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## Left bundle branch pacing vs biventricular pacing in heart failure patients with left bundle branch block: A systematic review and meta-analysis

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### Abstract

#### BACKGROUND

Left bundle branch pacing (LBBP) is a novel pacing modality of cardiac resynchronization therapy (CRT) that achieves more physiologic native ventricular activation than biventricular pacing (BiVP).

#### AIM

To explore the validity of electromechanical resynchronization, clinical and echocardiographic response of LBBP-CRT.

#### METHODS

Systematic review and Meta-analysis were conducted in accordance with the standard guidelines as mentioned in detail in the methodology section.

#### RESULTS

In our analysis, the success rate of LBBP-CRT was determined to be 91.1%. LBBP-



CRT significantly shortened QRS duration, with significant improvement in echocardiographic parameters, including left ventricular ejection fraction, left ventricular end-diastolic diameter and left ventricular end-systolic diameter in comparison with BiVP-CRT.

## CONCLUSION

A significant reduction in New York Heart Association class and B-type natriuretic peptide levels was also observed in the LBBP-CRT group vs BiVP-CRT group. Lastly, the LBBP-CRT cohort had a reduced pacing threshold at follow-up as compared to BiVP-CRT.

**Key Words:** Left bundle branch pacing; Biventricular pacing; QRS duration; Left ventricular ejection fraction; Heart failure

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**Core Tip:** Left bundle branch pacing (LBBP) is a unique pacing modality in cardio resynchronization therapy. LBBP-cardiac resynchronization therapy (CRT) improves the left ventricular ejection fraction, echocardiographic parameters, and clinical outcomes when compared to biventricular pacing (BiVP). It causes significant reduction in New York Heart Association class, pacing threshold and B-type natriuretic peptide. This systematic review and meta-analysis reviews and analyze the data comparing LBBP vs BiVP-CRT.

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## INTRODUCTION

Left bundle branch block (LBBB) is of paramount importance given the evidence of worse prognosis in severe, symptomatic heart failure (HF) patients[1,2]. Cardiac resynchronization therapy (CRT) carries a strong recommendation for symptomatic patients with sinus rhythm, QRS duration (QRSd)  $\geq 150$  ms with LBBB morphology, and left ventricular ejection fraction (LVEF)  $\leq 35\%$  despite optimal medical therapy, with the goal of relieving symptoms and minimizing morbidity and mortality[3]. Biventricular pacing (BiVP) is the conventional CRT for LBBB, with HF showing significantly improved patient mortality[4]. However, not all patients respond to it, with an alarming non-response rate of approximately one-third[5]. Left bundle branch pacing (LBBP), a sub-type of conduction system pacing (CSP), has increasingly gained traction lately as an emerging, effective mode of CRT since it first showed a complete reversal of LBBB in HF patients[6]. Both procedures are subjected to non-responses due to variable patterns of mechanical desynchrony in HF patients, left ventricular pacing site, and cause of HF[5]. LBBP is deemed to be a less complex procedure and can target distal and deeper to the bundle of His such that it now serves as a potential alternative to His bundle pacing (HBP), i.e., the more traditionally used type of CSP for LBBB[6]. Very recently, Wang *et al*[7] conducted the first randomized control trial (RCT) evaluating the efficacy of LBBP-CRT in improving echocardiographic parameters among patients with HF and reduced LVEF and demonstrated a greater degree of LVEF improvement with LBBP-CRT in comparison to BiVP-CRT. Another recent analysis by Chen *et al*[8] showed LBBP-CRT to have better electromechanical resynchronization, higher clinical and echocardiographic response, and especially higher rate of super-response than BiVP-CRT in patients with LVEF  $\leq 35\%$ , and LBBB with HF. A previous meta-analysis conducted by Cheng *et al*[9] excluded these studies, thus resulting in lower statistical power and inconsistent results. Hence, we performed an updated analysis pooling the first ever RCT published in the literature to provide a comprehensive clinical evaluation of the efficacy of LBBP-CRT and confirm the validity of the improved electromechanical resynchronization and clinical outcomes in comparison to BiVP-CRT.

