Am J Transl Res 2025;17(9):7426-7437
www.ajtr.org /ISSN:1943-8141/AJTR0166705

Original Article

Analysis of dapagliflozin combination therapy in heart failure with reduced ejection fraction and its correlation with inflammatory markers

Li'na Zhang[1], Weixin Dai[1], Shuai Zhang[2], Qingbo Li[3]

[1]Department of Cardiology, Jilin Province FAW General Hospital, Changchun 130013, Jilin, China; [2]Department of Endocrine and Metabolic Diseases, Jilin Province FAW General Hospital, Changchun 130013, Jilin, China; [3]Department of Clinical Pharmacy, Jilin Province FAW General Hospital, Changchun 130013, Jilin, China

Received June 11, 2025; Accepted September 8, 2025; Epub September 15, 2025; Published September 30, 2025

Abstract: Objective: To investigate the effects of the sodium-glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin on myocardial function, inflammatory markers, and cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Methods: A retrospective analysis was conducted on 107 hospitalized patients with HFrEF treated at our hospital between November 2022 and October 2024. Based on the treatment regimen, patients were divided into a control group (n = 52), which received standard therapy [diuretics, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and aldosterone antagonists], or into a dapagliflozin group (n = 55), which received dapagliflozin in addition to standard therapy. Outcomes assessed included: clinical efficacy; cardiac function [left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF)]; myocardial work indices [global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE)]; energy metabolism [free fatty acids (FFA) and β-hydroxybutyric acid (β-HB)], inflammatory markers [interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and IL-10]; quality of life, and the incidence of cardiovascular and other adverse reactions. Results: The dapagliflozin group achieved a significantly higher overall clinical efficacy rate than the control group (94.55% vs. 80.77%; $P < 0.05$). After 8 weeks of treatment, patients receiving dapagliflozin in addition to standard therapy showed significantly greater improvements in multiple cardiac function parameters compared to those receiving standard therapy alone ($P < 0.05$). GWI, GCW, and GWE were significantly higher, and GWW significantly lower, in the dapagliflozin group ($P < 0.05$). Indicators of energy metabolism were significantly higher in the dapagliflozin group ($P < 0.05$). Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) decreased, whereas the anti-inflammatory cytokine IL-10 increased more markedly in the dapagliflozin group compared to the control group ($P < 0.05$). After treatment, the dapagliflozin group showed greater improvements across multiple quality-of-life dimensions, and significantly lower incidence of cardiovascular adverse events (14.55% vs. 34.62%) ($P < 0.05$). The overall incidence of other adverse reactions did not differ significantly between groups ($P > 0.05$). Conclusion: In patients with HFrEF, the addition of dapagliflozin to standard therapy provides synergistic benefits in improving cardiac function, energy metabolism, and inflammatory status. These effects translate into improved quality of life and cardiovascular outcomes, highlighting dapagliflozin's clinical value in this population.

Keywords: Dapagliflozin, left ventricular function, chronic heart failure, energy metabolism, inflammatory biomarkers

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by symptoms such as dyspnea, cough, and fatigue, representing the advanced or end-stage of various cardiovascular diseases. Epidemiological data show that the prevalence of HF among individuals over 35 years of age in China is approximately 1.3%, with men accounting for nearly 60% of cases [1]. Clinically, HF is categorized according to left ventricular ejection fraction (LVEF) into three subtypes: heart failure with reduced ejection fraction (HFrEF), preserved ejection fraction

https://doi.org/10.62347/GXYF3086

(HFpEF), and mildly reduced ejection fraction (HFmrEF). Among these, HFrEF is the most prevalent and is associated with the poorest prognosis [2].

Current pharmacological management of HFrEF primarily targets neurohormonal regulation. Standard treatment strategies typically include agents that modulate the sympathetic nervous system activity, inhibit the renin-angiotensin system (RAS), and block aldosterone receptors, such as β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and aldosterone receptor antagonists. However, despite optimized standard therapy, a considerable proportion of patients continue to experience poor outcomes, and the long-term use of these therapies may be associated with cardiovascular adverse events [3]. Therefore, the identification of more effective treatments for HFrEF remains an urgent priority in clinical practice. In recent years, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been increasingly introduced into the management of cardiovascular diseases, demonstrating promising clinical potential. Dapagliflozin, a representative SGLT2 inhibitor, was originally approved for the treatment of type 2 diabetes mellitus, but its cardioprotective properties have been substantiated by multiple clinical trials [4]. Beyond its glucose-lowering effects, dapagliflozin may exert additional cardiovascular benefits by improving insulin sensitivity and attenuating inflammatory responses, thereby reducing the risk of disease recurrence and rehospitalization in patients with HF [5]. Emerging evidence further suggests that disease progression in HFrEF is influenced by factors such as myocardial work and inflammatory activity [6]. However, clinical data on the impact of dapagliflozin on myocardial work parameters and inflammatory cytokines in HFrEF patients remain limited. To address this gap, we conducted a retrospective analysis of recent clinical cases from our hospital to explore the impact of dapagliflozin on myocardial function, myocardial work indices, and inflammatory markers in HFrEF, with the aim of providing evidence to inform and optimize treatment strategies.

