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Comparison of Cardiac Structural Improvement in Patients with Primary Aldosteronism after Surgical Therapy and Drug Therapy: A Meta-Analysis

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Abstract

Background: At present, in clinical practice, patients with primary hyperaldosteronism (PA) are mainly treated by surgery or medical drugs (spironolactone/spironolactone, epridone, etc.). Some studies show that the left ventricular hypertrophy of patients can be significantly improved after treatment. However, at present, the relevant research is very limited, and there is still controversy on the improvement of cardiac structure and function between the two treatment methods. No reliable conclusions have been drawn. **Objective:** We conducted this meta-analysis to compare the improvement of cardiac structure of patients after surgical treatment and drug treatment, so as to clarify the efficacy of surgical treatment and drug treatment for PA patients. **Methods:** In order to examine the cardiac color ultrasound data of PA patients receiving surgical treatment and drug therapy (spironolactone, antisterone), randomized or observational studies were searched through Pubmed, Cochrane Library, and Embase. Meta-analysis was then carried out on the comprehensive and individual outcomes. The ROINBS-I scale is utilized to assess the offset risk of study inclusion. **Outcomes:** A total of nine studies involving 799 patients with PA into meta analysis, according to the results of the surgery in the treatment of patients with PA, left ventricular mass index (LVMI) changes in value (drop range) is significantly higher than drug therapy (Mean difference IV: −2.32, $P < 0.05$). In 6 studies, after surgical treatment of interventricular septal thickness (IVSD), changes in value (drop range) are also higher than drug therapy (Mean difference IV: −0.35, $P < 0.05$). In 2 studies, the surgical treatment of plasma aldosterone concentration (PAC) drop degree is superior to drug therapy (Mean difference IV: −12.63, $P < 0.05$), and blood pressure to improve the degree of surgery and drug treat-

ment has no obvious difference. **Conclusions:** This meta-analysis result confirmed that after medical and surgical treatment of PA can obviously improve the patient's blood pressure, and no difference between the two treatments. But for the heart structure improvement, including left ventricular hypertrophy and interventricular septum thickness, surgical treatment effect is significantly better than the medicine treatment, so the adrenalectomy can be used as unilateral PA optimal choice of treatment.

Keywords

Primary Aldosteronism, Adrenalectomy, Mineralocorticoid Receptor Antagonist, Left Ventricular Mass Fraction, Ventricular Septal Thickness

1. Introduction

Primary aldosteronism (Primary aldosteronism, PA) is the most common cause of secondary hypertension [1], and the prevalence of hypertension patients in a variety of clinical Settings to achieve 5% - 15% [2]. But in recent years, several studies have shown that PA patients increased the incidence and mortality of cardiovascular events, associated with plasma aldosterone concentration, and had nothing to do with the effect of blood pressure (BP) [3]. It may be due to the adrenal high aldosterone secretion which causes the change of cardiac structure and function, and by increasing the independent of blood pressure caused by myocardial fibrosis [4]. PA in patients with heart damage included left ventricular expansion, myocardial fibrosis and left ventricular hypertrophy (LVH) and so on, these damages were frequently reported [5]. Compared with patients with essential hypertension matching blood pressure, patients with PA have more obvious LVH [6] [7]. Changes in cardiac fibrosis with left ventricular diastolic dysfunction can increase the risk of left atrial dilatation and atrial fibrillation (AF) [8] [9] [10]. Whether these changes will disappear with the specific treatment of PA is uncertain, but specific treatment for primary aldosteronism, especially the prevention of cardiovascular complications, it is important to reduce the damage of heart organs [11].

At present for PA treatment, mainly divided into surgical treatment (adrenalectomy) and drug therapy (spironolactone/antisterone, eplerenone), the unilateral primary aldosteronism may be adrenalectomy effective treatment, and including mineralocorticoid receptor antagonist (MRA), such as spironolactone, antisterone, etc, which can be used in the treatment of bilateral aldosteronism and not suitable for surgical treatment of unilateral aldosteronism [12]. However, the published data on the changes of cardiac structure and function after surgery and drug treatment are very limited, and there is still controversy on the improvement of cardiac structure and function between the two treatment methods. Therefore, we conducted this meta-analysis to compare the improvement of cardiac structure of patients after surgery and drug treatment, so as to clarify

the efficacy of surgery and drug treatment on PA patients.

