆	☆	☆	☆	☆	8
Pimenta/2011	☆	☆	☆	☆	☆	☆	☆	—	7
Indra/2012	☆	☆	☆	☆	☆	☆	☆	—	7
Reincke/2012	☆	☆	☆	☆	☆	☆	☆	—	7
Fischer/2013	☆	☆	☆	☆	☆	☆	☆	☆	8
Hung/2013	☆	☆	☆	☆	☆	☆	☆	☆	8
Mulatero/2013	☆	☆	☆	☆	☆	☆	☆	—	7
Rossi/2013	☆	☆	☆	☆	☆	☆	☆	☆	8
Savard/2013	☆	☆	☆	☆	☆	☆	☆	—	7
Curione/2014	☆	☆	☆	☆	☆	☆	☆	—	7
Iacobellis/2016	☆	☆	☆	☆	☆	☆	☆	—	7
Monticone/2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Murata/2017	☆	☆	☆	☆	☆	☆	☆	—	7
Hundemer/2018	☆	☆	☆	☆	☆	☆	☆	☆	8
Rossi/2018	☆	☆	☆	☆	☆	☆	☆	—	7

* A study could be awarded a maximum of 1 star for each item except for the item Control for important factor or additional factor.

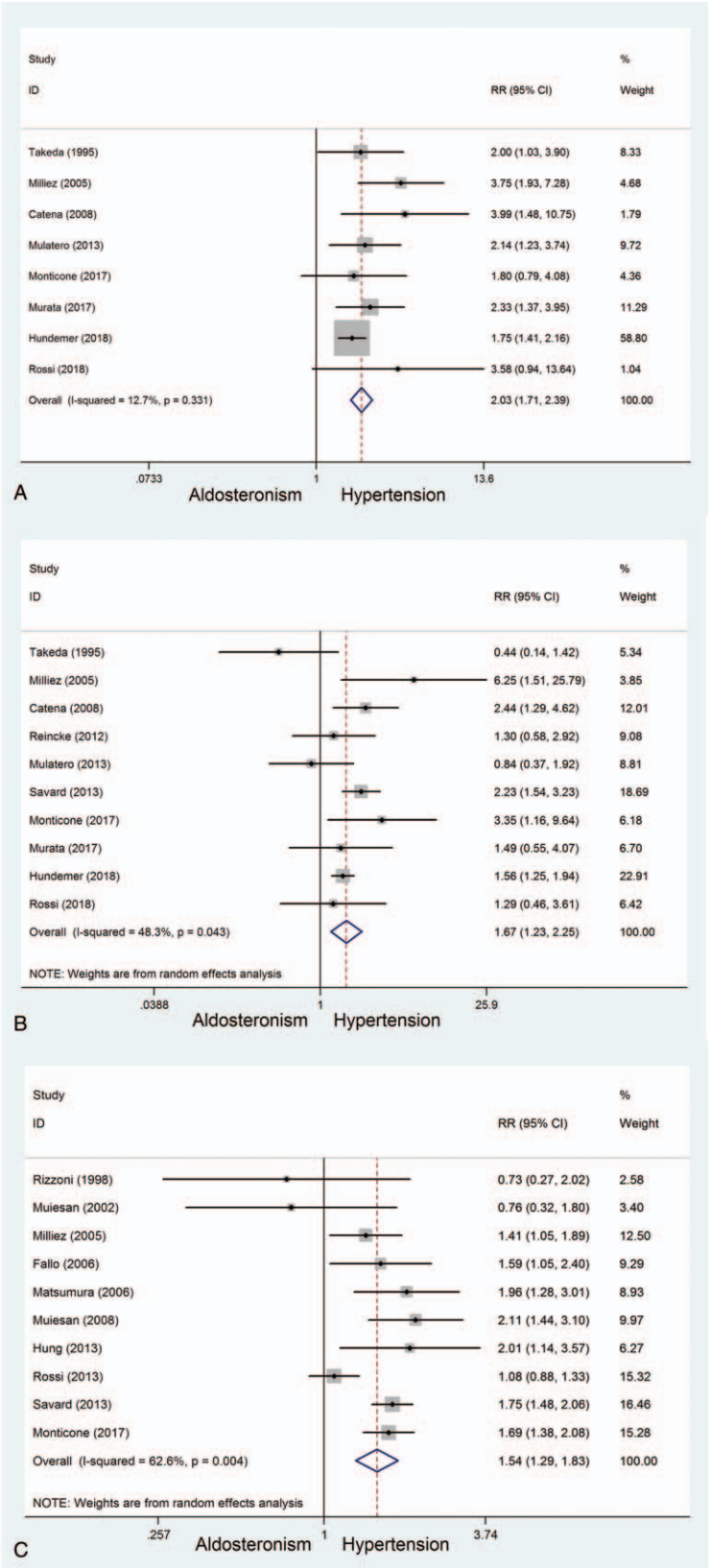

Figure 2. Forest plots showing the risk of cardiovascular and cerebrovascular complications in patients with primary aldosteronism. A, Stroke. B, Coronary artery disease. C, Left ventricular hypertrophy.