## MATERIALS AND METHODS

This systematic review and meta-analysis were conducted in accordance with the established methods recommended by the PRISMA, Cochrane, and AMSTAR-2 guidelines[10-12].

### Data source and search strategy

An extensive literature search was conducted using MEDLINE (PubMed), Cochrane Library, and Scopus from inception through October 2022 to identify relevant studies evaluating the clinical and echocardiographic metrics between LBBP-CRT vs BiVP-CRT among HF patients with LBBB. We applied Boolean Operators 'OR' and 'AND' among synonymous

and different Medical subject headings terms and keywords, including 'left bundle branch pacing' OR 'left bundle branch area pacing' AND 'left bundle branch block' AND 'heart failure'. We placed no restrictions based on time, language, year, or geographical location/country of publication. We further manually searched reference lists of retrieved original publications, review articles, editorials, and online databases comprising Clinicaltrials.gov and preprints *via* MedRx.org to identify any grey literature.

### Study selection and eligibility criteria

All the articles that were retrieved after the systematic search were exported to Endnote Reference Manager (Version X4; Clarivate Analytics, Philadelphia, PA, United States), where duplicates were identified and removed. Two independent reviewers (Moeed A and Raheel H) carefully examined the articles initially by title and abstract and then by full text to ensure relevance, and any disagreement was resolved through mutual consensus with the involvement of the senior investigator (Yasmin F). Articles with the following inclusion criteria were added to the review: (1) HF patients with LBBB; (2) comparative studies between LBBP and BVP; (3) studies reporting at least one of the outcomes of interest; and (4) retrospective or prospective cohort and RCT's.

### Data extraction and study quality assessment

Two investigators (Moeed A and Raheel H) independently extracted data from shortlisted studies using pre-specified collection forms. All data related to the population and study characteristics were collected in addition to the outcomes of interest. The primary outcome of interest was QRSd. Secondary outcomes included pacing threshold, New York Heart Association (NYHA) classification, B-type natriuretic peptide (BNP) level, and echocardiographic parameters, including LVEF, left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD). The quality assessment of the observational studies was performed using the Newcastle-Ottawa scale[13], based on the pre-specified criterion of comparability, selection, and outcome or exposure of included studies, while Cochrane Collaboration's risk of bias tool for randomized controlled trials[14] was used to assess the quality of the RCT.

### Statistical analysis

Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was utilized for all statistical analyses. A random-effects model was employed, and the effect size was pooled as mean differences (MD) with corresponding 95% confidence intervals (95% CIs). Heterogeneity across studies was evaluated using Higgins  $I^2$  statistics ( $I^2 = 25\%$ -50% was considered mild, 50%-75% moderate, and  $> 75\%$  severe heterogeneity)[15]. Sensitivity analysis was performed in which outlier studies having disproportionate effects on the overall effect size were excluded to address critical heterogeneity. A publication bias assessment could not be conducted as there were less than ten studies included in the meta-analysis as per the Cochrane guidelines[12]. A  $P < 0.05$  was considered statistically significant in all cases.

## RESULTS

### Study characteristics

A preliminary search of the electronic databases yielded a total of 790 results. Applying the aforementioned eligibility criteria, 6 studies were included in the review[8,7,16-19]. A detailed description of the complete search strategy applied for each database is given in [Supplementary Table 1](#), and the PRISMA flow chart summarizing the search and study selection process is given in [Figure 1](#). A total of 6 studies (1 RCT and 5 comparative observational studies) with 389 participants (159 in LBBP-CRT vs 230 in BiVP-CRT) across 12 centers were included with a median follow-up of 9 mo (IQR 6-12.6)[8,7,16-19]. The LBBP-CRT success rate was 91.1%. Overall, 50.3% of the population constituted of males, and the mean age was  $64 \pm 4$  years. Detailed study and patient characteristics are given in [Table 1](#).