2. Materials and Methods

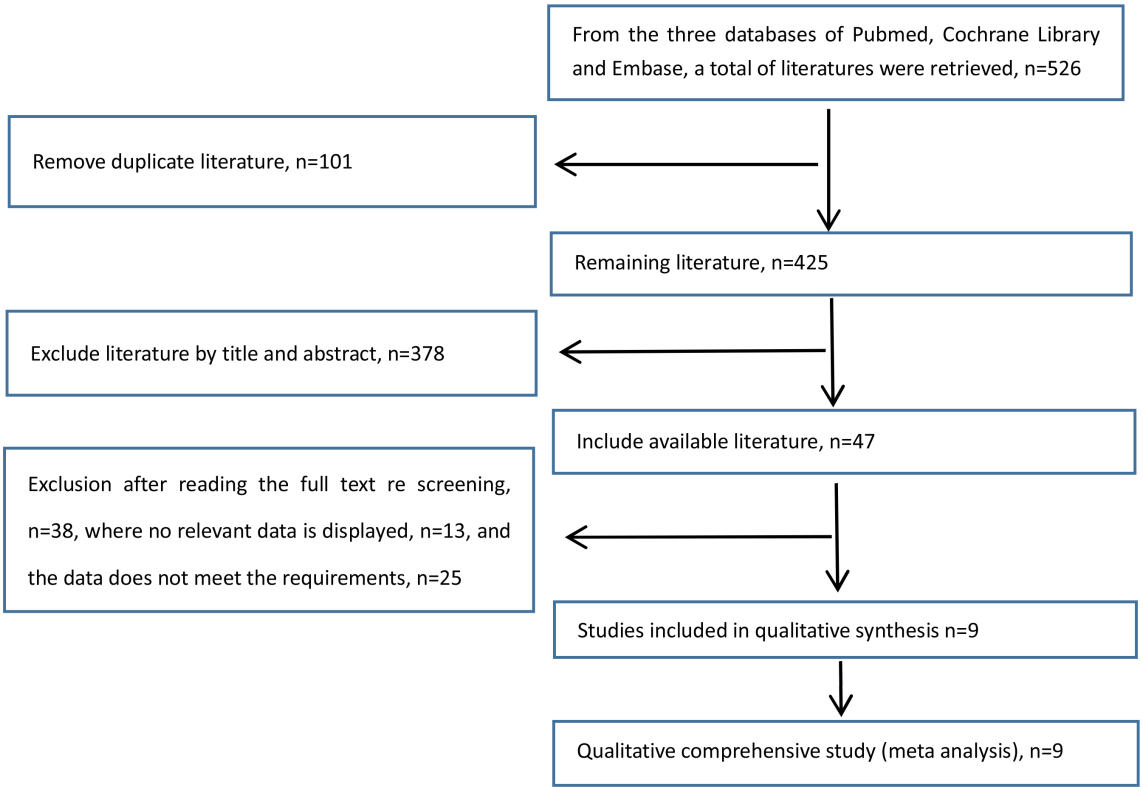
2.1. Search Strategy and Selection Methods

We searched three databases of PubMed, Embase and Cochrane Library, mainly using PA related terms to identify all eligible research. First of all, search is limited to human studies. In order to increase the number of studies included in screening, we have included any eligible studies published since 1978. The keywords used are "Hyperaldosteronism", "Aldosteronism" and "Echocardiography", and all the studies of the above keywords are covered in the article summary and title. The retrieval strategies are as follows: (Hyperaldosteronism* OR Aldosteronism*) and (Echocardiography*), and the retrieval time is up to June 15, 2022.

