Meta-analysis of Pulmonary Artery Denervation for Treatment of Pulmonary Hypertension

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Research article

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Abstract

Objective: Pulmonary artery denervation (PADN) can reduce sympathetic nervous system (SNS) activity in patients with pulmonary hypertension (PH), reduce pulmonary artery pressure (PAP) in PH patients, and improve the quality of life in PH patients. We conducted a systematic meta-analysis of the effectiveness of PADN in the treatment of PH patients.

Methods: All public clinical trials investigating the effects of PADN on PH. Outcomes were average pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), cardiac output (CO), right ventricular (RV) Tei index, 6-minute walk distance (6MWD), and New York Heart Association (NYHA) cardiac function grading.

Results: A total of eight clinical studies including 213 PH patients with PADN were included. Meta-analysis showed that after PADN, mPAP (MD -12.51, 95% CI -17.74 to -7.27, P 0.00001) (mmHg) and PVR (MD = -5.17, 95% CI -7.70 to -2.65, P <0.0001) (wood unit) decreased significantly, CO (MD 0.59, 95% CI 0.32 to 0.86, P 0.0001) (L/min) and 6MWD (MD 107.75, 95% CI 65.64 to 149.86, P 0.00001) (meter) increased significantly, and RV Tei index (MD -0.05, 95% CI -0.28 to 0.17, P = 0.63) did not change significantly. And after PADN, the proportion of NYHA cardiac function grading (RR = 0.23, 95% CI 0.14 to 0.37, P <0.00001) III and IV decreased significantly.

Conclusion: This meta-analysis supports PADN as a potential new treatment for PH. Further high-quality randomized controlled studies are needed.

1. Background

Pulmonary hypertension (PH) is a progressive, extremely malignant, and high-mortality pulmonary vascular disease [1]. It is mainly characterized by increased pulmonary vascular resistance (PVR) and continuous increase in pulmonary vascular pressure, which ultimately leads to right heart failure or even sudden death [2]. PH can be defined as a rise in pulmonary artery pressure (PAP) caused by various causes, including pre-capillary PH, post-capillary PH, and mixed PH [3]. The diagnostic criteria for PH: at sea level, the right heart catheter measures the mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest [3]. The first category of PH is also commonly called pulmonary arterial hypertension (PAH), which is caused by left heart disease PH, PH caused by respiratory diseases and / or hypoxia, PH caused by obstructive pulmonary artery disease and PH caused by unknown factors constitute the current clinical classification of PH [4].

The advent of various new targeted drugs has brought more choices and hopes for the treatment of PH and with the use of targeted drugs, the overall quality of life and survival rate of PAH patients have improved obviously [5]. However, most of the current targeted drugs for PAH are vasodilators, and none of them can reverse the progressive pathological remodeling of the pulmonary vessels and RV in PAH patients. In addition, vasodilators did not significantly reduce mortality in the long-term follow-up of PAH

patients and some PH patients do not response well to targeted drugs [6]. Therefore, it is imperative to actively explore new treatment approach for PH.

A large number of studies have shown that PH is associated with increased sympathetic nervous system (SNS) and renin-angiotensin-aldosterone-system (RAAS) activation. [7, 8]. SNS originates from the thoracolumbar region of the spinal cord. Short preganglionic fibers from the T1-L2 segments synapse on paravertebral or prevertebral ganglia, enabling long postganglionic fibers to innervate target organs such as the heart and lungs. The activation of SNS and RAAS to produce circulating neurohormone transmitters is an important contributing factor to the progress of PH [9, 10]. Therefore, pulmonary artery denervation (PADN) aimed at reducing SNS activation, has become a novel treatment modality [11, 12]. In 2020, A multi-center clinical trial proved that PADN can reduce PVR as well as increase 6-minute walk distance (6MWD) of PAH patients, and no adverse events related to surgery occurred, confirming the effectiveness and safety of PADN [13]. However, another clinical study found that the effect of PADN on some PAH patients is not obvious [14]. Moreover, the sample size of the current clinical research is too small. Against this background, this meta-analysis aimed to assess the effects of PADN on PH in order to provide evidence-based medical evidence for its clinical application.

2. Method

This meta-analysis was performed according to recommendations of Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.1 Search strategy

Two authors conducted a comprehensive literature search including all human clinical studies of PADN in the treatment of PAH. Literature search was performed with the key words ‘pulmonary artery denervation’ and ‘pulmonary hypertension’ in Pubmed and Embase.

2.2 Selection criteria and exclusion criteria

Selection criteria include: (1) The study object is PH patients. (2) The treatment is PADN. (3) The outcomes include at least one of mPAP, PVR, CO, RV Tei index, 6MWD, NYHA cardiac function grading. (4) There are no restrictions on the language, but valid data can be extracted from the text.

Exclusion criteria include: (1) Studies with a sample size of < 10 cases. (2) Reviews, animal studies, case reports and meeting reports. (3) Repeated published literature or periodic report of a research.

2.3 Quality assessment

Cochrane collaboration’s tool for assessing risk of bias and the Newcastle-Ottawa Scale (NOS) were used to assess the quality of included studies by two independent researchers. The items included in Cochrane collaboration’s tool were random sequence generation, allocation concealment, blinding of participants

and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting and other bias. And the items included in NOS were representativeness of exposed cohort, representativeness of non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of study, comparability, assessment of outcome, duration of follow-up, adequacy of follow-up.

