Postprint of a Study on Echocardiographic Outcome Measures in Randomized Controlled Trials of Heart Failure with Preserved Ejection Fraction

Authors: Liu Yongcheng, Liu Siyu, Liang Xiaoyu, Hao Xiaopeng, Wei Yue, Dong Guoju, Dong Guoju

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Abstract

Background The selection of echocardiographic outcome measures for heart failure with preserved ejection fraction (HFpEF) lacks unified standards. Objective To analyze echocardiographic outcome measures in HFpEF randomized controlled trials (RCTs) and provide reference for constructing a standardized efficacy evaluation system for HFpEF. Methods PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases were searched for HFpEF-related RCTs from January 1, 2021 to November 3, 2023. After screening literature according to inclusion and exclusion criteria, information including echocardiographic outcome measures was extracted. Frequencies and rates of echocardiographic outcome measures were statistically analyzed, and association rule analysis was performed. Results A total of 825 articles were retrieved, and 14 articles were ultimately included after screening. The 14 articles used 39 echocardiographic outcome measures in total, with individual studies using a minimum of 2 and a maximum of 18 measures. The top 10 most frequently used indicators were early mitral inflow velocity (E)/late mitral inflow velocity (A), left ventricular ejection fraction (LVEF), mean E/early diastolic mitral annular velocity (e'), left atrial volume index (LAVI), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), septal E/e' , left ventricular mass index (LVMI), E-wave deceleration time (EDT), and tricuspid annular plane systolic excursion (TAPSE). Association rule analysis showed that the rules with highest conditional support for different numbers of indicator combinations were mean E/e' →LAVI, LVEF+E/A→LVEDD, and LAVI+mean E/e' +LVEF→LVEDD, respectively. Conclusion Commonly used echocardiographic outcome measures in HFpEF RCTs include E/A, LVEF, and mean E/e' , with LAVI and LVEDD often used in combination with the above indicators. The selection of echocardiographic outcome measures in HFpEF RCTs suffers from issues of inconsistency, irrationality, lack of consensus, and non-standardization;

establishing a core outcome set may be an effective approach to address these problems.

Full Text

Analysis of Echocardiographic Outcome Measures in Randomized Controlled Trials in Heart Failure with Preserved Ejection Fraction

LIU Yongcheng[12], LIU Siyu[12], LIANG Xiaoyu[2], HAO Xiaopeng[2], WEI Yue[12], DONG Guoju[13]*

[1]Cardiovascular Department, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing 100091, China
[2]Graduate School, China Academy of Chinese Medical Sciences, Beijing 100007, China
[3]National Clinical Research Center for Cardiovascular Diseases of Traditional Chinese Medicine, Beijing 100091, China

Corresponding author: DONG Guoju, Chief physician/Doctoral supervisor; E-mail: 13691393589@163.com

Abstract

Background The selection of echocardiographic indexes for efficacy evaluation of heart failure with preserved ejection fraction (HFpEF) lacks a uniform standard. **Objective** Analyze the echocardiographic outcome measures in randomized controlled trials (RCT) of HFpEF to provide a reference for the development of a standardized efficacy evaluation system for HFpEF. **Methods** PubMed, Embase and Cochrane Central Register of Controlled Trials were searched for RCTs related to HFpEF from January 1, 2021 to November 3, 2023. Echocardiographic outcome measures and other information were extracted after literature screening according to eligibility criteria. The frequency and percentage of echocardiographic outcome measures were analyzed and an association rule analysis was conducted. **Results** A total of 825 literatures were obtained and 14 literatures were finally included after screening. A total of 39 echocardiographic outcome measures were used in 14 studies. The minimum number of echocardiographic outcome measures used in a single study was 2, and the maximum was 18. The top 10 echocardiographic outcome measures in terms of usage frequency were ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A), left ventricular ejection fraction (LVEF), average ratio of E to early diastolic mitral annular velocity (e'), left atrial volume index (LAVI), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), septal E/e' , left ventricular mass index (LVMI), E deceleration time (EDT) and tricuspid annular plane systolic excursion (TAPSE). The association rule analysis showed that when different quantitative indicators were combined, the rules with the highest support were respectively average E/e'

→ LAVI, LVEF+E/A → LVEDD and LAVI+average E/e' +LVEF → LVEDD. **Conclusion** In HFpEF RCTs, the commonly used echocardiographic outcome measures are E/A, LVEF, and average E/e' . Moreover, LAVI and LVEDD are often used in combination with the above indicators. Lack of consistency, rationality, recognition and standardization are the problems of echocardiographic outcome measures selection in HFpEF RCTs. The development of a core outcome set may be an effective way to solve the above problems.