As for the screening of articles, first evaluate the articles found at the title or abstract level, reach a consensus after the two reviewers (Cheng Junchi and Ma Ruohan) independently screen, and then seek the third reviewer (Wang Bo) to resolve the differences. If the searched articles have potential relevance, further search the full text according to the selection criteria for further evaluation. If the background of the study is to evaluate the results of patients with PA (including the results of cardiac color Doppler ultrasound), the study including prospective study or retrospective study shall be selected to compare the performance of cardiac color Doppler ultrasound after medical and surgical treatment. To determine whether they meet the inclusion criteria: 1) prospective or retrospective studies, with emphasis on hyperaldosteronism; 2) Use at least one confirmatory test in PA diagnosis; 3) Involve APA and IHA patients; 4) It also includes research on surgical and medical treatment of PA; 5) At least LVMI is included as the outcome variable of treatment; 6) The follow-up time of echocardiography was >6 months. Exclusion criteria are: animal experiment, repeated study, study without relevant result data, no control group, relevant data but no follow-up after treatment, medical record report, review, etc. The control group refers to the study with medical treatment results while exploring surgical treatment effects or the study with surgical treatment results while exploring medical treatment effects, So as to obtain the comparison results of the efficacy of PA patients after receiving medical or surgical treatment (See **Figure 1** for research screening process).

2.2. Data Extraction and Quality Assessment

In data extraction, two researchers (RuoHan Dai and RuoHan Ma) use standardized data extraction spreadsheets to extract data independently. In case of any discrepancy, the two researchers can reach an agreement through consultation or the third reviewer (Bo Wang) can solve it. The extracted data include the first author, country, year of publication, type of study design (prospective or retrospective), basic information of the study group, details of treatment of two groups



We retrieved 526 articles from Pubmed, Cochrane Library and Embase databases, and further reviewed 47 full-text articles after deleting irrelevant records such as duplicates, animal studies, reviews and case reports. Among them, 13 articles did not show relevant data, and 25 articles did not meet the requirements. Finally, 9 studies were included in this study.

Figure 1. Schematic diagram of document retrieval and research selection process.

of PA patients, follow-up time, number of participants in the study and relevant outcome indicators. For the research reported in multiple publications, it is extracted from the publication with the most complete data (see **Table 1** for the characteristics of the included research baseline).

The quality of the included study was independently evaluated by two researchers (RuoHan Dai and RuoHan Ma) using the ROBINS-I checklist in the non random intervention study, and the following seven areas of each study were scored: "confusion", "choice", "intervention classification", "intervention deviation", "missing data", "result measurement" and "repeated result selection". The scores of each field are "no information" (0), "low" (1-low deviation risk), "medium" (2-medium deviation risk), "serious" (3-serious deviation risk) and "critical" (4-serious deviation risk). If most fields are judged as low deviation risk, the study is classified as high-quality study [13].

2.3. Extraction of Main Outcome Indicators

The main outcome measures were left ventricular mass fraction (LVMI), plasma aldosterone level (PAC), ventricular septal thickness (IVSD), systolic blood pressure (SBP), and diastolic blood pressure (DBP). The collection of all efficacy

Table 1. Basic characteristics of 9 studies included in meta-analysis.

Research	country	research design	Average age (years)	The proportion of women is (%)	Average follow-up time (month)	Number of intervention (n)		Related outcome indicators
						S group	M group	
Cristiana *et al.* 2007 [14]	Italy	prospective	53	30	76.8	24	30	LVMI; PAC; IVSD; SBP; DBP
Gilberta *et al.* 2007 [15]	Italy	prospective	51	41	S: 34.4 M: 55.2	25	36	LVMI; IVSD; SBP; DBP
Gian *et al.* 2013 [16]	Italy	prospective	51	24	36	110	70	LVMI; PAC; IVSD; SBP; DBP
Tomáš *et al.* 2015 [17]	Nemocnice	prospective	S: 49 M: 51	35	64	15	16	LVMI; PAC; IVSD; SBP; DBP
Cristiana *et al.* 2016 [18]	Austria	prospective	52	53	12	30	35	LVMI; PAC; IVSD; SBP; DBP
Christian *et al.* 2018 [19]	Germany	prospective	S: 54 M: 49	38	12	45	28	LVMI; PAC
Anton *et al.* 2021 [20]	Germany	prospective	S: 50 M: 49	45	12	79	105	LVMI; PAC
Yi-Lin *et al.* 2021 [21]	China	prospective	49	72	6	39	28	LVMI
Arleen *et al.* 2022 [22]	Norway	prospective	56	27	12	41	43	LVMI; IVSD; SBP; DBP