### Primary outcome

All articles reported QRSd as an outcome. QRSd was significantly decreased with LBBP-CRT vs BiVP-CRT (LBBP-CRT mean 115.4 vs BiVP-CRT mean 138.0; MD = -22.65, 95% CI: -30.87 to -14.44,  $P < 0.00001$ ,  $I^2 = 88\%$ ) ([Figure 2](#)).

### Secondary outcomes and sensitivity analysis

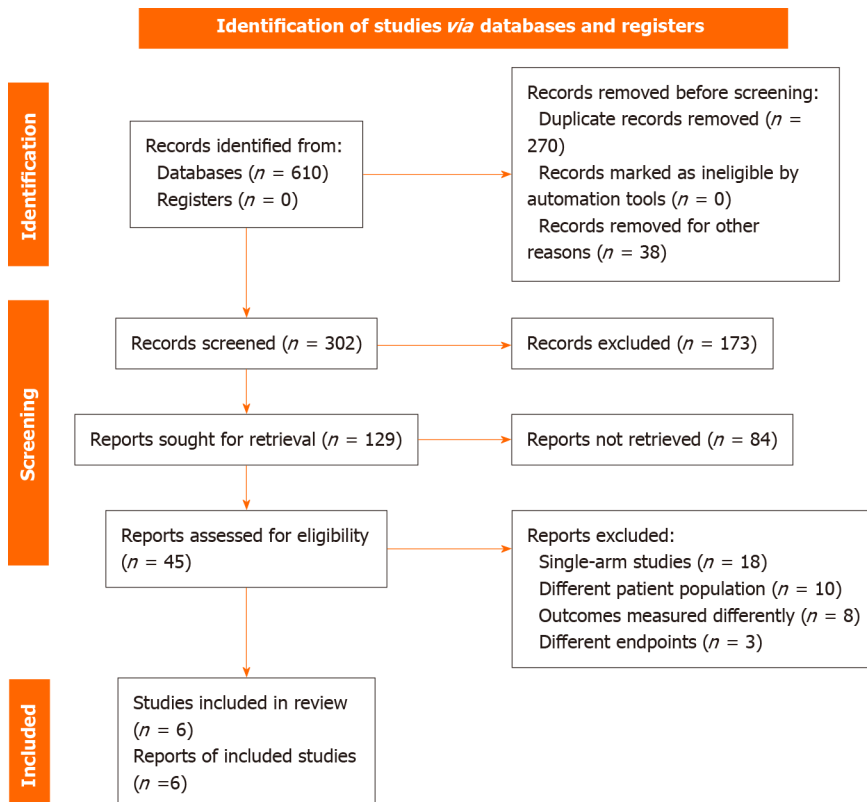
Pacing threshold was also significantly lower in LBBP-CRT group compared to BiVP-CRT (LBBP-CRT mean 0.69 vs BiVP-CRT mean 1.24; MD = -0.56, 95% CI: -0.69 to 0.43,  $P < 0.00001$ ,  $I^2 = 59\%$ ) ([Figure 3](#)). LBBP-CRT resulted in significantly increased LVEF (LBBP-CRT mean 43.8 vs BiVP-CRT mean 37.6; MD = 6.73, 95% CI: 4.48 to 8.97,  $P < 0.00001$ ,  $I^2 = 0\%$ ), significantly decreased LVEDD (LBBP-CRT mean 55.9 vs BiVP-CRT mean 60.6; MD = -5.12, 95% CI: -7.21 to -3.03,  $P < 0.00001$ ,  $I^2 = 5\%$ ), and reduced LVESD (LBBP-CRT mean 42.0 vs BiVP-CRT mean 47.3; MD = -5.57, 95% CI: -8.80 to -2.35,  $P < 0.00007$ ,  $I^2 = 0\%$ ) compared to BiVP-CRT (Figures 4-6). The pooled analysis showed a significant decrease in NYHA class in LBBP-CRT vs BiVP-CRT patients (LBBP-CRT mean 1.3 vs BiVP-CRT mean 1.8; MD = -0.47, 95% CI: -0.73 to -0.21,  $P < 0.00003$ ,  $I^2 = 65\%$ ) ([Figure 7](#)). LBBP-CRT showed a statistically significant decrease in BNP concentration on follow-up compared to BiVP-CRT (LBBP-CRT mean 311.3 vs BiVP-CRT mean 1145.3; SMD = -0.66, 95% CI: -0.96 to -0.35,  $P < 0.00001$ ,  $I^2 = 0\%$ ) ([Figure 8](#)).