Key words Heart failure; Heart failure with preserved ejection fraction; Randomized controlled trial; Clinical research; Echocardiography; Outcome measure

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Heart failure with preserved ejection fraction (HFpEF) is the main type of heart failure, accounting for approximately half of all heart failure patients [1-2]. Its incidence and prevalence continue to grow [3], accompanied by high mortality rates [4], making it a significant global public health concern. HFpEF patients typically exhibit multiple cardiac functional or structural abnormalities, including left ventricular diastolic dysfunction, mildly reduced left ventricular systolic function, chronotropic incompetence, atrial enlargement and dysfunction, and hemodynamic changes [5]. Compared with other examination methods, echocardiography offers advantages of convenience, low cost, and non-invasiveness, and has remained the primary means of evaluating cardiac structure and function for decades. However, the selection of echocardiographic efficacy evaluation indicators for HFpEF lacks a unified standard, leading to numerous problems in the application of echocardiographic outcome measures in clinical trials. These issues not only severely reduce the quality of evidence generation but also make it difficult for clinicians to compare and pool findings from similar studies, ultimately limiting evidence-based clinical decision-making.

This study employs a systematic review approach to retrieve HFpEF randomized controlled trials (RCTs) published internationally in the past three years, analyzing the current status and existing problems in the application of echocardiographic outcome measures to provide a reference for their standardized application in future studies and the construction of a standardized clinical efficacy evaluation system based on a core outcome set (COS).

1.1 Inclusion and Exclusion Criteria

Inclusion criteria: Studies with HFpEF patients who met the diagnostic criteria for HFpEF in the "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure" [6]; study type was RCT; outcome measures included echocardiography-related indicators.

Exclusion criteria: Literature for which full text could not be obtained; duplicate publications; non-Chinese or non-English literature.

1.2 Search Strategy

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for RCTs related to HFpEF from January 1, 2021 to November 3, 2023. A search strategy combining subject headings and free text was adopted, with search terms including "Heart Failure, Diastolic," "Diastolic Heart Failure," "Heart Failure With Preserved Ejection Fraction," "Heart Failure And Preserved Ejection Fraction," "Heart Failure With Normal Ejection Fraction," "Heart Failure And Normal Ejection Fraction," "randomized," "controlled clinical trial," "placebo," "randomly," etc.

1.3 Literature Screening

Retrieved literature was imported into NoteExpress reference management software. Duplicate literature was removed using a combination of the software' s automatic deduplication function and manual deduplication. After removing duplicates, two researchers independently screened the literature according to the inclusion and exclusion criteria: first, reading titles and abstracts to exclude literature that clearly did not meet the criteria; second, reading the full text of remaining literature for further screening, attempting to contact authors by email when full text could not be downloaded or information was incomplete; finally, two researchers cross-checked their selections, resolving disagreements through discussion or consultation with a third, more experienced researcher when necessary.

1.5 Data Extraction and Bias Risk Assessment

Two researchers independently extracted data using a pre-designed data extraction form, followed by cross-checking. Extracted data included: basic literature information (title, first author, publication year), information related to bias risk assessment, sample size, patient characteristics (age, sex, cardiac function classification, etc.), intervention measures and treatment duration, and echocardiographic indicators.

According to the Cochrane risk of bias assessment tool, each included study was evaluated for seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other biases, with each aspect rated as "low risk," "high risk," or "unclear" [7].

2.1 Literature Screening Process

A total of 825 articles were retrieved, including 93 from PubMed, 282 from Embase, and 450 from the Cochrane Central Register of Controlled Trials. After removing 353 duplicate articles, 472 articles remained. Reading titles and abstracts excluded 413 articles, leaving 59 articles for full-text review. Full-text reading excluded 45 articles, ultimately leaving 14 articles included in this study.

The literature screening process is shown in Figure 1 [Figure 1: see original paper].

