Research Paper

Effects of Right Ventricular Non-Apical Pacing and Right Ventricular Apical Pacing on Left Ventricular Function: A Systematic Review and Meta-Analysis

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Early studies suggested that right ventricular apical pacing could have non-beneficial effects on left ventricular function. While right ventricular non-apical pacing may have significantly beneficial effects and could be a good alternative to right ventricular apical pacing is unknown. A systematic review and meta-analysis were conducted to compare the mid and long-term effects of right ventricular non-apical pacing and right ventricular apical pacing on left ventricular function. We conducted randomized controlled trials and retrospective cohort studies on patients with pacemakers to compare right ventricular apical and right ventricular non-apical. We evaluated patient's left ventricular ejection fraction, 6 min walk test, blood N-terminal pro-brain peptide, or brain natriuretic peptide. The results are expressed as the mean difference of the 95 % confidence interval. A total of 1181 references were included for evaluating the relevance. From this, 10 studies with 1246 patients have fulfilled the inclusion criteria (mean age ranged from 55 y to 85 y; male 62 %; 622 (50 %) right ventricular apical; 624 (50 %) right ventricular non-apical). There was no difference between the right ventricular apical and right ventricular non-apical groups in baseline left ventricular ejection fraction groups (mean difference=0.32, 95 % confidence interval (-0.70, 1.34), p=0.98, random effect model) and postoperative 6 min walking test (mean difference=5.14, 95 % confidence interval (-6.60, 16.89), p=0.51, I_2=0 %). In terms of left ventricular ejection fraction index and N-terminal pro-brain natriuretic peptide or brain natriuretic peptides, the right ventricular non-apical group was better than the right ventricular apical group (mean difference=-0.74, 95 % confidence interval (-2.24, 0.77), p<0.0001, I_2=56 %). Sensitivity analysis and funnel chart showed that our research is robust and has low publication bias. Our results showed that right ventricular non-apical pacing had significant beneficial effects on postoperative left ventricular ejection fraction than right ventricular apical pacing in patients with a pacemaker implanted for more than 1 y.

Key words: Right ventricular non-apical, atrial fibrillation, right ventricular apical, pacemaker, heart failure

Since applying the transvenous pacing system in the clinic, it has been considered the most suitable pacing site due to the stability and reliability of Right Ventricular Apex (RVA) pacing[1,2]. However, many clinical trials show that right ventricular apical pacing is defective, which can increase the incidence of atrial fibrillation and heart failure. Therefore, ventricular pacing should be minimized in patients with normal atrioventricular function. In contrast, patients with atrioventricular block who need ventricular pacing need to choose other ideal pacing sites to replace them[3-5].

Right Ventricular Non-Apical (RVNA) (mainly including right ventricular outflow tract, high septum, and median septum) pacing has become a research hotspot because it is closer to physiological conduction[6-8]. With the development of cardiac pacing technology, the indications of pacemaker placement are also expanding, and the number of pacemakers is increasing. Therefore, it is essential

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to follow up with the patients regularly. We should know whether the performance and working condition of the pacemaker are average and know the heart's function[9,10].

Studies have shown that the left ventricular systolic asynchrony caused by RVA pacing is significantly correlated with long-term follow-up mortality and hospitalization rate of heart failure. Myocardial relaxation depends on preload, afterload, and the consistency of myocardial contraction to peace[11-13]. RVA pacing can lead to the asynchrony of the systolic process, which further impairs the function of the ventricular diastole[14-16].

This systematic review study aims to evaluate the effects of RVNA pacing and RVA pacing on the medium and long term of left ventricular function.

MATERIALS AND METHODS

Literature search strategy:

A comprehensive literature search was conducted on the abstracts and full-text articles published in the electronic databases MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of controlled trials (central) from June 2006 to March 2016. Right ventricular apical; left ventricular function; meta and pacing. These keywords were combined with the Boolean operators 'AND' or 'OR' to search literature.

A comprehensive search of the literature has been carried out, and there are no restrictions on the publication status. Two individual reviewers identified and reviewed full-text articles and abstracts deemed relevant by screening the list of titles. Disagreements between the two reviewers were resolved with consensus.

Study selection:

Randomized clinical trials were included if they were published in English. If studies provided relevant information on the effects of RVNA pacing and right ventricular apical pacing on left ventricular cardiac function (i.e., participants, interventions, comparisons, results, and study design), these studies were included in this systematic review and meta-analysis

After the preliminary screening study, the possible relevant research texts were reviewed, and the included studies need to meet the following criteria.