We additionally performed a series of sensitivity analysis to determine if any outlier study had disproportionate effects on the pooled estimates for the outcomes of QRSd, pacing threshold, and NYHA class. We found no change in the

**Table 1** General characteristics of the included studies

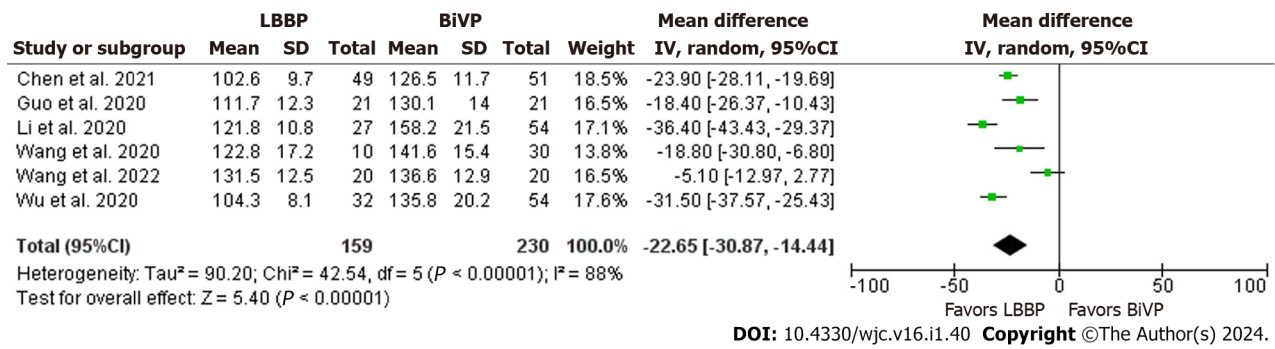
Ref.	Area	Centre	Study design	Number of participants in LBBP	Number of participants in BiVP	Patients	Male sex in LBBP (%)	Age (yr) in LBBP	Success rate in LBBP (%)	Follow up (mo)	ICM (%) in LBBP
Wang <i>et al</i> [16], 2020	China	1	Matched case-control	10	30	HF, LBBB	90.0	64.8 ± 7.1	100.0	6.0	10
Guo <i>et al</i> [17], 2020	China	1	Prospective observational	21	21	HF, LBBB	42.9	66.1 ± 9.7	87.5	14.3	9.5
Wu <i>et al</i> [18], 2021	China	1	Prospective non-randomized	32	54	HF, LBBB	43.8	67.2 ± 13	100.0	12.0	3.1
Li <i>et al</i> [19], 2020	China	3	Prospective observational	27	54	HF, LBBB	58.1	56.8 ± 10.1	81.1	6.0	18.9
Chen <i>et al</i> [8], 2022	China	4	Prospective observational	49	51	HF, LBBB	50.0	67.1 ± 8.9	91.1	12.0	0
Wang <i>et al</i> [7], 2022	China	2	Randomized controlled trial	20	20	HF, LBBB	35.0	62.3 ± 11.2	90.0	6.0	0

LBBP: Left bundle branch pacing; BiVP: Biventricular pacing; ICM: Implantable Cardiac Monitor; HF: Heart failure; LBBB: Left bundle branch block.