2.4 Data extraction and outcome measures

Two independent reviewers performed the data extraction and synthesis. Data extracted from studies included study characteristics, patient characteristics and outcomes. Outcomes include mPAP, PVR, CO, RV Tei index, NYHA cardiac function grading and 6MWD.

2.5 Statistical analysis

This meta-analysis was performed by Review Manager 5.3. Outcome data were extracted as risk ratios (RRs) and 95% CIs or mean differences (MDs) and 95% CIs. Q test and I^2 test were performed to assess the heterogeneity of the included studies [15]. When P value $\geq$ 0.1 indicates no heterogeneity and $I^2 \leq$ 50% indicates that the heterogeneity is not significant. Funnel plot is used to evaluate publication bias. Sensitivity analysis was conduct, in which 1 study was removed at a time to assess the influence of individual study on results.

3. Result

3.1 Literature search results

A total of 188 articles were retrieved and 8 studies were finally included, which are all prospective studies and involve a total of 213 patients [13, 16-22]. All patients were treated with PADN and followed up for 1-12 months. The literature screening process and quality evaluation is shown in Figure 1 and Figure 2. And characteristics of the included studies are summarized in Table 1.

3.2 Hemodynamic parameters

8 studies (n = 213) reported the mPAP [13, 16-22]. These studies had obvious heterogeneity, so the random effects model was used (P < 0.00001; I^2 = 85%). The results showed that after PADN, the mPAP decreased significantly (MD -12.51, 95% CI -17.74 to -7.27, P□0.00001) (mmHg) (Figure 3A). 8 studies (n = 213) for meta-analysis of PVR [13, 16-22]. Meta-analysis results showed that there was significant heterogeneity between the literatures (P <0.00001, I^2 = 93%), which was analyzed using a random effects model. The difference between the two groups was significant (MD = -5.17, 95% CI -7.70 to -2.65, P <0.0001) (wood unit). Compared with the pre-PADN, PADN could significantly reduce the PVR of PH patients (Figure 3B).

7 studies (n = 201) reported the CO [13, 16-19, 21, 22]. These studies had heterogeneity and the random effects model was used (P = 0.007; I^2 = 66%) (L/min). The results indicated that after PADN, the CO increased significantly (MD 0.59, 95% CI 0.32 to 0.86, P□0.0001) (L/min) (Figure 4A). 4 studies (n = 137) reported the RV Tei index [16, 17, 21, 22]. These studies had heterogeneity and the random effects model was used (P <0.00001; I^2 = 99%). The results indicated that after PADN, Tei index had no obvious change (MD -0.05, 95% CI -0.28 to 0.17, P = 0.63) (Figure 4B).

3.3 Quality of life

5 studies (n = 124) reported 6MWD [16, 17, 19-22]. There was obvious heterogeneity in these studies (P □ 0.00001 ; I^2 = 85%) and the random effects model was conducted. The results showed that after PADN, 6MWD increased significantly (MD 107.75, 95% CI 65.64 to 149.86, P □0.00001) (meter) (Figure 5A). 3 studies (n = 71) reported changes in NYHA cardiac function grading [16, 21, 22]. Meta-analysis results showed that the studies were homogenous (P = 0.67, I^2 = 0%), and fixed-effect model analysis was used. There was a significant difference between pre-PADN and post-PADN (RR = 0.23, 95% CI 0.14 to 0.37, P <0.00001). Compared with pre-PADN, the proportion of NYHA cardiac function grading III and IV of post-PADN decreased (Figure 5B).

3.4 Heterogeneity and sensitivity analysis

The results of this meta-analysis showed that the heterogeneity of mPAP, PVR, RV Tei index and 6MWD was high. After excluding the individual studies one by one, the meta-analysis results showed that the heterogeneity was still high. The difference between pre-PADN and post-PADN was statistically significant. This showed that the results of this meta-analysis are relatively reliable. The source of heterogeneity may be related to the different follow-up time and type of PHs between studies. A subgroup analysis of mPAP, PVR, and CO showed that the heterogeneity of 5 studies with a measurement time of 6 months was significantly reduced [13, 16, 17, 21, 22]. For mPAP, there were homogenous (P = 0.79, I^2 = 0%) of 5 studies with a measurement time of 6 months, and the difference between the two groups was significant (MD = -9.0, 95% CI -11.70 to -6.31, P <0.00001) (mmHg) (Figure 6A). For PVR the heterogeneity of 5 studies with a measurement time of 6 months was significantly reduced (P = 0.03, I^2 = 63%). Subgroup analysis showed compared with the pre-PADN, PADN could significantly reduce the PVR of PH patients (MD = -3.57, 95% CI -5.31 to -1.82, P <0.0001) (wood unit) (Figure 6B). For CO, there were homogenous (P = 0.51, I^2 = 0%) of 5 studies with a measurement time of 6 months, and the difference between the two groups was significant (MD = 0.63, 95% CI 0.42 to 0.85, P <0.00001) (L/min) (Figure 6C).

3.5 Publication bias analysis

Use funnel plots for publication bias analysis. The points of the corresponding funnel plots are symmetrical (Supplement Figure 1-6).

4. Discussion

To our knowledge, this is the first meta-analysis to evaluate the effect of PADN on PH. We included a total of 8 PADN clinical studies including 213 patients with PADN. The results showed that after PADN, mPAP and PVR of patients were reduced, CO was significantly increased, but RV Tei index had no obvious changes. 6MWD and cardiac function of PH patients was significantly improved after PADN.