Table 1 sorts out the basic information of 9 studies, including the author, country, average age of patients, sex ratio, follow-up time, number of patients undergoing surgery and drug treatment, relevant outcome indicators, etc. (Specific data of outcome indicators are not shown in this table). Remarks: S group: Surgical (adrenalectomy) treatment group; M group: Drug treatment group; PAC: Plasma aldosterone concentration; LVMI: Left ventricular mass fraction; IVSD: Interventricular septal thickness; SBP: systolic pressure; DBP: diastolic pressure.

results includes data before treatment and after follow-up, including mean and standard deviation (SD). The formula is used to calculate the difference between the data before and after follow-up, which is the change value. The change value is included in the statistical analysis and the forest map is drawn. The change value of the mean value is directly calculated by subtracting the difference value before and after the follow-up, and the change value of the standard deviation is calculated by the following formula:

$$\mathrm{SD}_1(\mathrm{C}) = \sqrt{\mathrm{SD}_1(\mathrm{B})^2 + \mathrm{SD}_1(\mathrm{F})^2 - \left(2 \times \mathrm{R}_1 \times \mathrm{SD}_1(\mathrm{B}) \times \mathrm{SD}_1(\mathrm{F})\right)},$$

where is a constant (R = 0.4 or 0.5, for the convenience of calculation, R is taken as 0.5 in this study) [23]. The data extraction and calculation were independently completed by two researchers. If there were differences in the results, they should calculate again to reach an agreement.

2.4. Statistical Method

The statistical analysis method used in this study: use standardized data tables to extract statistical analysis data, and resolve any differences through consensus. In order to compare the difference in the incidence of events between the two treatment groups, with the help of RevMan 5.4, Mantel Haenszel fixed effect model was used to build a combined Mean difference IV with corresponding 95% CI. The weights specified in the fixed effect model take into account the variance within and between studies. Evaluate the heterogeneity between studies and reject homogeneity if the p value found is less than 0.10. The degree of heterogeneity is further classified according to the I^2 value: mild (less than 30%), moderate (30% - 50%) and substantial (>50%). The generated funnel graph is graphically checked to detect publication bias.

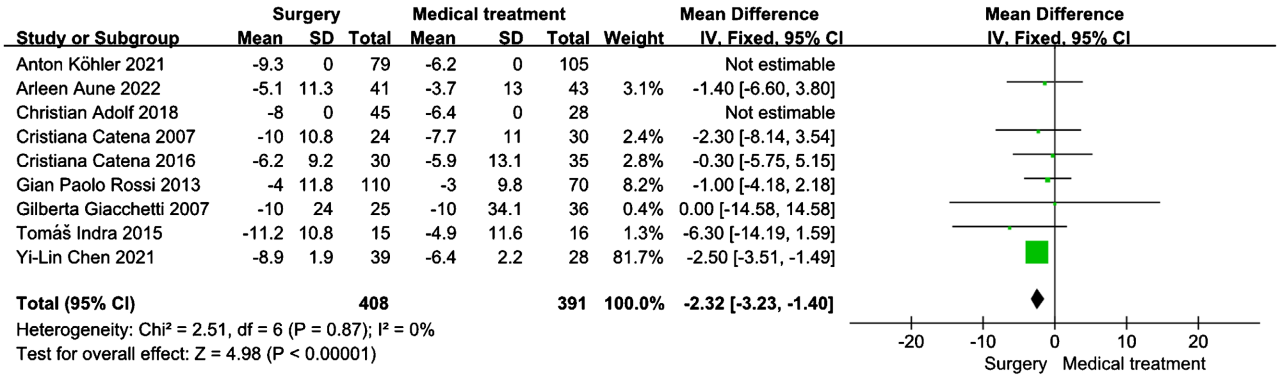
3. Result

3.1. Included Studies

We retrieved a total of 526 articles from three major databases, manually retrieved references by applying retrieval strategies, further evaluated their qualifications at the title or abstract level, and then conducted full-text reading screening. Finally, 9 studies were included in this meta-analysis [14]-[22]. The type of study is prospective study (basic characteristics of 9 studies are shown in **Table 1**). A total of 799 PA patients received surgical treatment (408 cases) or drug treatment (391 cases) respectively. In **Table 1**, a descriptive summary of each included study was made.