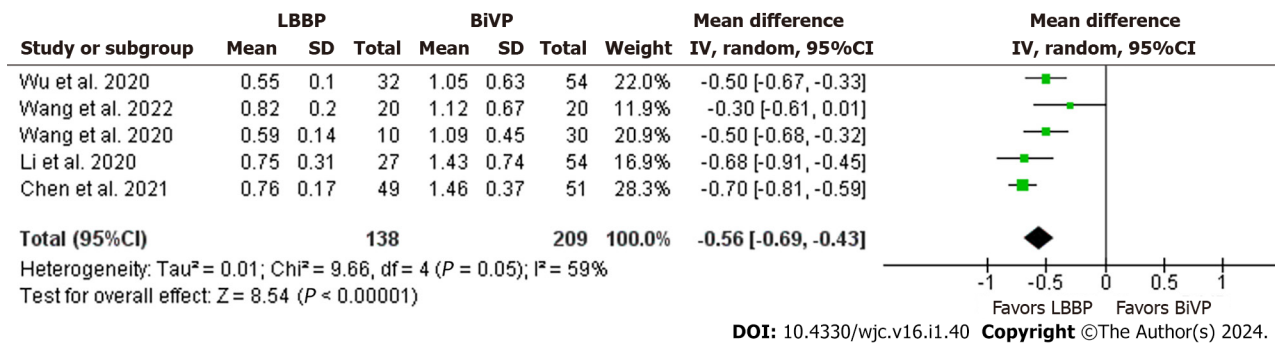


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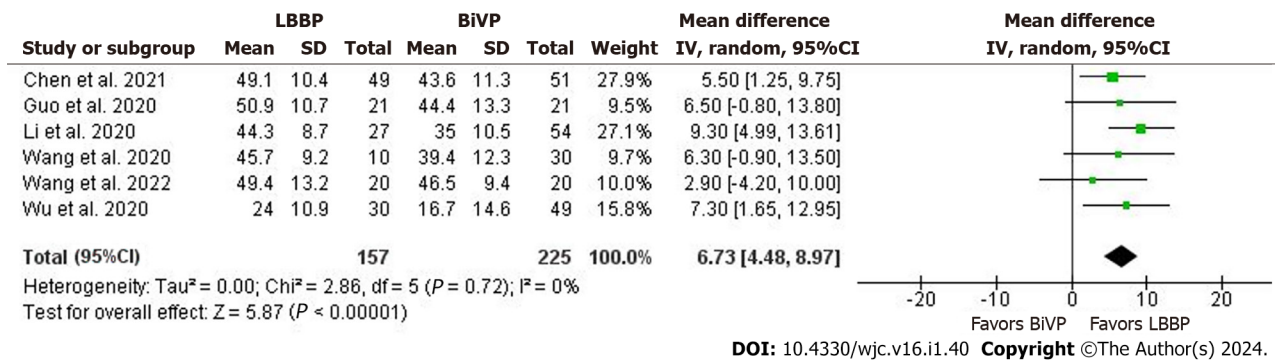
**Figure 1** PRISMA flowchart.



**Figure 2** Forest plot comparing paced QRS duration between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.



**Figure 3** Forest plot comparing pacing threshold at follow-up between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.



**Figure 4** Forest plot comparing paced left ventricular ejection fraction between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

significance of the pooled results (Supplementary Figures 1-3).