PH is a pulmonary vascular disease with complicated etiology and various treatment methods. There are a number of studies indicating sympathetic excitement involvement in the pathogenesis of PAH models and patients, so PADN targeting SNS could be a therapeutic strategy for PAH and right heart failure. The earliest animal experiment proved that PADN treatment could completely eliminate PH caused by balloon occlusion of the left pulmonary artery interlobar artery [23]. In dog, porcine and canine PH model, PADN improved the hemodynamics and alleviated right ventricular (RV) dysfunction [24, 25]. There were ablation damages to the blood vessels in the ablation zone, including intimal damage, thrombosis, elastic fiber damage and the reduction of the thickness of middle layer of blood vessel wall in porcine model [25]. In canine model, compared with the sham operation group, the thickness of the vascular wall and the pulmonary muscularization rate decreased in the surgical group, and the pulmonary artery remodeling was significantly improved [26]. Besides, PADN could inhibited the messenger ribonucleic acid expression of genes correlated with inflammation, proliferation, and vasoconstriction [26]. Huang et al. also proved that serum interleukins IL-1β, IL-6 and malondialdehyde levels in the PADN group were significantly lower than those in the sham operation group, and the activity of superoxide dismutase was significantly increased, suggesting that PADN may inhibit lung tissue inflammation and oxidative stress reduces PAH[27]. The above animal studies proved that PADN could improve PH hemodynamic parameters, and significantly improved vascular remodeling, reduced RV dysfunction and inflammation, but also caused vascular damage, which provided a basis for the clinical application of PADN. This study uses the basic principles and methods of evidence-based medicine to comprehensively analyze the published clinical studies on the PH of PADN. This study found that PADN could effectively improve the hemodynamic parameters of PH patients. However, the heterogeneity of these studies is high, and the source of the heterogeneity may be due to the difference in follow-up time, the types of PH and the use of targeted drugs after PADN of each study.

Some studies have reported that sympathetic nerve regeneration could occur in animal models with PADN, which might be related to sympathetic axon growth mediated by nerve growth factor secreted by abnormally proliferating pulmonary artery smooth muscle cells [26, 28]. Therefore, whether the effect of PADN decays with time deserves further study. Chen et al. showed that all variables of right heart catheterization and 6MWD improved significantly at 6-month follow-up and were nonsignificant different between 6-month and 1-year [17]. Current clinical studies have been followed up for up to 1 year, and no effect of PADN has been found to decrease with time [13, 17]. Therefore, we selected the data of

6 months and the closest follow-up time for 6 months for meta-analysis. 6-month follow-up studies conducted a subgroup analysis and found that the heterogeneity of mPAP, PVR and CO was significantly reduced, which indicated that differences in follow-up time might be one of the sources of heterogeneity

The use of PH-targeted drugs after PADN may also affect outcome indicators, but the studies we included involve both postoperative use and unused PAH targeted drugs. Various studies have shown that regardless of whether PAH targeted drugs are used after surgery, PADN can significantly improve the hemodynamic parameters and the life quality of PH patients. This meta-analysis also reached the same conclusion, but due to the unclear explanation of the postoperative medication history and insufficient research, no subgroup analysis was performed. As long as a reasonable control group is set up, the use of PAH targeted drugs after surgery will not affect the judgment of the efficacy of PADN.

Studies on PADN improving right heart function and which PH is more suitable for PADN are insufficient. Because RV function plays a critical role in the prognosis of PH patients, measuring RV function is essential to guide treatment and evaluate the progress of the disease [29, 30]. However, there is no accurate index to assess RV function. RV Tei index, tricuspid annular plane systolic excursion (TAPSE) and RV area change fraction (RVFAC) are currently the most commonly used methods for evaluating RV contractile function [31–34]. This meta-analysis found that PADN did not significantly change the Tei index of PH, which might be due to too little data Moreover, TAPSE and RVFAC are incomplete, so meta-analysis cannot be performed. In addition, global RV longitudinal peak systolic strain (RV-LS) is another indicator of right heart function, which is closely related to the clinical outcomes of PH patients, and is recommended as the preferred prognostic parameter [35–37]. Chen et al. reported for the first time the changes of RV function measures after PADN in Group I PAH patients and found that PADN could improve PH hemodynamic parameters, RV functional parameters and 6MWD, which were related to baseline RV-LS [18]. Specifically, baseline RV-LS $\geq -11.3\%$ might useful to predict which patients might benefit from PADN [18]. More clinical studies are required to assess the benefits of PADN in improving RV function and these parameters that reflect RV function should be valued.

In addition, Mechanisms, treatment methods and responses to treatment of different types of PH are different [38]. Apart from targeted drug therapy and etiological treatment, some patients with confirmed chronic thromboembolic pulmonary hypertension (CTEPH) can be cured by pulmonary artery endarterectomy (PAE) [39, 40]. PADN also could be used in in CTEPH patients with residual pulmonary hypertension after PEA [19]. And the research also proves that PADN has effects on many types of PAH such as connective tissue disease-related PAH, drug-related PAH, and idiopathic PAH [13]. However, due to the lack of current clinical research, most of the types of PH are not separately counted, so we cannot analyze whether there are differential effects of PADN on various PH. Furthermore, PADN could reduce the inflammatory response of PH animal models, but current clinical studies have not compared whether there is a difference in inflammation indicators pre-and post-PADN.