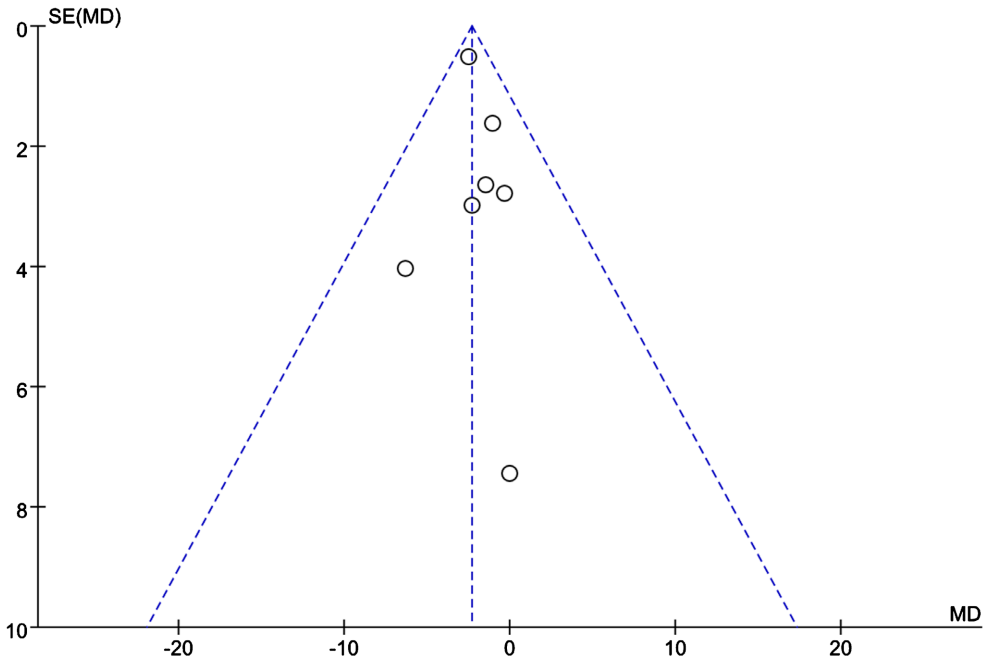
3.2. Main Results

A total of 9 studies were included in the meta-analysis. A total of 799 PA patients collected data on changes in left ventricular mass fraction (LVMI) and collated the meta-analysis (7 studies were actually included because no standard deviation was provided for the outcome indicators of the 2 studies). The results showed that among PA patients receiving surgical treatment, the changes in left ventricular mass fraction (LVMI) (the range of decline) was significantly higher than that of drug treatment (Mean difference IV: −2.32, $P < 0.05$), As shown in **Figure 2**, its funnel is shown in **Figure 3**. The results of 6 studies showed that the change (decrease) of ventricular septal thickness (IVSD) after surgical treatment was also higher than that of drug treatment (Mean difference IV: −0.35, $P < 0.05$), as shown in **Figure 4**. Since there is no follow-up data for the outcome indicators of many studies, the decline of aldosterone level (PAC) was only obtained in two studies, as shown in **Figure 5**, reflecting that surgical treatment is still superior to drug treatment (Mean difference IV: −12.63, $P < 0.05$). However, the results of several studies showed that there was no significant difference in the decrease of systolic and diastolic blood pressure, surgical treatment and drug treatment, as shown in **Figure 6** and **Figure 7**.



Forest map of the impact of medical and surgical treatment on left ventricular mass in patients with PA. The central square of each horizontal line represents the standardized mean difference IV of each study. The line represents the range of the 95% confidence interval (CI). If the value is 0, the vertical line is the line without difference between treatments. The relative weight percentage represents the effect of each study on the combined mean difference. Using Cochrane Q statistics, the P value of heterogeneity was 0.87. Heterogeneous I^2 Statistics are 0%.