Materials and methods

General information

This retrospective cohort study analyzed electronic medical records of HF patients with HFrEF who were hospitalized in the Cardiology Department at our hospital between November 2023 and October 2024. Inclusion criteria were as follows: diagnosis of HFrEF meeting established diagnostic criteria [7]; aged between 50 and 80 years; complete medical records and compliance with study requirements; normal mental status and good treatment adherence; and New York Heart Association (NYHA) functional class II-IV. Exclusion criteria included: congenital heart disease; malignancy; type 1 diabetes mellitus; severe cardiovascular or cerebrovascular diseases; and use of medications within the past month that could affect cardiac function or inflammatory status, including other SGLT2 inhibitors (e.g., empagliflozin, canagliflozin), glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, semaglutide), thiazolidinediones (e.g., pioglitazone), glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or other agents known to significantly interfere with the evaluation of cardiac function or inflammatory biomarkers. A total of 127 HFrEF patients met the preliminary eligibility criteria. After excluding those with incomplete data (n = 12), severe hepatic or renal dysfunction (n = 5), or missing follow-up information (n = 3), 107 patients were included in the final analysis. Based on discharge prescriptions and medication records, patients were divided into either a conventional treatment group (n = 52) or a dapagliflozin combination therapy group (n = 55). This study was approved by the Ethics Committee of Jilin Province FAW General Hospital and conducted in accordance with the principles of the Helsinki Declaration. All data were collected in compliance with relevant privacy and confidentiality regulations.

Study design

This study is a single-center, retrospective observational study. Data were obtained from the electronic medical records of patients hospitalized with a diagnosis of HF with reduced ejection fraction (HFrEF) at our hospital between November 2023 and October 2024. Relevant clinical information - including demographic characteristics, medical history, laboratory test results, echocardiographic findings, treatment regimens, and records of adverse events - was independently extracted by two researchers.

All patients received standard therapy consisting of diuretics, β-blockers, ACEIs, and aldosterone antagonists. The specific drugs included furosemide (20-80 mg/day), metoprolol (23.75-190 mg/day), perindopril (4-8 mg/day), and spironolactone (20-40 mg/day). Four patients did not receive aldosterone antagonists due to a high risk of hypotension or hyperkalemia. In addition to standard therapy, patients in the dapagliflozin group were administered oral dapagliflozin (10 mg once daily). Both groups underwent continuous treatment for 8 weeks. Treatment adherence was verified by cross-referencing daily nursing records with inpatient medication dispensing logs.

Observation indicators

(1) Clinical efficacy: Treatment efficacy was assessed according to criteria outlined in the "Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (2021 Edition)" [8]. Outcomes were categorized as markedly effective, effective, or ineffective. The total effective rate was calculated as: Total effective rate (%) = (markedly effective cases + effective cases)/ total cases × 100%.

(2) Cardiac function parameters: Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF) were measured using color Doppler echocardiography before treatment and after 8 weeks of therapy.

(3) Myocardial work indicators: Left ventricular longitudinal strain curves were acquired using two-dimensional speckle-tracking echocardiography and combined with cuff-measured systolic blood pressure to construct non-invasive left ventricular pressure-strain loops (PSLs). Myocardial work parameters were derived from the area enclosed by these loops, including the Global Work Index (GWI), defined as the total area under the pressure-strain loop from isovolumetric contraction to isovolumetric relaxation, expressed in units of mmHg%. GWI reflects the total mechanical work performed by the myocardium during systole. Global Constructive Work (GCW) refers to the effective work performed by the myocardium during systolic shortening and diastolic lengthening strains, representing the energy expenditure that effectively contributes to ventricular ejection. Global Wasted Work (GWW) denotes the inefficient work generated during systolic lengthening or diastolic shortening strains, reflecting energy consumed without contributing to ventricular ejection. Global Work Efficiency (GWE) is calculated as GCW divided by the sum of GCW and GWW, multiplied by 100%, and serves as an indicator of myocardial energy utilization efficiency.

All computations were performed using integrated automated algorithms within the ultrasound workstation (e.g., GE EchoPAC or Philips QLAB). The analyst manually delineated the left ventricular endocardium, followed by automated tracking to ensure synchronization between strain curves and pressure data.