Most studies did not observe the occurrence of surgery-related adverse events, such as pulmonary artery perforation and the formation of dissection aneurysm or acute thrombus [13, 16, 17, 20]. Zhang et al

confirmed that compared with the sildenafil group, the improvement of mPAP and 6MWD in the PADN group was more obvious, and the clinical worsening was less frequent [22]. These results confirm the safety and effectiveness of PADN. Based on the meta-analysis of these clinical studies, we came to a conclusion that PADN was a promising new strategy for the treatment of PH.

5. Limitations

There were a few limitations in this meta-analysis. Although a large number of studies have demonstrated the potential of PADN to treat PAH, there are few clinical trials to date, so the sample size of this study is relatively small. In addition, there are differences in the types of PH, follow-up time, PADN methods and whether PAH targeted drugs are used after PADN of these clinical studies. Furthermore, studies included in this meta-analysis are almost the before-after study in the same patient, which can obtain the difference in the curative effect of the subjects before and after treatment to a certain extent but is more likely to be affected by confounding factors. It is difficult to prove that the difference between before and after treatment is entirely due to the role of surgical intervention. Anyway, in the absence of high-quality randomized controlled studies, the existing evidence of efficacy based on the before-after study in the same patient can still provide a reference for clinical practice.

6. Conclusion

In conclusion, PADN significantly reduced mPAP and PVR as well as increased CO, but did not increase the Tei index of PH patients. Moreover, PADN increases 6MWD and improved cardiac function of PH patients. In the present meta-analysis, PADN was associated with improved hemodynamics and life quality of PH patients. Further high-quality randomized controlled studies are needed, and in part ongoing.

Abbreviations

PADN: Pulmonary artery denervation; SNS: sympathetic nervous system; PH: pulmonary hypertension; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CO: cardiac output; RV: right ventricular; 6MWD: 6-minute walk distance; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; RAAS: renin-angiotensin-aldosterone-system; NOS: Newcastle-Ottawa Scale; RRs: risk ratios; MDs: mean differences; TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular area change fraction; CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary artery endarterectomy.

Declarations

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None.

Authors’ contributions

Study designing: Wanyun Zuo and Qiming Liu; data search Wanyun Zuo, Na Liu and Yunbin Xiao; data extraction: Wanyun Zuo, Na Liu and Yunbin Xiao; data analysis and interpretation: Wanyun Zuo and Yonghui Xie; Manuscript drafting: Na Liu and Qiming Liu; manuscript critical intellectual content revision: Na Liu and Qiming Liu. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