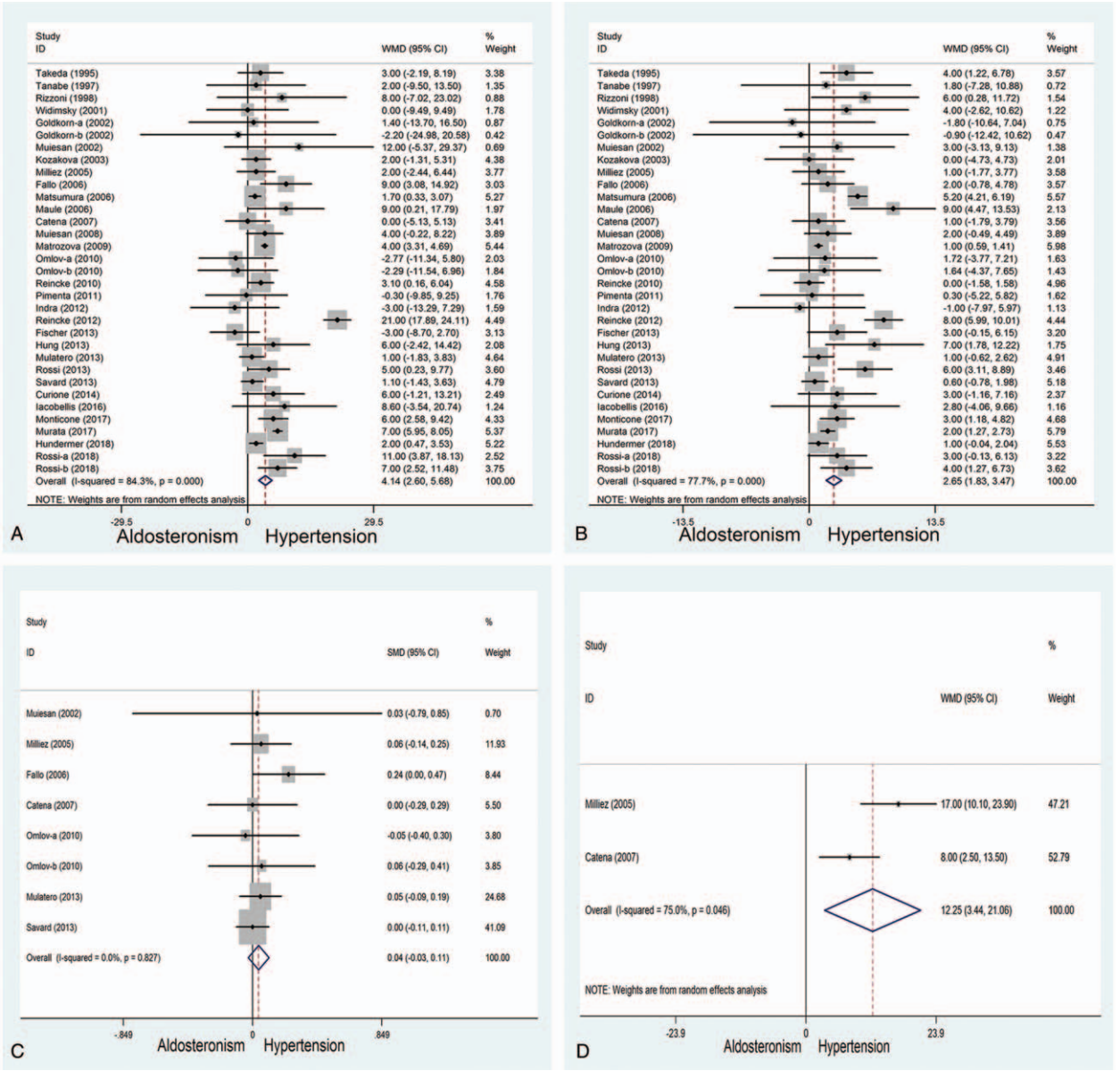

Figure 3. Forest plots showing clinical outcome in patients with primary aldosteronism versus essential hypertension. A, SBP. B, DBP. C, Blood glucose. D, Urinary potassium.

the EH group (WMD = 12.25, 95% CI = 3.44–21.06, $P_{\text{heterogeneity}}$ = .046, I^2 = 75%) (Fig. 3D).