(4) Energy metabolism indicators: Fasting venous blood samples were collected in the early morning, and levels of free fatty acids (FFA) and β-hydroxybutyric acid (β-HB) were measured using an enzymatic colorimetric assay.

(5) Inflammatory factors: Serum concentrations of interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) and IL-10 were determined using enzyme-linked immunosorbent assay (ELISA).

(6) Quality of life: The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to evaluate the changes in quality of life across emotional, physical and other relevant dimensions before and after treatment.

(7) Adverse cardiovascular events: Incidence of adverse cardiovascular outcomes, including worsening acute HF, arrhythmia, and cardiogenic death, was recorded during the treatment period.

(8) Other adverse reactions: Non-cardiovascular adverse events such as nausea, dizziness, and hypotension were documented.

Statistical analysis

Data were analyzed using SPSS 25.0 software. Categorical variables, including clinical efficacy, cardiovascular adverse events, and other adverse reactions, were expressed as percentages and compared using the chi-square (χ^2) test. Continuous variables, such as cardiac function parameters, energy metabolism indices, myocardial work indices, inflam-

Table 1. Comparison of baseline data between the two groups

Clinical indicators	Control group (n = 52)	Dapagliflozin group (n = 55)	*P*
Gender (Male/Female)	32/20	34/21	0.976
Average age (years)	65.82 ± 6.03	64.70 ± 7.12	0.383
Etiological types of HF			
Ischemic cardiomyopathy	30	33	0.808
Non-ischemic cardiomyopathy	22	22	
NYHA Functional Classification			
Class II	18	16	0.816
Class III	22	26	
Class IV	12	13	
Average disease duration (years)	4.38 ± 1.34	4.22 ± 1.29	0.531

Note: HF, heart failure; NYHA, New York Heart Association.

matory markers, and quality-of-life scores, were presented as mean ± standard deviation ($\bar{x}$ ± s) and compared using the t-test. All statistical tests were two-tailed, and statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics

A total of 107 patients with HFrEF were included in this study, including 52 in the control group and 55 in the dapagliflozin group. In the control group, the mean age was 65.82 ± 6.03 years, with 32 males and 20 females. In the dapagliflozin group, the mean age was 64.70 ± 7.12 years, with 34 males and 21 females. There were no statistically significant differences between the two groups in terms of sex, age, etiology, and functional class ($P > 0.05$). Baseline demographic characteristics, clinical features, and disease duration were well balanced between groups. Detailed information is provided in **Table 1**.

Cardiac function

As shown in **Figure 1**, both groups exhibited significant improvements in cardiac function after 8 weeks of treatment compared with baseline, with the dapagliflozin group demonstrating more pronounced changes. In the dapagliflozin group, LVEDD decreased significantly after treatment, indicating marked attenuation of left ventricular dilatation and notable improvement in ventricular remodeling ($P < 0.001$). The control group showed a similar trend ($P < 0.001$). Post-treatment LVEDD was significantly smaller in the dapagliflozin group than in the control group ($P < 0.001$). Similarly, LVESD (**Figure 1B**) decreased significantly in both groups compared to baseline ($P < 0.001$), with the dapagliflozin group showing a significantly greater reduction than the control group ($P < 0.001$). For LVEF (**Figure 1C**), both groups showed significant post-treatment increases ($P < 0.001$), with the dapagliflozin group achieving significantly higher values than the control group ($P < 0.001$). These results suggest that dapagliflozin, when added to standard therapy, confers greater improvement in left ventricular structure and systolic function compared with conventional treatment alone in patients with HFrEF. See **Figure 1**.

To further illustrate the effect of dapagliflozin on cardiac function in patients with HFrEF, one representative patient from each group was selected for detailed echocardiographic comparison before and after treatment. **Figure 2A** and **2B** show four-chamber echocardiographic images of a patient from the dapagliflozin group. Prior to treatment, the patient's LVEF was 35%, with LVEDD and LVESD measuring 65 mm and 59 mm, respectively, indicating marked left ventricular enlargement and severely impaired systolic function. Following 8 weeks of dapagliflozin combined therapy, LVEF increased to 42%, while LVEDD and LVESD decreased to 61 mm and 48 mm, respectively, reflecting substantial improvement in ventricular geometry and systolic performance. **Figure 2C** and **2D** present the corresponding findings for a patient in the control group. Before treatment, LVEF was 39%, and LVEDD and LVESD were 63 mm and 55 mm, respectively. After standard therapy, LVEF increased modestly to 44%, and LVEDD and LVESD improved to 60 mm and 52 mm, indicating only limited recovery in ventricular structure and function. These representative cases reinforce the overall study findings, demonstrating that dapagliflozin in combination with standard therapy yields greater improvement in left ventricular remodeling and systolic function than conventional treatment alone.