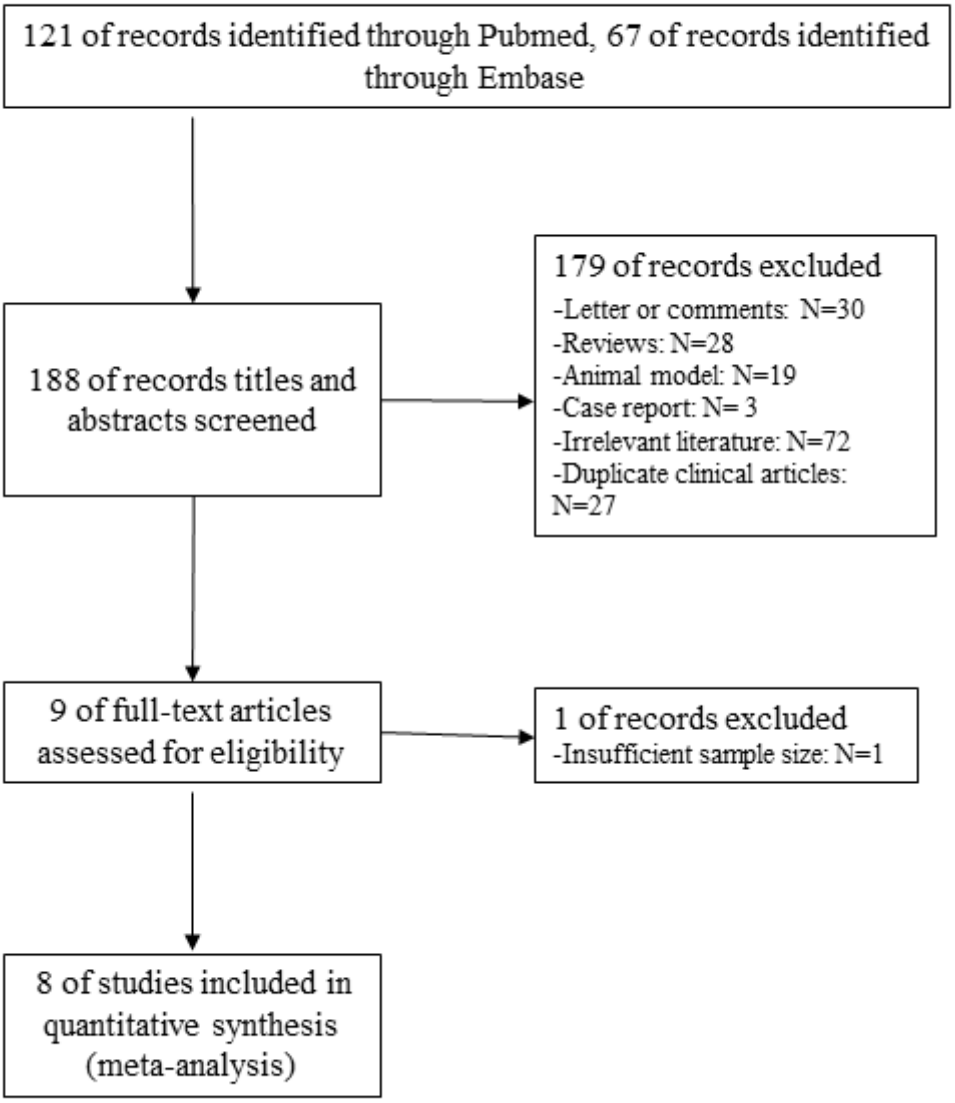
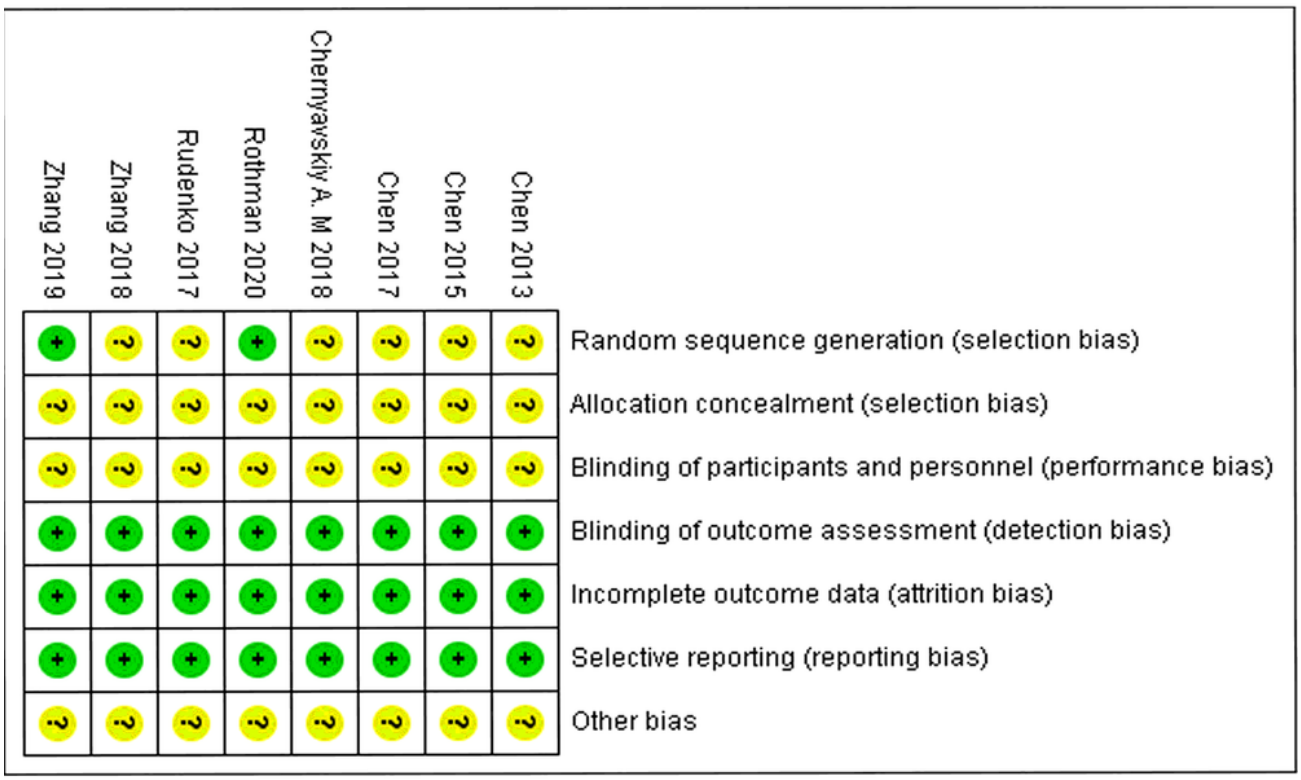


Figure 1

PRISMA flow chart of study selection.



Study	Year	NOS Quality Evaluation								
		a	b	c	d	e	f	g	h	total
Chen	2013	1	0	1	1	0	1	0	1	5
Chen	2015	1	0	1	1	0	1	1	1	6
Chen	2017	1	0	1	1	0	1	1	1	6
Chernyavskiy	2018	1	0	1	1	0	1	0	1	5
Rothman	2020	1	0	1	1	0	1	1	1	6
Rudenko	2017	1	0	1	1	0	1	1	1	6
Zhang	2018	1	0	1	1	0	1	1	1	6
Zhang	2019	1	1	1	1	0	1	1	1	7

Figure 2

Risk of bias graph: Red is low risk of bias, yellow is unclear risk of bias, red is high risk of bias. Newcastle-Ottawa Scale (NOS): a. representativeness of exposed cohort; b. representativeness of non-exposed cohort; c. ascertainment of exposure; d. demonstration that outcome of interest was not present at the start of study; e. comparability; f. assessment of outcome; g. duration of follow-up; h. adequacy of follow-up.