2.3 Bias Risk Assessment Results

Random sequence generation: 12 studies were rated as "low risk," 1 study as "high risk," and 1 study as "unclear risk." **Allocation concealment:** 6 studies were rated as "low risk" and 8 studies as "unclear risk." **Blinding of participants and personnel:** 5 studies were rated as "low risk" and 9 studies as "unclear risk." **Blinding of outcome assessors:** 7 studies were rated as "low risk,"2 studies as "high risk,"and 5 studies as "unclear risk."**Completeness of outcome data:** 12 studies were rated as "low risk" and 2 studies as "high risk." **Selective reporting:** 10 studies were rated as "low risk" and 4 studies as "unclear risk." **Other biases:** 2 studies were rated as "high risk" and 12 studies as "unclear risk." The bias risk assessment results are shown in Figure 2 [Figure 2: see original paper] and Figure 3 [Figure 3: see original paper].

The 14 included RCTs were conducted in 11 countries, with 6 studies in East Asia, 4 in Europe, 2 in North America, 1 in Oceania, and 1 in West Asia. Eight studies were single-center, 2 were dual-center, 3 were multi-center, and 1 did not specify. The 14 RCTs included a total of 1,192 HFpEF patients (473 male, 719 female). Patients' NYHA cardiac function classification ranged from I to IV, with 8 studies including Class II and III patients, 2 studies including Class II-IV patients, 1 study including Class I-II patients, 1 study including Class I-IV patients, and 2 studies not specifying cardiac function classification. Intervention measures included Western medicine, Chinese herbal formulas, lifestyle modification, and interventional therapy, with treatment durations ranging from 2 weeks to 12 months (see Table 1).

2.4.3 Association Rule Analysis

The 14 studies involved a total of 39 echocardiographic indicators, with cumulative usage of 107 times. The minimum number of echocardiographic outcome measures used in a single study was 2, and the maximum was 18 (see Table 2).

Among the 39 echocardiographic outcome measures, the highest usage frequency was 10 times and the lowest was 1 time. The top 10 indicators by usage frequency were E/A, LVEF, average E/e' , LAVI, LVEDD, LAD, septal E/e' , LVMI, EDT, and TAPSE (see Table 3).

Association rule analysis of the 39 echocardiographic outcome measures yielded 24 association rules, with conditional support ranging from 28.6% to 50%, rule confidence from 71.4% to 100%, and lift from 1.1% to 3.5%. Sorted by conditional support, the rules with highest support for different numbers of indicator combinations were average E/e' → LAVI, LVEF+E/A → LVEDD, and LAVI+average E/e' +LVEF → LVEDD (see Table 4). The association rule network for echocardiographic indicators with usage frequency $ $3 is shown in Figure 4 [Figure 4: see original paper].

3.1 Importance of Echocardiography in HFpEF Assessment

Invasive hemodynamic examination, while the gold standard for assessing left ventricular filling pressure, has significant limitations in clinical application due to its difficulty, high cost, and invasive nature. Echocardiography has become the most commonly used method for evaluating cardiac structure and function in heart failure patients due to its wide availability, lack of ionizing radiation, ability to provide extensive diagnostic and prognostic information, and high consistency with invasive hemodynamic examination. Research indicates that multiple echocardiographic indicators have predictive value for long-term prognosis in HFpEF patients [22]. However, the current lack of standardized selection criteria for echocardiographic assessment indicators in HFpEF creates numerous problems in their application in related clinical research.

3.2 Problems with Echocardiographic Outcome Measures in HFpEF RCTs

This study systematically searched HFpEF RCTs published internationally in the past three years, finally including 14 eligible articles. Analysis of the echocardiographic outcome measures revealed problems of inconsistency, irrationality, lack of recognition, and non-standardization in the application of echocardiographic outcome measures in current HFpEF RCTs.

The 14 articles involved 39 echocardiographic indicators, with single studies using between 2 and 18 outcome measures, showing substantial variation in both type and number of indicators across studies. Heterogeneity of outcome measures in similar studies is a common problem in clinical research that makes it difficult to compare findings or pool data in systematic reviews/meta-analyses, reducing research value and evidence quality and wasting research resources [23-24].

3.2.2 Unreasonable Number of Echocardiographic Indicators Outcome measures are defined as the content being evaluated to examine the effects of interventions [25]. Selecting appropriate outcome measures is crucial for measuring and evaluating the true effects of interventions. Different outcome measures may lead to completely different conclusions about the same intervention [26]. Researchers should also pay attention to the number of outcome measures—too few may compromise efficacy assessment, while too many may produce misleading results [27]. HFpEF involves pathological changes in multiple aspects including cardiac diastolic function, systolic function, and structure [28], making accurate and comprehensive assessment difficult with just a few echocardiographic indicators. To avoid the limitations of single indicators, current guidelines recommend using multiple indicators in combination [29]. This study found that some literature used too few echocardiographic outcome measures to comprehensively evaluate improvements in various pathological aspects after intervention, reducing credibility of results. Conversely, some literature

selected overly redundant echocardiographic indicators with overlapping functions, increasing research burden and waste.