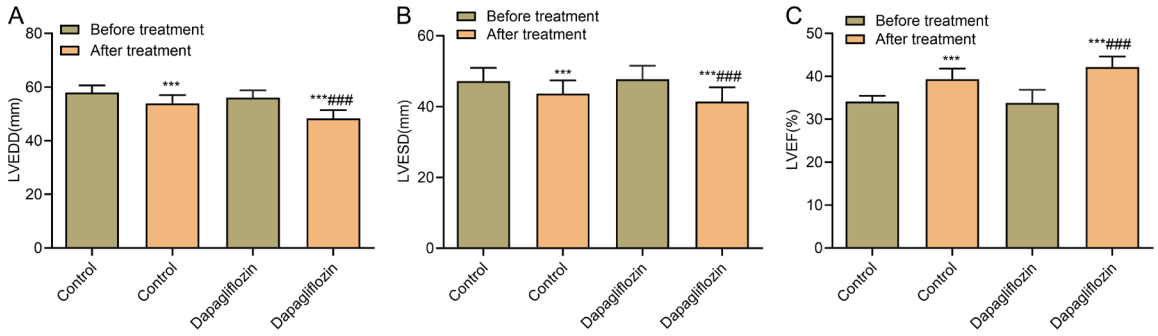
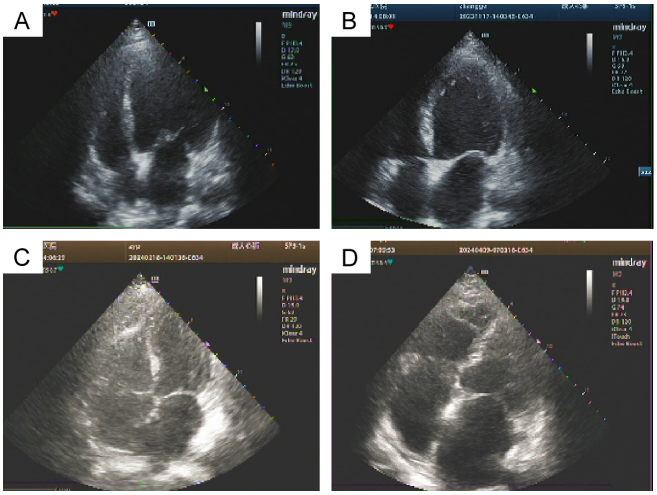


Figure 1. Comparison of cardiac function indicators between the two groups. A: Left Ventricular End-Diastolic Diameter (LVEDD, mm); B: Left Ventricular End-Systolic Diameter (LVESD, mm); C: Left Ventricular Ejection Fraction (LVEF, %). Compared with before treatment, ***P < 0.001; Compared with the control group, ###P < 0.001.



	Before treatment	After treatment
LVEF	35	42
LVEDD	65	61
LVESD	59	48

	Before treatment	After treatment
LVEF	39	44
LVEDD	62	58
LVESD	50	42

Figure 2. Representative cases. (A and B) depict a typical case from the Dapagliflozin treatment group, while (C and D) illustrate a representative case from the control group.

Myocardial work

Before treatment, there were no significant differences between the dapagliflozin and control groups in myocardial work parameters, including GWI, GCW, GWE, and GWW, indicating good comparability (P > 0.05). After 8 weeks of treatment, both groups showed varying degrees of increase in GWI, GCW, and GWE, alongside decreases in GWW, reflecting enhanced myocardial work capacity and efficiency following therapeutic intervention. Notably, the magnitude of improvement in these parameters was significantly greater in the dapagliflozin group compared to controls. After treatment, the dapagliflozin group showed markedly higher GWI, GCW, and GWE values, indicating superior enhancement of myocardial mechanical efficiency. Concurrently, GWW was significantly lower in the dapagliflozin group, indicating reduced myocardial wasted work and more efficient energy utilization, potentially attributable to dapagliflozin's regulatory effects on myocardial metabolism. All intergroup differences reached statistical significance (P < 0.05). These results suggest that dapagliflozin, when added to standard therapy, further improves myocardial mechanical performance, likely through improved energy metabolism and mechanical efficiency, thereby enhancing cardiac pump function in patients with HF. See **Table 2**.