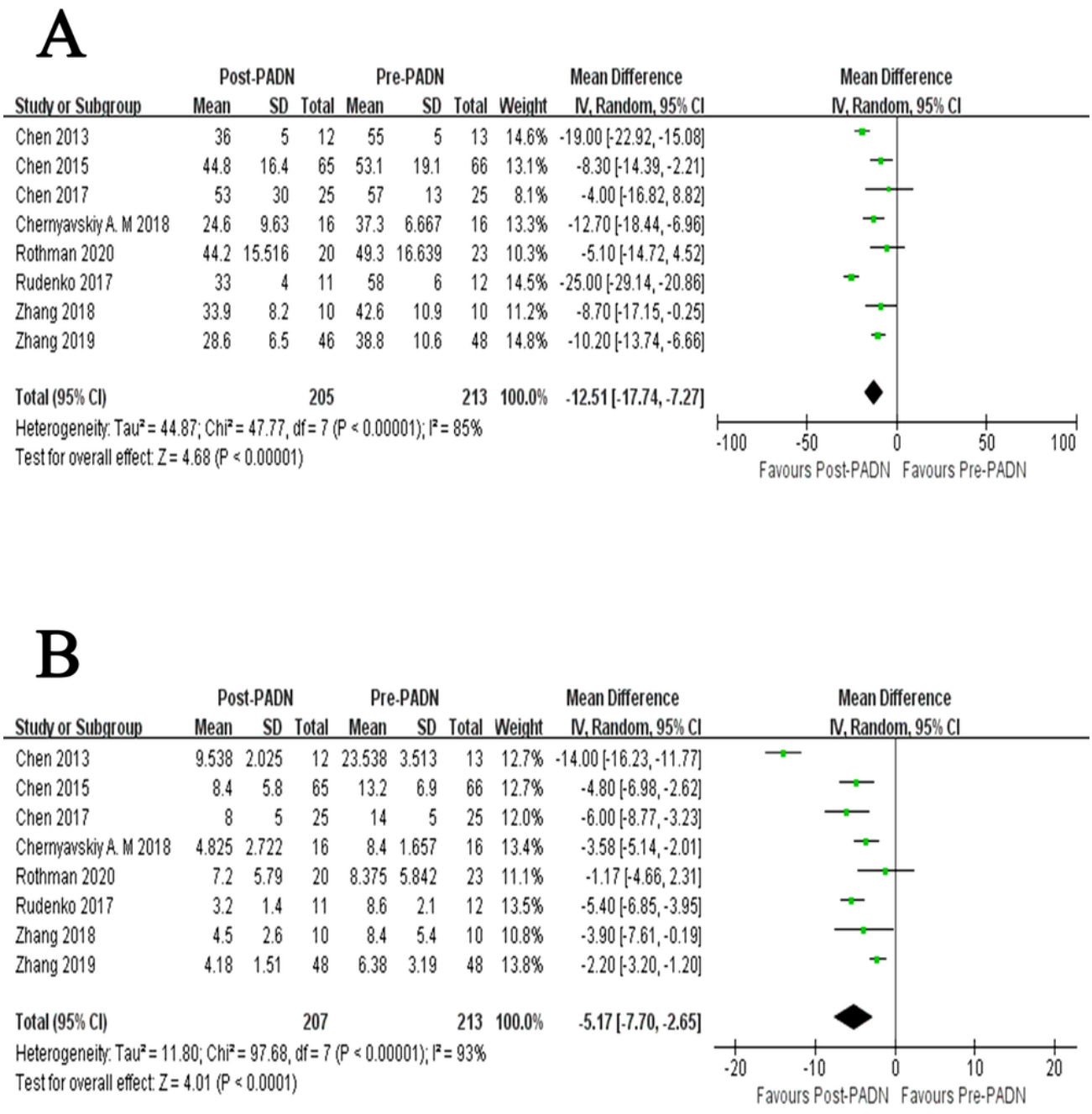


Figure 3

Forest plot for comparison of hemodynamic parameters between post-PAND and pre-PADN: A. mean pulmonary artery pressure (mPAP) (mmHg); B. pulmonary vascular resistance (PVR) (wood unit).