3.2.3 Unrecognized and Non-standardized Echocardiographic Indicators Although there is currently no unified standard for using echocardiography to evaluate HFpEF, multiple authoritative guidelines and consensus statements have provided recommendations. For example, the 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging recommended using four indicators—average E/e' , septal e' or lateral e' , TRV, and LAVI—to assess diastolic function in patients with normal ejection fraction [30]. The 2019 Heart Failure Association of the European Society of Cardiology proposed the HFA-PEFF diagnostic algorithm [31], which was also introduced in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [6], including echocardiographic indicators such as average E/e' , septal e' , lateral e' , TRV, left ventricular global longitudinal strain, LAVI, LVMI, RWT, and left ventricular wall thickness.

Among the included literature, some frequently used indicators lacked sufficient recognition. For example, E/A had the highest usage frequency but was not recommended by the above guidelines, due to its limitations including pseudonormalization, significant age effects, and inapplicability to patients with atrial fibrillation/flutter. Conversely, indicators recommended by guidelines had low usage frequencies, such as septal e' , lateral e' , and TRV. Additionally, there was confusion in using similar indicators like average E/e' versus septal (or lateral) E/e' , LAVI versus LAV, and LVMI versus LVM. These issues of unrecognized and non-standardized efficacy evaluation indicators reduce the credibility of research results.

3.3 COS as a Solution to HFpEF Echocardiographic Outcome Measure Problems

A Core Outcome Set (COS) is a standardized collection of outcome measures that should be measured and reported in all clinical trials in a specific field [32]. Developing a COS helps reduce heterogeneity of outcome measures in similar clinical studies, enabling comparison and pooling of results, standardizing outcome measure application, and integrating multidisciplinary expertise to select more scientifically sound indicators, thereby improving research quality [23,33]. This study summarized echocardiographic outcome measures in HFpEF RCTs published internationally in the past three years, initially establishing an indicator pool. Frequency analysis showed that three indicators—E/A, LVEF, and average E/e' —were most commonly used, each with frequency $ $50%.

The HFpEF efficacy evaluation clinical trial COS development led by our research team (registered protocol: https://www.comet-initiative.org/Studies/Details/3142) is currently in press. Through Delphi surveys and expert consensus meetings, a COS containing 6 items (belonging to 3 domains: symptoms and signs, physical and chemical tests, and quality of life) was developed for HFpEF

efficacy evaluation. The echocardiography component included "LVEF" and "average E/e' or E/A (with priority given to average E/e')." LVEF is a key indicator related to whether the HFpEF diagnosis remains valid, and its value and changes are of great significance for heart failure classification and efficacy evaluation [34]. Both average E/e' and E/A assess left ventricular diastolic function, but current guidelines [6,35] favor the former, so reporting average E/e' is recommended, with E/A as an alternative when average E/e' cannot be measured due to practical limitations. In this study, indicators such as LAVI and LVEDD also had relatively high usage frequencies, and association rule analysis showed certain correlations with the above COS indicators. However, considering factors such as Delphi scores, measurement requirements, intervention periods for detectable changes, they were not included in the COS but may be selected as complementary measures in future studies reporting the HFpEF efficacy evaluation COS.

In summary, this study analyzed echocardiographic outcome measures in HFpEF RCTs published internationally in the past three years and identified problems of inconsistency, irrationality, lack of recognition, and non-standardization. Developing an HFpEF echocardiographic COS may be an effective solution to these problems. This study did not analyze measurement methods or time points, representing a certain limitation.

Author Contributions: LIU Yongcheng was responsible for designing the research protocol, implementing the research process, performing statistical analysis, creating figures and tables, and writing the article; LIU Siyu and LIANG Xiaoyu were responsible for literature screening and data extraction; HAO Xiaopeng and WEI Yue were responsible for literature retrieval; DONG Guoju proposed the research idea, supervised the research process, and was responsible for quality control and review of the article.

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Note: Figure translations are in progress. See original paper for figures.