Energy metabolism

Baseline levels of free fatty acids (FFA) and β-hydroxybutyrate (β-HB) were comparable between the two groups (P > 0.05), indicating

Table 2. Comparison of myocardial work indicators between the two groups ($\bar{x} \pm s$)

Group	GWI (mmHg%)		GCW (mmHg%)		GWW (mmHg%)		GWE (%)	
	Before treatment	After 8 weeks of treatment	Before treatment	After 8 weeks of treatment	Before treatment	After 8 weeks of treatment	Before treatment	After 8 weeks of treatment
Control group (n = 52)	711.30 ± 75.63	814.28 ± 89.06*	940.33 ± 115.20	983.22 ± 52.55*	183.55 ± 25.80	166.33 ± 21.33*	81.88 ± 7.12	84.24 ± 3.44*
Dapagliflozin group (n = 55)	718.45 ± 89.44	866.32 ± 95.70*	933.12 ± 98.57	1014.12 ± 55.20*	189.12 ± 32.42	151.25 ± 25.40*	81.20 ± 6.43	86.11 ± 3.55*
t	0.445	2.908	0.349	2.952	0.980	3.316	0.519	2.765
P	0.657	0.004	0.728	0.004	0.329	0.001	0.605	0.007

Note: Compared with before treatment, *P < 0.05. GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency.

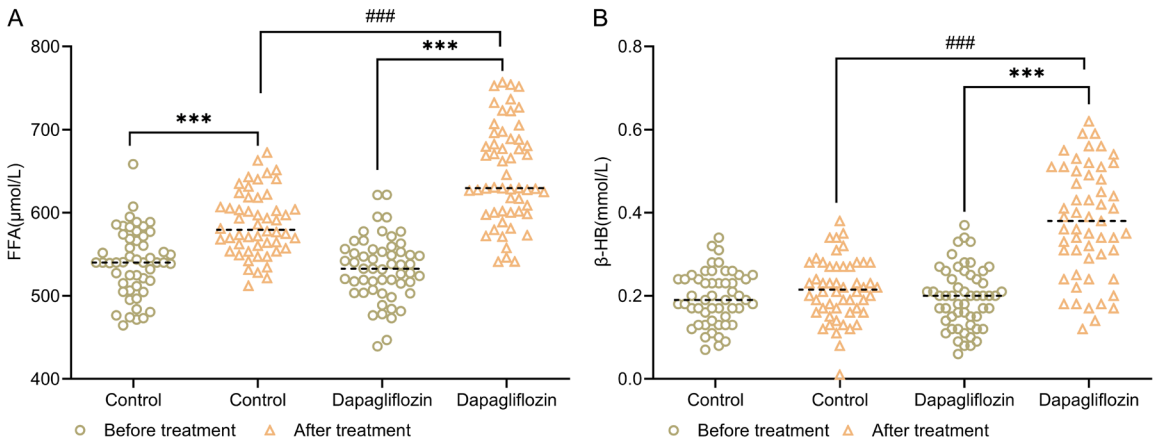


Figure 3. Comparison of energy metabolism indicators between the two groups. A: Free Fatty Acids (FFA, μmol/L); B: β-Hydroxybutyrate (β-HB, mmol/L). Compared with before treatment, ***P < 0.001; Compared with the control group, ###P < 0.001.

Table 3. Comparison of clinical efficacy between the two groups after treatment

Group	Markedly effective (n, %)	Effective (n, %)	Ineffective (n, %)	Total effective rate (%)
Control group (n = 52)	19 (36.54%)	23 (44.23%)	10 (19.23%)	80.77%
Dapagliflozin group (n = 55)	28 (50.91%)	24 (43.64%)	3 (5.45%)	94.55%

no initial metabolic differences that might confound intervention outcomes. After 8 weeks of treatment, the dapagliflozin group exhibited a significant increase in both FFA and β-HB levels, suggesting enhanced fatty acid metabolism and ketogenesis. This change likely reflects dapagliflozin's dual regulatory effects on myocardial energy supply pathways. Although the control group showed a similar upward trend, the magnitude of change was markedly less pronounced. Intergroup comparisons confirmed that dapagliflozin combined therapy more effectively improves myocardial energy metabolism. See **Figure 3**.

Clinical efficacy

Clinical efficacy was assessed according to the Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (2021 Edition), with results summarized in **Table 3**. In the dapagliflozin group, 28 patients achieved marked improvement, 24 showed moderate improvement, and 3 were classified as ineffective, resulting in a total effective rate of 94.55%. In contrast, the control group had 19 markedly improved cases, 23 moderately improved cases, and 10 ineffective cases, yielding a total effective rate of 80.77%. The difference in total effective rates between the two groups was statistically significant (P = 0.037), indicating that dapagliflozin combined therapy offers superior benefits in alleviating clinical symptoms of patients with HFrEF.

Inflammatory factors

Baseline levels of inflammatory markers, including IL-1β, IL-6, TNF-α, and IL-10, were comparable between groups, with no statistically significant differences (P > 0.05), confirming similar inflammatory status prior to intervention. After 8 weeks of treatment, both groups exhibited significant reductions in the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, suggesting attenuation of systemic inflammation. The dapagliflozin group showed significantly greater decreases in these pro-inflammatory markers compared to controls, indicating that dapagliflozin may intervene in the progression of HFrEF by attenuating systemic inflammation. Additionally, levels of the anti-inflammatory cytokine IL-10 increased in the dapagliflozin group, further supporting its modulatory role in inflammatory regulation during HFrEF management. Relevant results are shown in **Figure 4**.