Inclusion criteria: Patients with cardiac pacemakers; comparison of Left Ventricular Ejection Fraction (LVEF); the follow-up time of various indexes was ≥6 mo and provide full text.

The exclusion criteria: Not original research; no complete research text and meeting summary or presentation.

Data extraction and quality assessment:

Two co-authors independently extracted relevant data parameters. In the event of disagreement, rechecking of the original article followed by discussion was used to reach a consensus.

First author's name, patient's age and gender, country of origin, year of publication, sample size, and study duration. Two independent reviewers assessed the quality of the included studies using the Cochrane Collaboration risk-of-bias tool.

Statistical analysis:

The review manager (Version 5.2, Cochrane Collaboration, 2011) was used to estimate the impact of the results in the selected report. Specifically, data for effect sizes of continuous outcomes were extracted or recalculated as Mean Difference (MD), which expresses the mean difference between the intervention and control groups in standard deviation units, with 95 % Confidence Interval (CI). Statistical heterogeneity between studies was assessed with chi-square test or Cochran's Q test, and the I^2 statistic, which measures inconsistency across study results and describes the proportion of total variation in study estimates due to heterogeneity rather than sampling error.

In detail, I_2 values of 0 % indicate no heterogeneity, 25 % low heterogeneity, 25 %-50 % moderate heterogeneity, and 50 % high heterogeneity. A fixed-effect model was applied in the absence of minor heterogeneity, and a random effect model was adopted for significant heterogeneity. Funnel plots and Egger's test were used to examine potential publication bias. Sensitivity analysis was conducted by deleting a single study each time to observe the influence of the individual outcome on the overall analysis.

RESULTS AND DISCUSSION

The flow diagram of the article selection process is illustrated in fig. 1, which resulted in the

inclusion of 10 studies. After removing duplicates, 871 records remained. By screening the titles and abstracts, an additional 681 records were excluded because they were review articles, letters, case reports, comments, or editorials. In consideration of the study design and insufficient data presented, 180 articles were removed. Finally, 10 studies, including 1246 subjects, met the inclusion criteria and were included in this meta-analysis. A total of 10 studies were retrieved by our search that fulfilled all inclusion criteria (fig. 1).

The sample size in the individual studies ranged from 22 to 132 participants. Out of the 1246 participants, 775 (62 %) were male. Mean age ranged from 55 y to 85 y old. The primary outcome measures were LVEF, 6 Min Walking Test (6MWT), and N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) or Brain Natriuretic Peptides (BNP). A total of 1246 patients were available for the meta-analysis, including 622 patients who received RVA and 624 patients who received RVNA[17-26]. Among the studies, all studies were published in the English language; four studies were from China, the other six were from the USA, Iran, India, and Australia. Baseline characteristics of this study were presented in Table 1.

Risk of bias assessment was performed at the study level, and methodological quality assessment was performed using the Cochrane bias risk assessment tool (fig. 2).

Two independent reviewers evaluated the quality of studies included in the review, with differences resolved by consensus or through a third reviewer if required. A summary of all kinds of bias in each study is shown in fig. 3. There are two trials with bias risk, and eight trials have no chance.