Figure 2. LVMI change value forest map.



Funnel diagram of left ventricular mass change in PA patients after medical and surgical treatment. A funnel chart was constructed to assess possible publication bias. The vertical line represents the standardized mean difference of the overall estimated treatment effect. The diagonal line represents the pseudo 95% confidence interval of the estimated therapeutic effect. The white circle indicates the treatment effect of each study. In the absence of publication bias, the graph is funnel-shaped, and individual studies are clustered symmetrically around the overall estimated treatment effect.

Figure 3. LVMI change value funnel diagram.

4. Discussion

Our meta-analysis included a total of 799 patients with PA, including meta-analysis of 9 studies, and systematically reviewed the results of color Doppler echocardiography of patients after surgery and drug treatment. In the nine

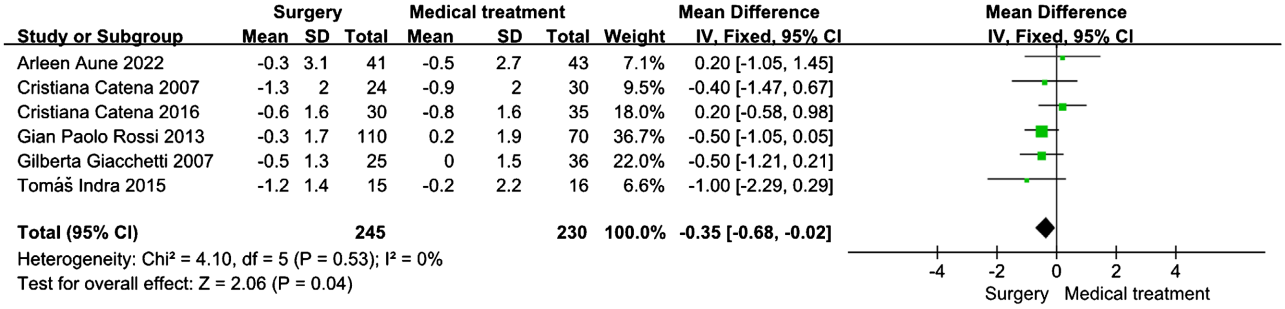


Figure 4. IVSD change value forest map.

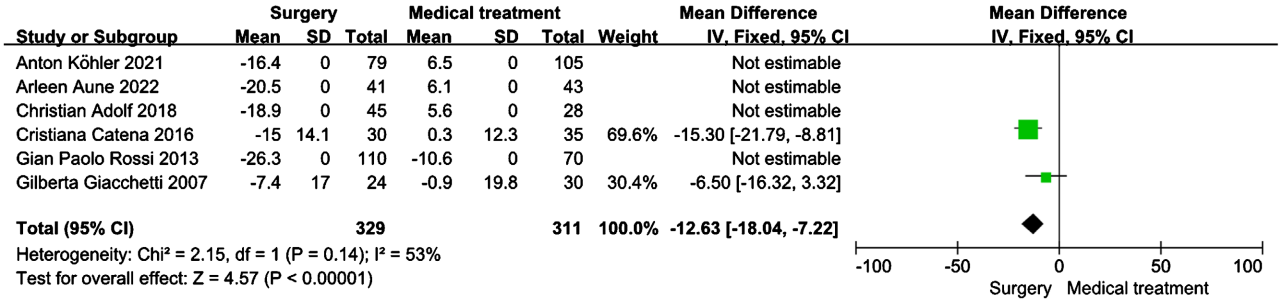


Figure 5. PAC change value forest map.