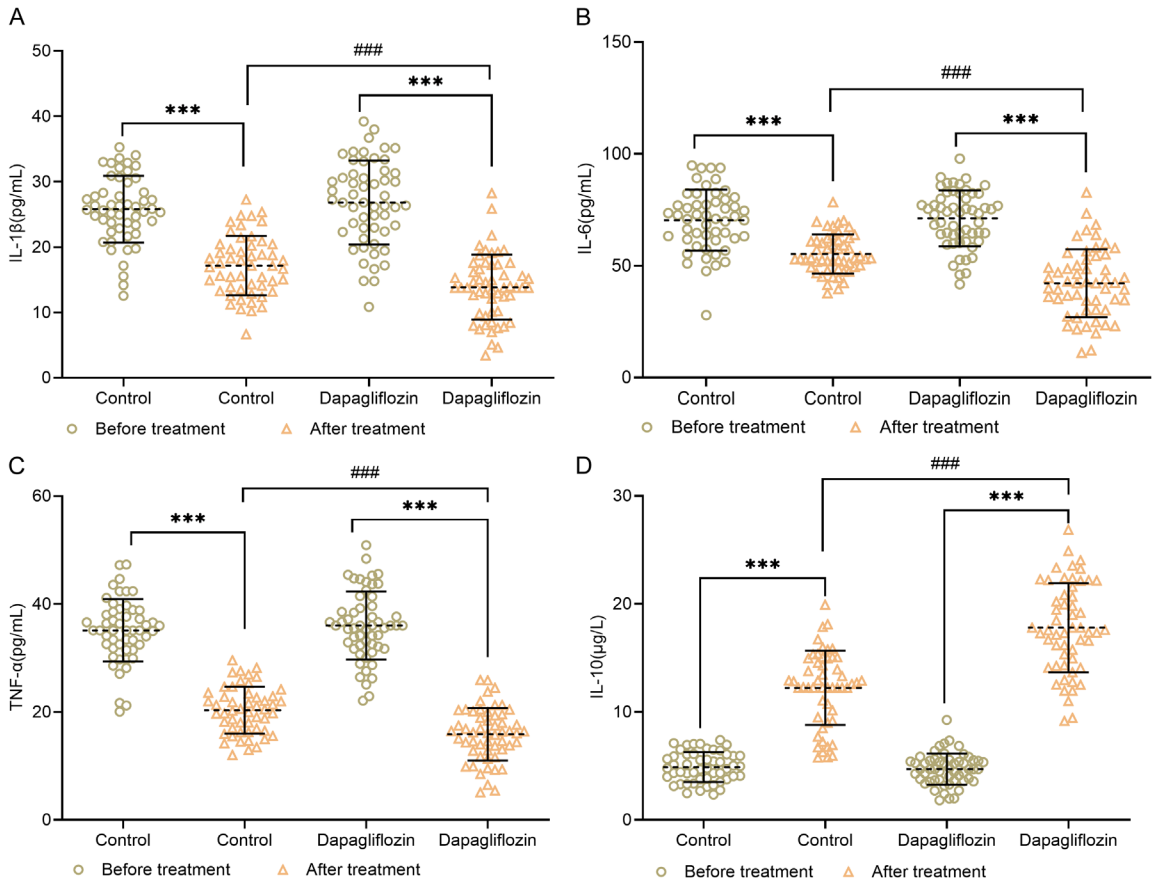


Figure 4. Comparison of inflammatory factors between the two groups. A: Interleukin-1β (IL-1β, pg/mL); B: Interleukin-6 (IL-6, pg/mL); C: Tumor Necrosis Factor-α (TNF-α, pg/mL); D: Interleukin-10 (IL-10, μg/L). Compared with before treatment, $^{***}P < 0.001$; Compared with the control group, $^{###}P < 0.001$.

Quality of life

At baseline, no statistically significant differences were found between the two groups in any dimensions of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores ($P > 0.05$), indicating comparable quality of life. After treatment, both groups experienced reductions in MLHFQ scores, reflecting improvement in patients' perceived health status, particularly in physical functioning and emotional well-being. The dapagliflozin group demonstrated a greater decrease, indicating more pronounced relief of symptoms and overall enhancement in quality of life. See **Figure 5** for details.

Cardiovascular adverse events

During the 8-week follow-up period, the incidence of cardiovascular adverse events was significantly lower in the dapagliflozin group (14.55%) compared to the control group (34.62%). This reduction may be attributed to dapagliflozin's effects on modulating cardiac workload and the neuroendocrine environment, underscoring its potential to mitigate cardiovascular risk in patients with HFrEF. See **Figure 6**.