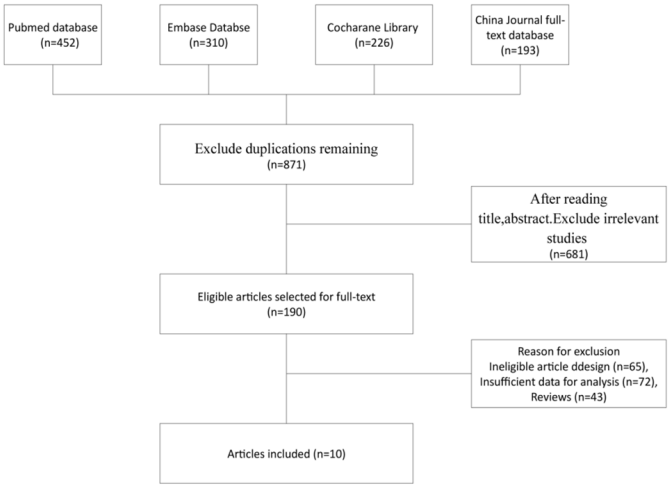

Fig. 1: PRISMA flow diagram of the study selection process

TABLE 1: CHARACTERISTICS OF STUDIES INCLUDED IN THE META-ANALYSIS

Study	Year	Language	Country	No. of patients (male/ female)	Age range (mean)	No. of RVA group	No. of RVNA group	Year of onset
Bai	2016	English	China	60/36	66.7+10.7	46	50	August 2011 to August 2014
Chen	2014	English	China	55/37	75±10	47	45	August 2008 to August 2011
Gong	2009	English	China	52/38	70±11	44	46	June 2006 to September 2008
Hemayat	2014	English	Iran	68/96	63.93±16.1	82	82	October 2008 to July 2011
Kaye	2014	English	Australia	161/79	73.7±11.1	120	120	March 2007 to January 2011
Leclercq	2016	English	France	191/72	63.8+9.5	132	131	November 2010 to August 2013
Saito	2015	English	Australia	97/48	75+5.5	76	69	August 2007 to December 2011
Singh	2015	English	India	29/22	57.4±10.62	22	29	March 2010 to October 2011
Schleifer	2018	English	America	29/16	78.4±5.7	23	22	July 2013 to August 2016
Xu	2017	English	China	33/27	67.1±7.5	30	30	January 2012 and December 2015

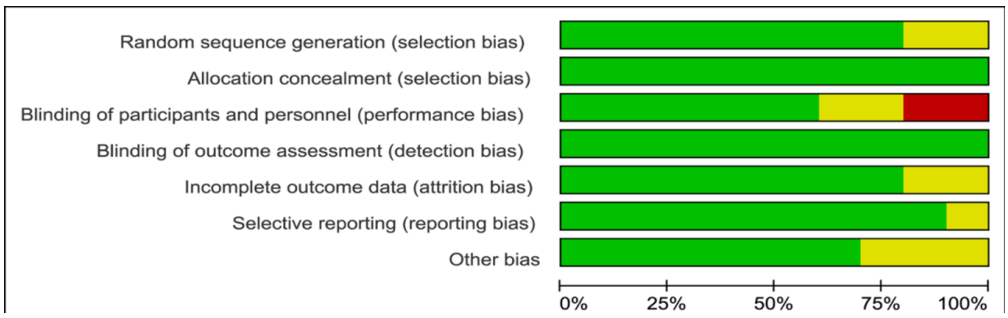

Fig. 2: Risk of bias of included studies
Note: ( ): Low risk of bias; ( ): Unclear risk of bias and ( ): High risk of bias

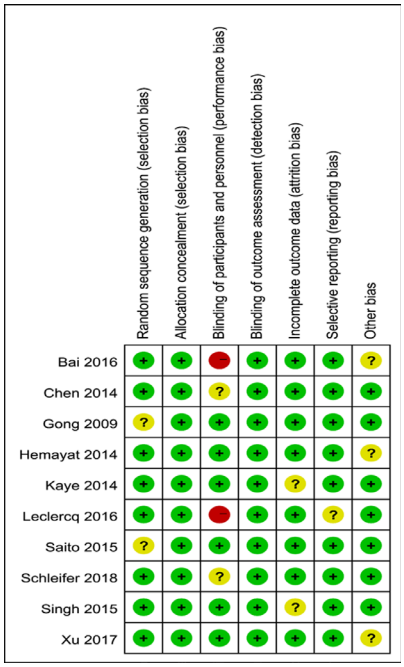

Fig. 3: Risk of bias summary of the studies included

In 5 studies involving 633 patients, NT-proBNP or BNP levels were compared between the RNA and RVNA groups. The meta-analysis showed that there was a difference between the two groups (MD=259.07, 95 % CI (3.31, 514.83), p<0.01, random-effects model) (fig. 4). We performed a meta-analysis of LVEF at baseline in patients in the RVA and RVNA groups. The results showed that there was no significant difference in LVEF between the two groups (MD=0.32, 95 % CI (-0.70, 1.34), p=0.98, random effect model) (fig. 5). We performed a meta-analysis of the postoperative LVEF of patients in the RVA and RVNA groups. The results showed that there was a significant difference in postoperative LVEF between the two groups of patients (MD=-0.74, 95 % CI (-2.24, 0.77), p=0.03, random-effects model) (fig. 6). As shown in fig. 7, included studies were involved. The results showed that there was no difference in 6MWT between the two groups (MD=5.14, 95 % CI (-6.60, 16.89), p=0.51, I_2= 0 %, fig. 7).