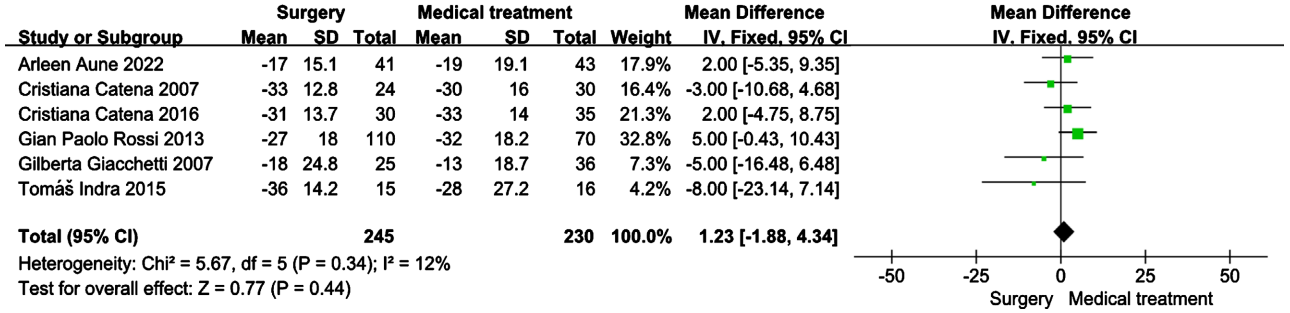


Figure 6. SBP change value forest map.

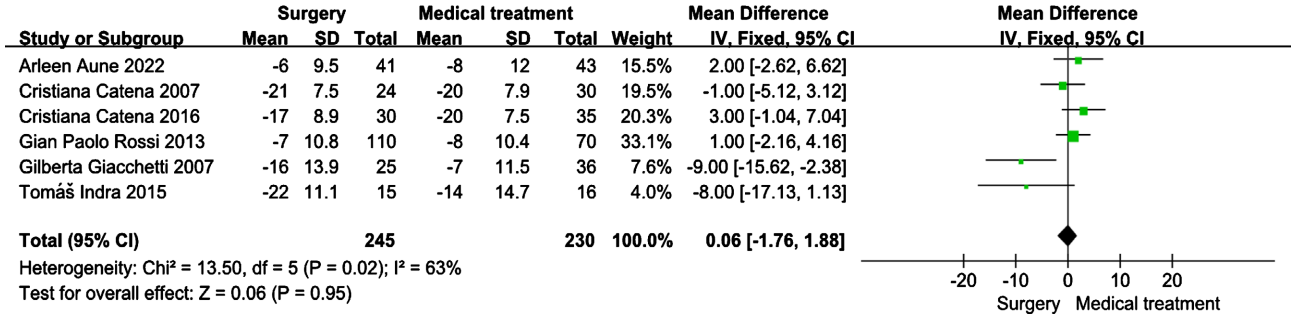


Figure 7. DBP change value forest map.

included studies, whether medical or surgical treatment, it can be reflected that the patient's heart structure has improved significantly after treatment, including the decrease of left ventricular mass fraction and the decrease of ventricular septal thickness. In the seven studies, we found that the improvement of left ventricular hypertrophy after surgical treatment was more obvious than that of

drug treatment, as shown in **Figure 2**. In 6 studies, the improvement of ventricular septal thickness after surgical treatment was also better than that of drug treatment, as shown in **Figure 4**. The comprehensive results showed that although the two treatment methods can control hypertension, the surgical method is more effective in improving the cardiac structure of patients. This remarkable finding suggests that adrenalectomy is an effective method to treat unilateral PA patients.

Some previous studies have found that for the treatment of PA, surgery and drug therapy (spironolactone or spironolactone) can both control hypertension, but surgery is more effective in reducing left ventricular hypertrophy. Catena *et al.* reported for the first time on drug treatment and surgical treatment for PA and proposed that both methods can reduce the left ventricular mass in long-term follow-up. However, compared with spironolactone treatment, these changes occur earlier after adrenalectomy, and most patients can occur within 1 year [24].

Tomas *et al.* showed that the reduction of left ventricular mass after adrenalectomy may be due to the simultaneous reduction of wall thickness and left ventricular cavity diameter, while MR antagonist treatment can only cause the reduction of left ventricular cavity, without signs of wall attenuation. However, both methods improved the diastolic function of left ventricle, the reversal of left ventricular hypertrophy is mainly caused by the attenuation of left ventricular wall [17]. In addition, Rossi GP *et al.* found that in the large cohort of PA patients receiving adrenalectomy or spironolactone treatment, the reduction of left ventricular mass index and left ventricular hypertrophy was mainly through the inward remodeling of the left ventricle and the reduction of the diameter of the left ventricular cavity, but no effect of specific treatment wall thickness was observed [25]. In our meta-analysis, we found that the improvement of left ventricular hypertrophy in patients after adrenalectomy was more obvious than that of drug treatment, and the thickness of ventricular septum was significantly attenuated. Therefore, it was not ruled out that after adrenalectomy, the thickness of left ventricular wall and the diameter of left ventricular cavity were attenuated at the same time. However, at present, there is no obvious evidence to prove this view in relevant studies, the view that both treatment methods can improve the left ventricular diastolic function of patients has reached a consensus.