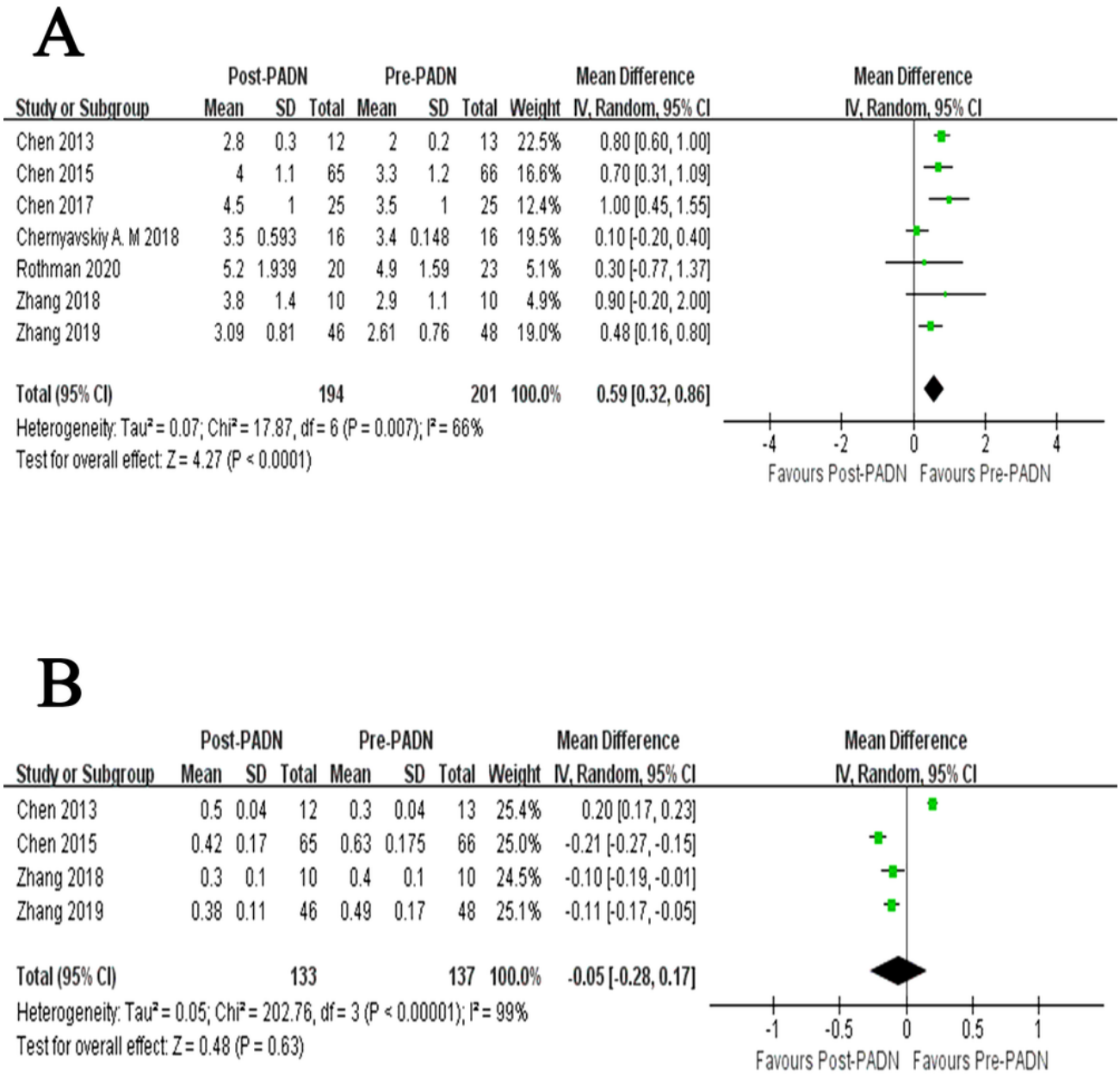


Figure 4

Forest plot for comparison of hemodynamic parameters between post-PAND and pre-PADN: A. cardiac output (CO) (L/min); B. right ventricular (RV) Tei index.