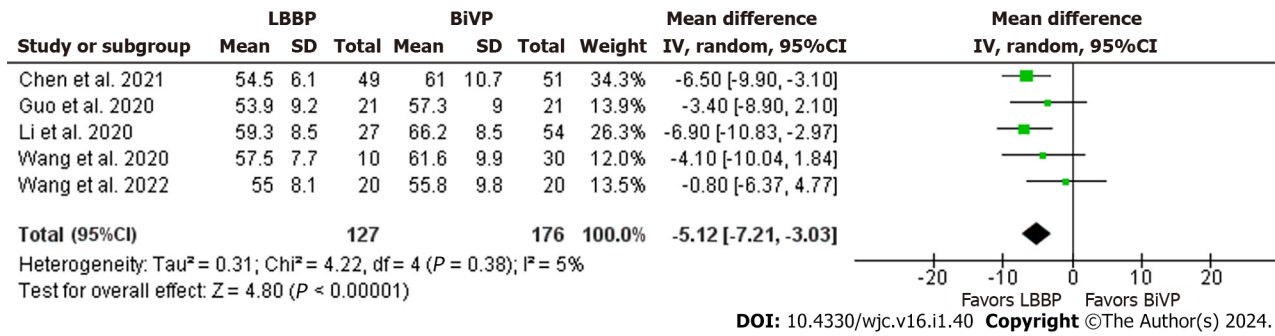
**Quality assessment**

Owing to the robust methodology, most cohort studies were categorized as moderate to high quality on the NOS assessment tool. Wang *et al*[7] 2022 study was the only clinical trial included in the review, which was assessed through Cochrane risk of bias. All domains had a low risk of bias except the deviation from the intended interventions domain. The results of the quality assessment are mentioned in Supplementary Tables 2 and 3. The PRISMA and AMSTAR checklists have been included in Supplementary Tables 4 and 5.

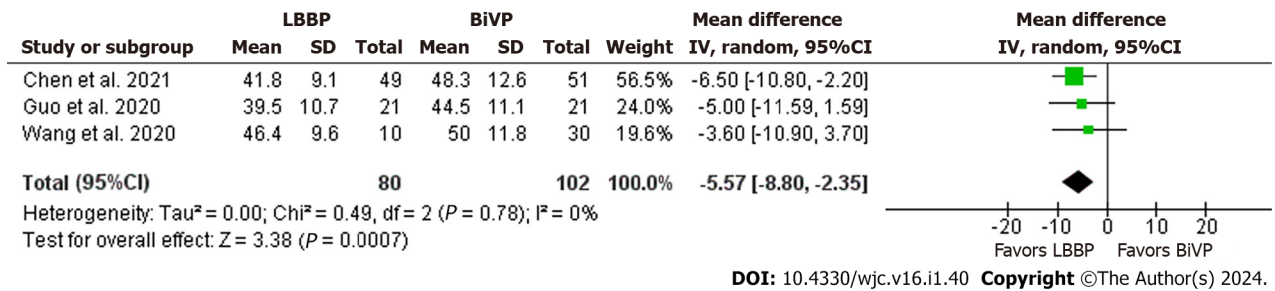
**DISCUSSION**

In comparison to BiVP-CRT, LBBP-CRT was demonstrated to be safe and effective in enhancing LVEF with a low and consistent threshold. A smaller QRSd has been linked to improved mechanical synchronization of the ventricle[20]. Thus,