In addition, in this meta-analysis, it was found that for patients with PA, their blood pressure could be well controlled regardless of drug treatment or adrenalectomy, and there was no significant difference in the improvement of blood pressure between the two treatments, but there was difference in the improvement of heart structure. It can be seen that the heart damage of patients with PA was more likely related to the level of aldosterone. Previous studies have also shown that the occurrence and development of cardiovascular diseases in patients with PA are obviously unrelated to the blood pressure level. Compared with patients with primary hypertension, high blood pressure caused by the endocrine disorder may be associated with a higher left ventricular mass [10] [26]

[27]. Experimental animal studies have found that patients with PA excess aldosterone can induce deposition of extracellular matrix and collagen, especially in the presence of high dietary salt intake. Fibroblast proliferation and collagen synthesis of stimulus may be related to human myocardial cells associated cortical hormone receptor activation. Induced inflammatory process and the specific ion motions with angiotensin, slow excitation peptide and the interaction of endothelin system to adjust, and these processes may be evidence of left ventricular hypertrophy [28] [29] [30]. So after special treatment, quality of the left ventricle in patients with PA fade, it may prove that because excessive aldosterone mediates the activation of mineralocorticoid receptors, which results in the way of left ventricular hypertrophy was cut off.Through our meta-analysis, we found that adrenalectomy has a better effect on improving the quality of the left ventricle, which may prove that adrenalectomy is more beneficial for cutting off the pathway of aldosterone mediated left ventricular hypertrophy.

There may be many factors affecting left ventricular hypertrophy in patients with PA, which may not be limited to excessive aldosterone level. Yi Lin Chen *et al.* compared the observational study on the treatment of PA between the adrenalectomy group and the drug treatment group, and followed up the changes of aldosterone level and cardiac function of patients before and after treatment. They found that the changes of cardiac function in the drug treatment group were significantly related to the changes of aldosterone level, but not in the operation group, suggesting that adrenalectomy may have therapeutic effects other than reducing the aldosterone level [21]. It reflects the therapeutic advantages of adrenalectomy.In a recent meta-analysis found that included 6148 patients with PA, in a composite cardiovascular outcome and not cure the low incidence of aspects of hypertension, surgical treatment is superior to the same drug treatment [31]. In addition, many cases of large series have confirmed that surgical treatment (unilateral adrenalectomy) is safe, lower incidence of postoperative complications. The cure rate of no significant difference between different surgical techniques, but some authors have identified predict characteristics of the cure [32] [33] [34].

We have to admit that our meta-analysis has some limitations. First, and most importantly, the number of patients involved is limited. Only 799 PA patients were included in this study. The limitation of the number of patients may lead to deviation of the results. In addition, due to the insufficient statistical capacity of this study, it is impossible to classify and compare the pathological types of patients. There may be different treatment methods for unilateral PA or bilateral PA (after all, surgery is not the treatment option for patients with bilateral PA), and different improvements in cardiac structure lead to deviation. At the same time, the duration of PA in the drug group and the operation group is different, which may lead to different results and result in deviation. In addition, we cannot determine the compliance of all patients with drug treatment, and we cannot rule out the deviation of cardiac function improvement caused by compliance. Finally, because the meta-analysis itself may introduce greater heterogeneity,

especially due to significant differences in the sample size included in the study, the final results may still be biased.

Finally, we said that in terms of the improvement of cardiac structure in patients with PA, the therapeutic effect of adrenalectomy was significantly better than that of drug therapy, so it was suggested that patients with unilateral PA should give priority to adrenalectomy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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