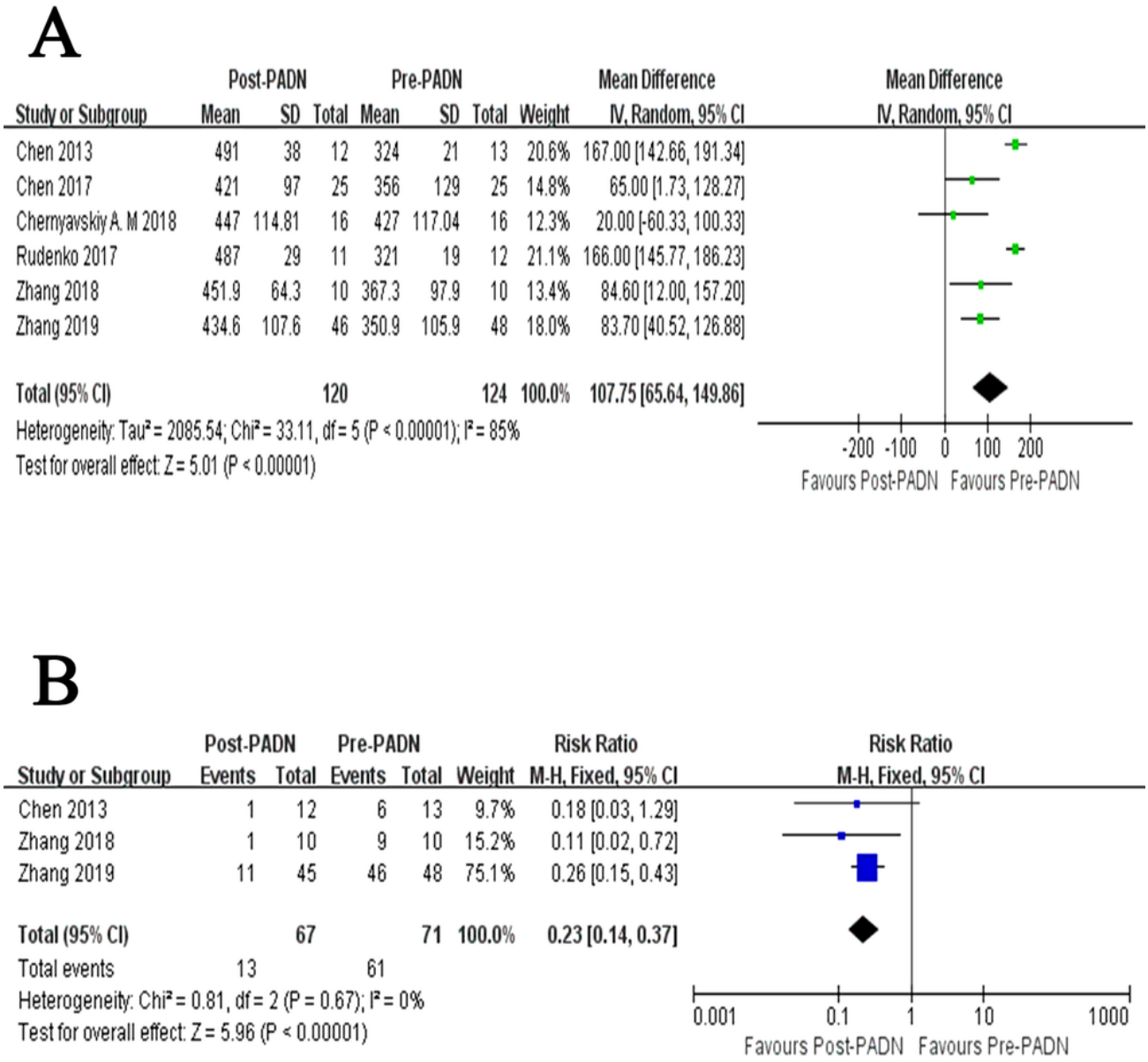


Figure 5

Forest plot for comparison of quality of life between post-PAND and pre-PADN: A. 6-minute walk distance (6MWD) (meter); B. New York Heart Association (NYHA) cardiac function grading.

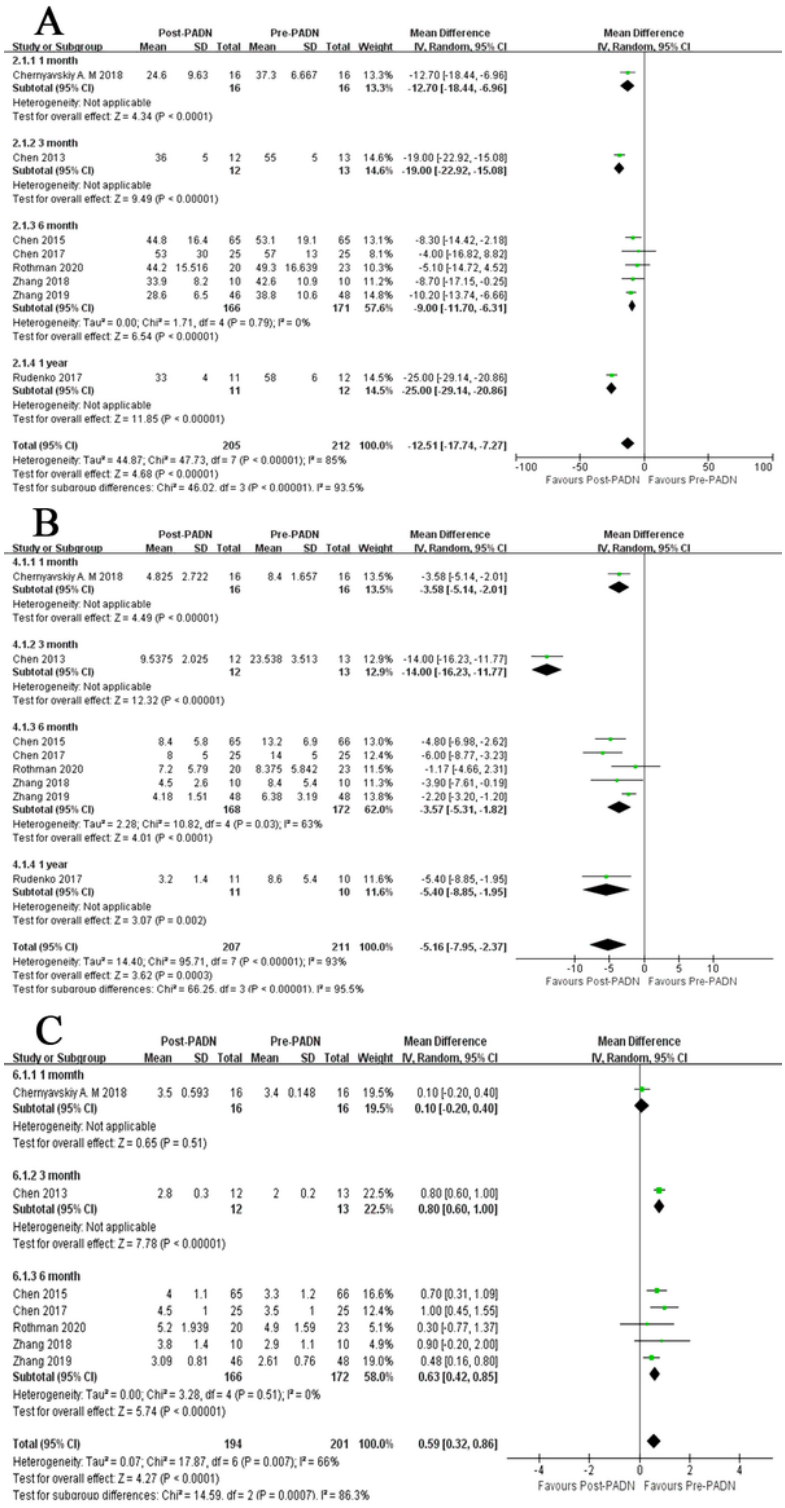


Figure 6

Subgroup analysis: A. pulmonary artery denervation (mPAP) (mmHg); B. pulmonary vascular resistance (PVR) (wood unit); C. cardiac output (CO) (L/min).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAChecklist.doc
- SupplementaryFigure2.png
- SupplementaryFigure6.png
- SupplementaryFigure5.png
- SupplementaryFigure4.png
- SupplementaryFigure3.png
- SupplementaryFigure1.png
- Table1.xlsx