Other adverse reactions

The total incidence of non-cardiovascular adverse reactions was 5.77% in the dapagliflozin group and 9.09% in the control group, with no significant difference between the two groups ($P > 0.05$). See **Table 4**.

Discussion

HFrEF is a common type of HF, predominantly affecting the elderly population. Among hospitalized HFrEF patients, the 5-year mortality rate can reach up to 75%, underscoring the critical

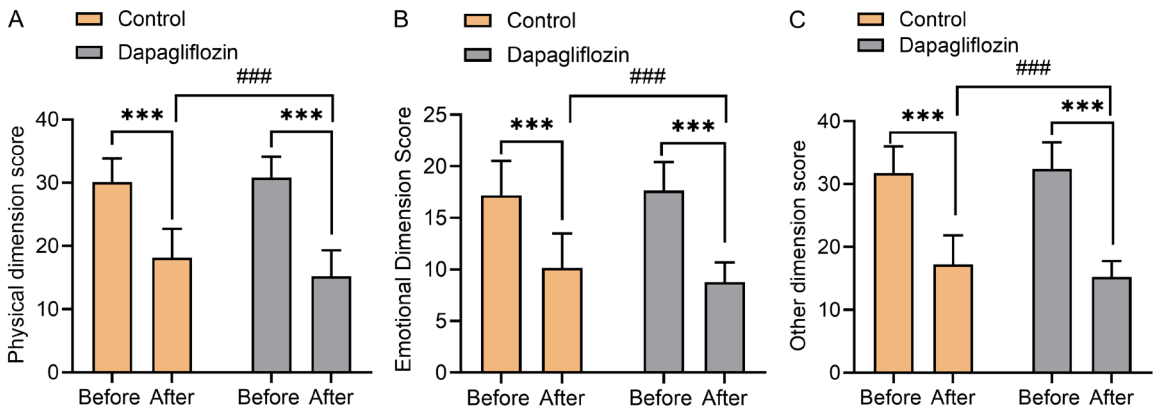


Figure 5. Comparison of quality of life assessed by MLHFQ scores between groups. A: Physical dimension; B: Emotional dimension; C: Other dimension. Compared with before treatment, $^{***}P < 0.001$; Compared with the control group, $^{###}P < 0.001$.

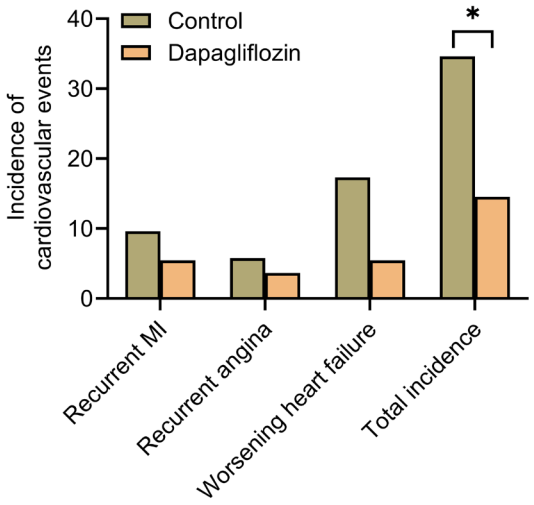


Figure 6. Comparison of cardiovascular adverse events between the two groups [n (%)]. Compared with the control group, $^{*}P < 0.05$.

need for timely and effective therapeutic interventions [9]. The pathogenesis of HFrEF is multifactorial and involves complex neuroendocrine dysfunction, such as excessive activation of the sympathetic nervous system (SNS) and persistent overactivation of the renin-angiotensin-aldosterone system (RAAS). Enhanced sympathetic excitation is recognized as a key driver of myocardial remodeling and functional impairment [10, 11]. In the early stages of the disease, stimulation of stress receptors leads to heightened SNS activity and excessive catecholamine release. This catecholamine surge exerts direct cardiotoxic effects, inducing cardiomyocyte apoptosis and promoting adverse myocardial remodeling [12]. Meanwhile, elevated catecholamine levels increase peripheral vascular resistance, thereby augmenting cardiac afterload and exacerbating myocardial stress, which may ultimately lead to patient death [13]. Therefore, strategies aimed at attenuating SNS overactivity and restoring neuroendocrine balance are crucial in treating HFrEF.