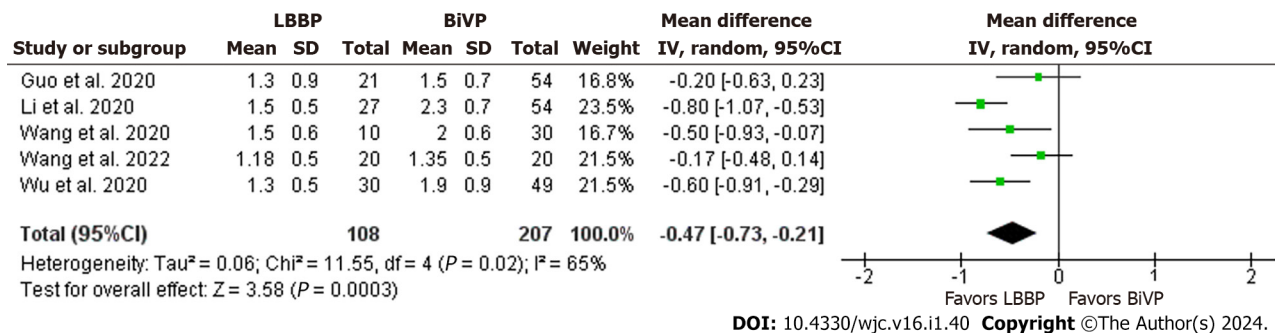




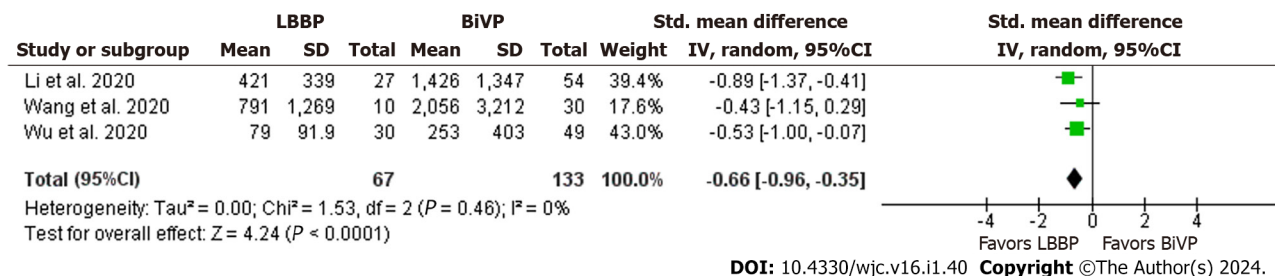
**Figure 5 Forest plot comparing paced left ventricular end-diastolic diameter between left bundle branch pacing and biventricular pacing groups.** 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.



**Figure 6 Forest plot comparing paced left ventricular end-systolic diameter between left bundle branch pacing and biventricular pacing groups.** 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.



**Figure 7 Forest plot comparing New York Heart Association classification between left bundle branch pacing and biventricular pacing groups.** 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.



**Figure 8 Forest plot comparing B-type natriuretic peptide levels between left bundle branch pacing and biventricular pacing groups.** 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

our meta-analysis revealed that CRT provided more effective electrical and mechanical resynchronization *via* LBBP. Our study analyzed the pacing threshold at the time of implant and the pacing threshold at the time of follow-up. Five studies included in our analysis reported that the pacing threshold in LBBP-CRT was much lower than in BiVP-CRT. This is consistent with previous studies in which the pacing threshold at implant was lower in LBBP-CRT *vs* BiVP-CRT, and remained considerably lower in LBBP-CRT at 6-months and 1-year follow-up[8]. All six of our studies reported LVEF data. When compared to BiVP-CRT, LBBP-CRT dramatically raised LVEF. This is consistent with earlier studies in which patients in the LBBP-CRT group had significantly greater LVEF at 6-month follow-up than patients in the BiVP-CRT group[8], and a recent study by Vijayaraman *et al*[21] found a greater increase in LVEF with LBBP. In our analysis, five studies reported a substantial reduction in LVEDD with LBBP-CRT compared to BiVP-CRT. This is consistent with prior research, including a report by Huang *et al*[6], who first described LBBB and dilated cardiomyopathy in a 72-year-old lady with HF treated with LBBP.

They employed a low-pacing output to rectify the LBBB on the electrocardiogram, which RBBB accompanied. At one year, they discovered that LVEDD decreased to 42 mm from a baseline 76 mm[6].

Three studies reported on follow-up LVESD, which was much lower in LBBP-CRT patients compared to BiVP-CRT, which is consistent with earlier research in which LVESD was also significantly lower[22,23]. Furthermore, three studies reported increased BNP levels to have a strong clinical and hemodynamic correlation with the degree of left ventricular dysfunction. Our study demonstrated that LBBP-CRT patients had a statistically significant lower BNP concentration on follow-up than BiVP-CRT patients. Similar prior studies, such as Huang *et al*[6], reported a decrease in the BNP concentration from baseline. Moreover, NYHA classification was assessed when patients were followed up, and five studies revealed a substantial drop-in NYHA class in LBBP-CRT patients compared to BiVP-CRT patients. This is consistent with previous studies, which have shown that in comparison to BiVP-CRT, LBBP-CRT may reduce NYHA class[9].