3.3. Sensitivity analysis

Sensitivity analysis was conducted by excluding 1 study at a time to gauge the stability of the results. As shown in Figure 4, the corresponding pooled results showed no significant changes, regardless of which study was deleted, suggesting that the obtained results were robust.

3.4. Publication bias

In this meta-analysis, publication bias was tested using Begg test and Egger test. The Begg test and Egger test for SBP (Begg test P = .198; Egger test P = .887, Fig. 5A) and DBP (Begg test P = .988; Egger test P = .078, Fig. 5B) showed no publication bias.

4. Discussion

The prevalence of PA differs significantly among various hypertensive patients due to differences in patient's selection, the diagnostic methods used, and the severity of hypertension. According to some cross-sectional and prospective studies in patients with no selected hypertension, the prevalence of PA was much higher than previously reported, and that the range of diagnostic trials varied significantly from 4.6 to16.6%.[39] The current meta-analysis demonstrated that PA was associated with significantly increased risk of stroke, coronary artery disease, and LVH when compared with EH group. Moreover, PA resulted in significantly higher levels of SBP, DBP, and urinary potassium. However, no significant differences were found in the levels of blood glucose between the groups.

The risk of cardiovascular complications in patients with PA has been investigated in previous meta-analysis studies. Recently,

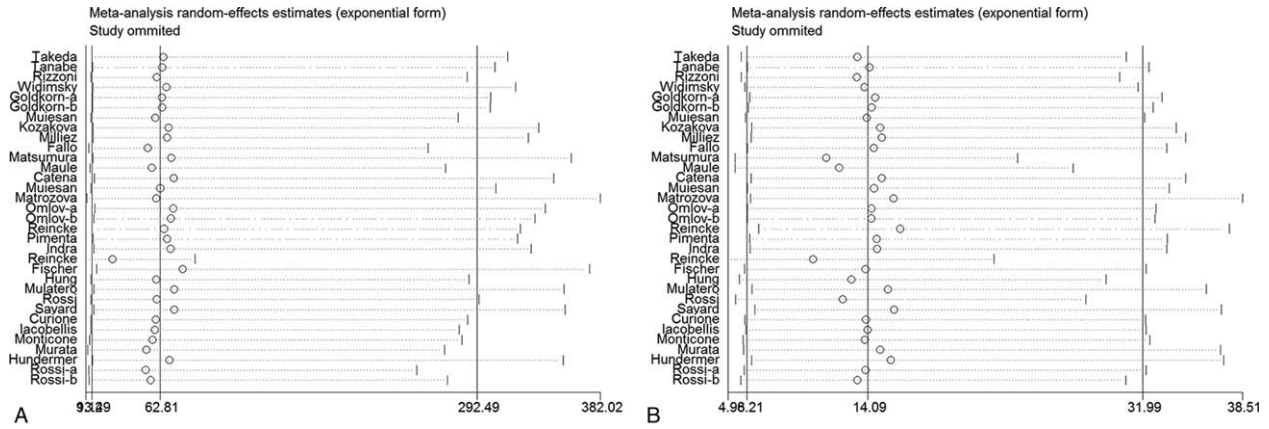

Figure 4. Sensitivity analysis of clinical outcomes in patients with primary aldosteronism versus essential hypertension. A, SBP. B, DBP.

Monticone et al[40] conducted a systematic review and meta-analysis to assess the association between PA and the cardiac and cerebrovascular adverse events. The results demonstrated that PA increased the risk of stroke and coronary artery disease, and the results were in line with the results of our study. Moreover, our study also found that PA resulted in significantly higher SBP, DBP, and urinary potassium levels, while Monticone et al study did not evaluate these. In the current study, heterogeneity was demonstrated and the random-effects model was employed for analysis. Therefore, the estimated pooled results showed no significant changes in sensitivity analysis, enhancing the reliability of our results in the present study.