A total of 7 studies reported on postoperative LVEF. The forest plot shows that the RVNA group is better than the RVA group (MD=-0.74, 95 % CI (-2.24, 0.77), p<0.0001, I^2=56 %, fig. 7). We performed a sensitivity analysis by deleting the Singh 2015 study. The results did not change much, with I^2 changing from 56 % to 59 % (fig. 8), which indicates that the results of the included articles are robust.

We also drew a funnel chart to assess the publication bias of NT-proBNP and BNP; the figure shows that the shape is not symmetrical. The output result suggests limited publication bias in this meta-analysis (fig. 9).

Since the last century, cardiac pacing has been successfully applied in clinical practice. Its application has brought new life to patients, improved their quality of life, and restored their working ability. RVA pacing is usually used in the conventional site[24,27]. Because the lead wire of

this site is easy to locate and fix firmly, it has been widely used for a long time. However, long-term pacing can directly damage ventricular function, affect myocardial perfusion and lead to myocardial remodeling[28,29].

RVNA pacing can make the ventricular activation sequence close to physiological and obtain better hemodynamic effects. According to the anatomical characteristics of the right ventricular septum, domestic and foreign scholars have performed direct his bundle pacing, right ventricular inflow septal pacing, right ventricular outflow septal pacing, right ventricular apical septal pacing, and right ventricular septal pacing-the practice of pacing at the ventricular septum[30,31]. Most studies have confirmed that right ventricular septal pacing is technically safe, feasible, and effective. Still, different heart parts affect cardiac function, especially left ventricular function. Zhu's research has shown that for patients with permanent pacemaker implantation whose basal state LVEF is reduced (≤40 %-45 %) or who have been followed up for >1 y, RVNA pacing has less impact on postoperative LVEF than RVA pacing. The conclusions are similar[32,33].

During RVA, pacing, electrical pulses are retrograde conducted from the apex to the ventricular septum. Most of the left ventricle is undertaken through the myocardium. The depolarization speed is slow. The abnormal movement of the posterior wall of the ventricle causes the entire heart to contract out of synchronization, loses overall coordination, and reduces ventricular compliance, which has many adverse effects on hemodynamic and cardiac function.

During RVNA pacing, the ECG is similar to its sinus rhythm. In conventional pacemaker implantation, the very easy-to-collect QRS time limit is a valuable indicator of left ventricular activity[34,35]. It has also been confirmed in the experiment that the shortening of the wave duration by changing the pacing position will lead to the improvement of left ventricular function. One of the major limitations of this systematic review study does not analyze the dynamic changes of LVEF from preoperative to postoperative. Second, no further stratified comparison was made on the specific parts of RVNA pacing[36-38].

This meta-analysis identified a significant prevalence of RVNA pacing and RVA pacing in patients with a pacemaker implanted for >1 y. Our study suggests that RVNA pacing is more beneficial to LVEF than RVA. Though this finding is exciting, its beneficial clinical effect is uncertain. The data available for endpoints other than LVEF are not enough and conclusive. There is a need for large relevance references to evaluate and compare the safety and efficacy of RVNA and RVA pacing.