### Limitations

This meta-analysis has some limitations. All of the studies included in the quantitative synthesis were conducted in China. Thus, the results may not be applicable to a more diverse population. The median follow-up time of the included studies was 9 mo, serving as a limitation in judging the long-term efficacy of either of the two pacing methods. Although we included the first and only RCT published in the literature in our analysis, the majority of our pooled comparative studies were observational with small to moderate sample sizes. This could have introduced significant heterogeneity, however, to mitigate this compromise, we chose a random-effects methodology for our analysis. Thus, to ascertain the benefit of LBBP or BiVP in LBBB patients, it is imperative to conduct large-scale RCTs to solidify which pacing method is more appropriate in HF patients.

## CONCLUSION

To conclude, our meta-analysis provided further clarity regarding the benefits of the novel LBBP-CRT in improving LVEF, cardiac echocardiographic parameters, and clinical outcomes when compared to BiVP-CRT.

## ARTICLE HIGHLIGHTS

### Research background

Biventricular pacing (BiVP) is the conventional mode of cardiac resynchronization therapy (CRT) for left bundle branch block (LBBB) with heart failure (HF), and shows significantly improved patient mortality. However, approximately one-third of the patients fail to respond to it. Left bundle branch pacing (LBBP) has gained increasing attention recently as an effective mode of CRT showing complete reversal of LBBB among HF patients.

### Research motivation

Several clinical studies evaluating the efficacy of LBBP-CRT in improving electromechanical resynchronization, clinical, and echocardiographic response in comparison to BiVP-CRT among patients with reduced left ventricular ejection fraction (LVEF), LBBP, and HF have been published but the results remain inconclusive. Hence, we performed an updated analysis pooling the recent clinical data to provide a comprehensive clinical evaluation of the efficacy of LBBP-CRT and confirm the validity of the improved electromechanical resynchronization and clinical outcomes in comparison to BiVP-CRT.

### Research objectives

The primary outcome of interest was QRS duration. Secondary outcomes included pacing threshold, New York Heart Association (NYHA) classification, B-type natriuretic peptide (BNP) level, and echocardiographic parameters, including LVEF, left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD).

### Research methods

An extensive literature search was conducted using MEDLINE (PubMed), Cochrane Library, and Scopus from inception through October 2022 to identify relevant studies evaluating the clinical and echocardiographic metrics between LBBP-

CRT *vs* BiVP-CRT among HF patients with LBBB. A random-effects model was employed, and the effect size was pooled as mean differences with corresponding 95% confidence intervals. A  $P < 0.05$  was considered statistically significant in all cases.

### Research results

The success rate of LBBP-CRT was observed to be 91.1% in our analysis. LBBP-CRT resulted in increased LVEF, reduction in LVEDD, and LVESD compared to BiVP-CRT. Significantly reduced BNP levels, and NYHA class was also noted in the LBBP-CRT group *vs* BiVP-CRT group. Lastly, the LBBP-CRT cohort had a reduced pacing threshold at follow-up as compared to BiVP-CRT.

### Research conclusions

Our analysis compared success rate, echocardiographic parameters and clinical response between LBBP-CRT *vs* BiVP-CRT and demonstrated LBBP-CRT to result in significantly improved cardiac echocardiographic parameters, and clinical outcomes when compared to BiVP-CRT.

### Research perspectives

LBBP-CRT resulting in significant improvement in the echocardiographic parameters and clinical outcomes can help shape the clinical practice. Further larger randomized control trials are needed.

## FOOTNOTES

**Author contributions:** Yasmin F, Moeed A, Ochani RK participated in the conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing of the original draft; Raheel H, Awan MAE, Liaquat A, Saleem A were involved in project administration, and writing of the original draft; Yasmin F, Moeed A, Aamir M, Hawwa N, and Surani S were involved in the formal analysis, project administration, supervision, validation, visualization, and writing - review & editing.

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