In general, our results clearly demonstrated increased risk of cardiac and cerebrovascular (CCV) complications in patients with PA, and suggested the need for strict monitoring of CCV risk factors and early signs of CCV in this clinical setting. As a result, compared with EH patients, an increased risk of major CCV events and CCV deaths were observed in PA patients.[7,41] The German Conn's Registry recently reported that the leading cause of death in patients with PA was due to CCV events (50% versus 34% in EH). More and more evidences have shown that long-term exposure to high aldosterone levels induced harmful effects, such as mechanisms other than sodium water retention and the effect of hypertension on the CCV system.[42] Excessive aldosterone could cause arterial wall fibrosis and thickening, and adversely affecting the endothelial function by enhancing the oxidative stress and inflammation.[43] It was suggested that aldosterone could induce hypertrophy of vascular smooth muscle cells or hyperplasia with adventitial cell migration.[44] In addition, excess aldosterone was associated with cardiac hypertrophy.[45] The changes associated with the levels of aldosterone led to vascular remodeling, with increased left ventricular mass and increased intima-media thickness.[46] Aldosterone also induced the changes in the extracellular matrix, leading to collagen deposition, followed by arteriosclerosis and myocardial fibrosis.[47] Visual field defects and papilledema are the common complications reported in PA patients.[48] The role of aldosterone in the changes of vascular collagen accumulation further confirmed that aldosterone antagonist spironolactone could prevent aortic fibrosis in animal models.[49] In PA, the excess secretion of aldosterone and activation of MNR led to an enhancement in the function of epithelial sodium channel and the expression of basolateral sodium–potassium pump, resulting in the retention of sodium ions and water and the secretion of potassium ions and protons into the urine.[50] Therefore, pooled results showed a significantly higher urinary potassium levels in PA group.

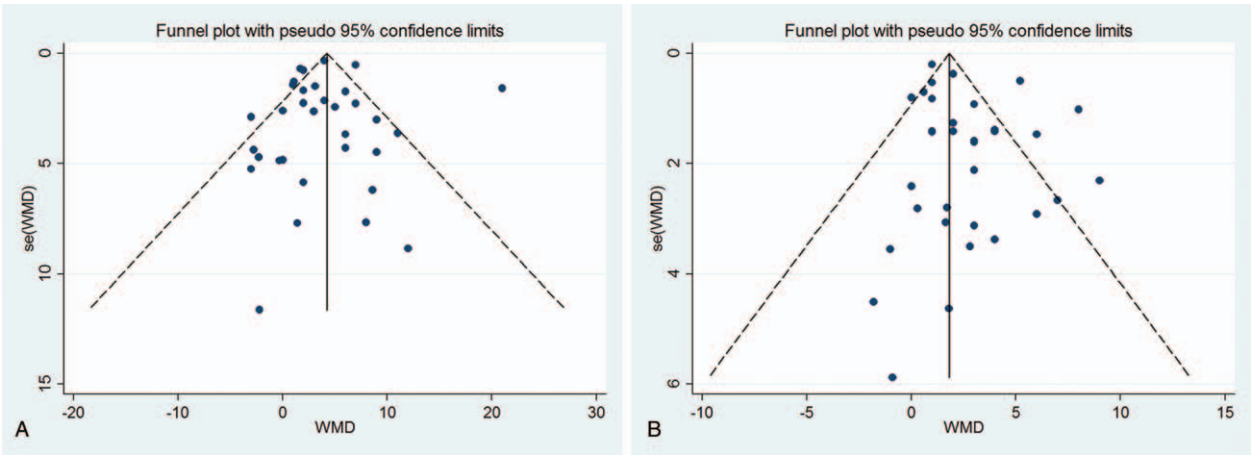

Figure 5. Begg funnel plot for publication bias test. Each point represents a separate study for the indicated association. A, SBP. B, DBP.

In interpreting the results, some of the limitations of this meta-analysis should be noted. First, the heterogeneity between studies was usually significant. Although it was not possible to determine the origin of heterogeneity, all the results are confirmed by sensitivity analysis. The second potential limitation was that the number of studies used to analyze few parameters was small and the statistical power was reduced. Third, the presence of other clinical conditions might affect the levels of aldosterone (i.e., chronic kidney disease). The included studies did not report the number of patients with any of these diseases. Therefore, it is not possible to assess the impact on our results. Fourth, there might be a selection bias due to drug treatment and degree of BP control. Finally, all the included studies provided unadjusted results and pooled analysis of unadjusted data would be confounded by differences in PA and EH patients.

Despite these limitations, our meta-analysis confirmed that PA significantly increased the CCV events. Thus, patients with PA might benefit by a periodic assessment of CCV risk. Furthermore, well-designed studies with larger sample size are required to assess the risk of CCV events in PA patients.

Author contributions

Conceptualization: Xueyi Wu, Haoming Tian.
Data curation: Xueyi Wu, Jie Yu.
Formal analysis: Xueyi Wu, Jie Yu, Haoming Tian.
Project administration: Haoming Tian.
Writing – original draft: Xueyi Wu.
Writing – review & editing: Jie Yu, Haoming Tian.

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