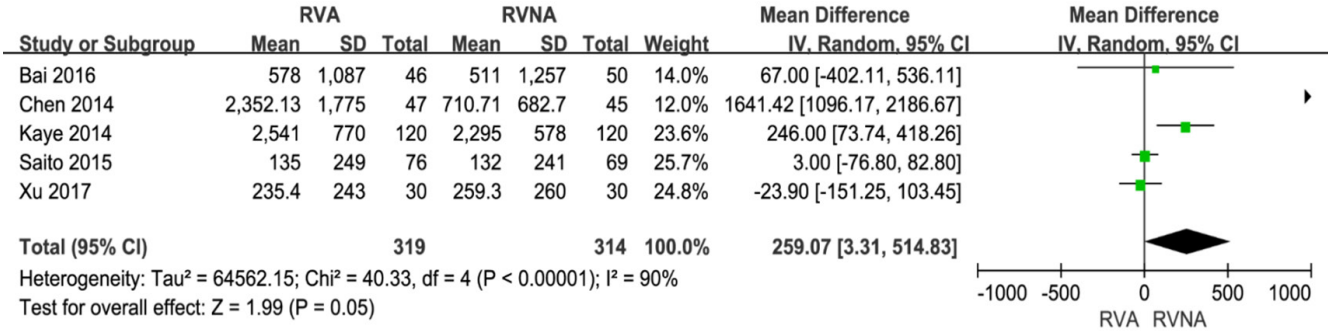

Fig. 4: Comparison of NT-proBNP or BNP levels between the two groups

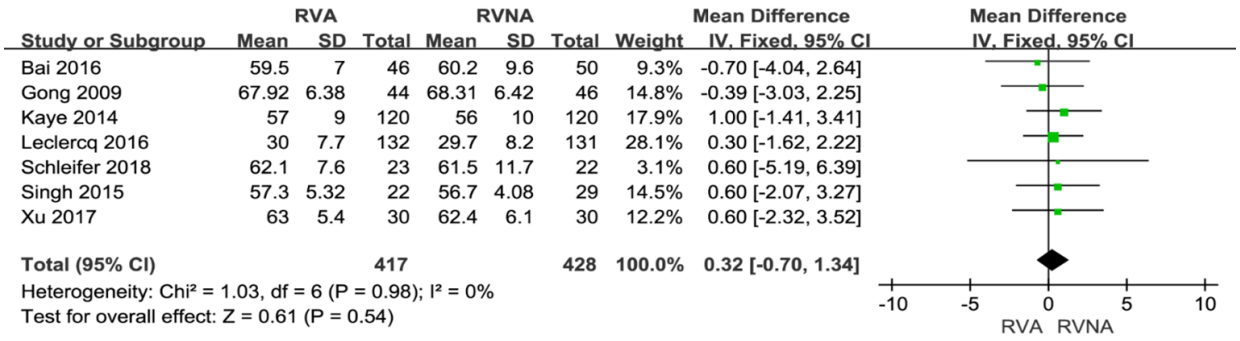

Fig. 5: Comparison of LVEF between the two groups of patients at baseline

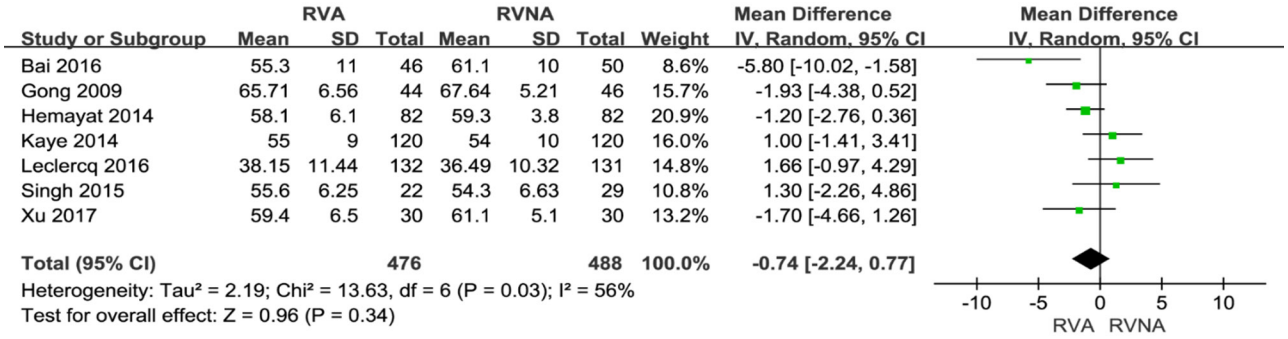

Fig. 6: Comparison of postoperative LVEF between the two groups

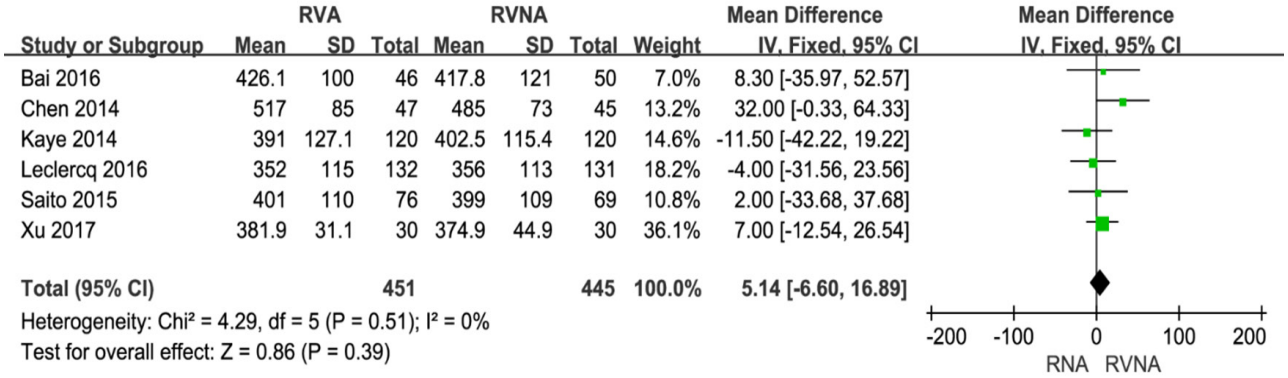

Fig. 7: Comparison of 6MWT after operation between the two groups

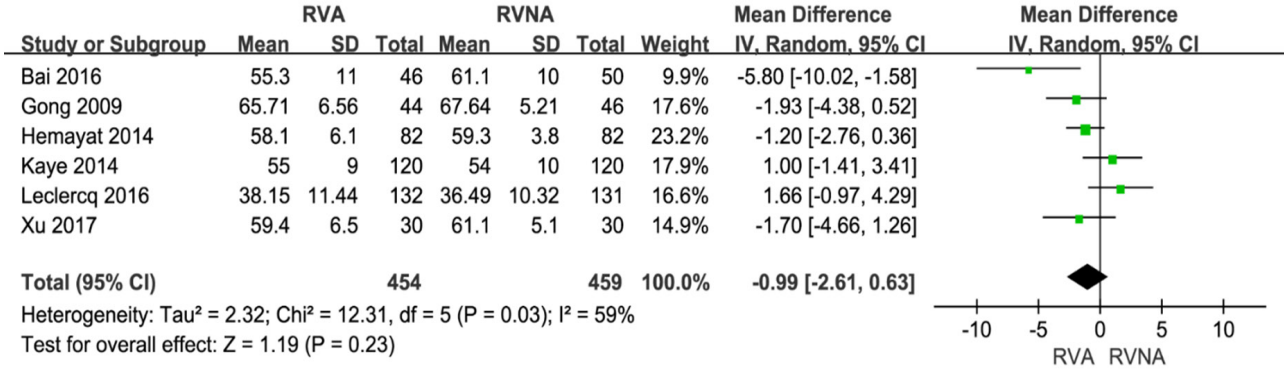

Fig. 8: Forest plot of sensitivity analysis of postoperative LVEF

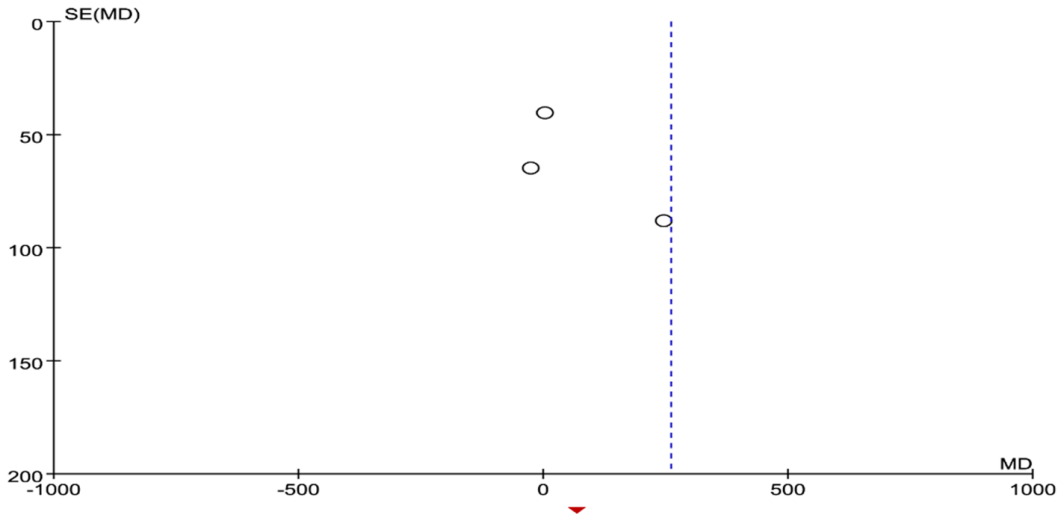

Fig. 9: Funnel plot for potential publication bias

Author's contributions:

Yingbiao Wu, Jie Su, and Qing Yuan Jiang participated in the conception and design of the study, library searches and assembling of relevant literature, critical review of the paper, supervising the writing of the paper, and database management; Xinpeng Cong and Luoning Zhu participated in data collection, library searches assembling relevant literature, writing the paper, and critical review. Yingbiao Wu and Jie Su have contributed equally to this work.

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Conflict of interests:

The authors declared no conflict of interests.

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