In recent years, sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a promising therapeutic option for HFrEF, demonstrating significant efficacy and promising clinical prospects [14, 15]. Dapagliflozin, a commonly used SGLT2 inhibitor, not only lowers blood glucose levels but also modulates neuroendocrine function and reduces cardiovascular adverse events [16]. In this study, dapagliflozin combined with standard therapy significantly improved clinical outcomes in HFrEF patients, with a total effective rate of 94.55%, markedly higher than the 80.77% observed in the control group. After 8 weeks of treatment, the dapagliflozin group exhibited significantly reduced LVEDD and LVESD, alongside increased LVEF compared to controls ($P < 0.05$). These findings suggest that dapagliflozin, when added to conventional therapy, effectively alleviates symptoms and enhances cardiac function, likely through multifaceted mechanisms involving volume load reduction, myocardial energy metabolism optimization, and attenuation of inflammatory responses. Specifically, dapagliflozin's inhibition of SGLT2 promotes glucosuria and osmotic diuresis,

Table 4. Comparison of other adverse reactions between the two groups [n (%)]

Group	Nausea	Dizziness	Hypotension	Total
Control group (n = 52)	2 (3.85)	1 (1.92)	0 (0.00)	3 (5.77)
Dapagliflozin group (n = 55)	2 (3.64)	2 (3.64)	1 (1.82)	5 (9.09)
χ^2				0.810
P				0.775

thereby reducing fluid retention and lowering circulatory volume load. Additionally, the drug may improve vascular compliance and substrate utilization, contributing to enhanced cardiac metabolic status. By decreasing vascular stiffness, dapagliflozin further reduces cardiac afterload. Furthermore, through reduced myocardial glucose uptake and increased ketone body utilization, such as β-hydroxybutyrate, dapagliflozin optimizes myocardial energy metabolism, enhances myocardial contractility, and promotes cardiac functional recovery [17, 18].

Clinical studies have found that myocardial work and energy metabolism are closely linked to the prognosis of HFrEF patients. The present study further analyzed myocardial work parameters derived from two-dimensional speckle-tracking echocardiography. After 8 weeks of treatment, both patient groups demonstrated improvements in myocardial work efficiency and performance; however, the Dapagliflozin group exhibited more pronounced enhancements. These findings suggest that Dapagliflozin may confer unique advantages in optimizing myocardial energy metabolism and improving mechanical efficiency, thereby augmenting cardiac pump function in patients with heart failure. Dapagliflozin may enhance myocardial energy supply by activating ketone body metabolic pathways, thereby optimizing myocardial contractile efficiency. The significant improvement in energy metabolism indicators observed in this study lends preliminary support to this hypothesis. Moreover, dapagliflozin's modulation of inflammatory factors suggests potential anti-inflammatory effects that could mitigate the chronic inflammation associated with HF. This effect is likely attributable to the role of ketone bodies as a highly efficient energy substrate. Dapagliflozin promotes ketone body production and utilization by cardiomyocytes, improving myocardial energy metabolism and utilization efficiency, which in turn enhances contractility and myocardial work capacity. Additionally, dapagliflozin may inhibit left ventricular dilation and facilitate cardiac remodeling, thereby promoting the recovery of cardiac function and further enhancing myocardial performance [19]. Inflammatory responses are critically involved in myocardial hypertrophy, fibrosis, and apoptosis, which are key pathological processes driving the development and progression of HFrEF [20]. HF patients often exhibit dysregulated cytokine networks characterized by excessive secretion of pro-inflammatory mediators such as IL-1β, IL-6, and TNF-α. This pro-inflammatory milieu exacerbates neuroendocrine overactivation, leading to cardiac dysfunction and adverse clinical outcomes. In this study, after 8 weeks of treatment, the dapagliflozin group showed significantly lower levels of IL-1β, IL-6, and TNF-α, alongside elevated levels of the anti-inflammatory cytokine IL-10 compared to controls ($P < 0.05$). These findings suggest that dapagliflozin's anti-inflammatory effects may be mediated through modulation of the NF-κB signaling pathway and other immune-related mechanisms, thereby alleviating local myocardial inflammation and reducing tissue damage.

The treatment goals for HF with HFrEF extend beyond symptomatic relief to include the optimization of long-term prognosis. Cardiovascular outcomes are essential clinical indicators for evaluating therapeutic efficacy and risk stratification, providing a robust measure of treatment safety and effectiveness. In this study, the overall incidence of cardiovascular adverse events was significantly lower in the dapagliflozin group (14.55%) compared to the control group (34.62%), indicating that dapagliflozin is associated with improved cardiovascular outcomes in HFrEF patients. Furthermore, after 8 weeks of treatment, patients receiving dapagliflozin demonstrated significantly better quality of life, as evidenced by lower scores across all domains of the MLHFQ questionnaire compared to controls ($P < 0.05$). The incidence of other treatment-related

adverse events did not differ significantly between groups ($P > 0.05$), suggesting that dapagliflozin effectively improves quality of life in HFrEF patients while maintaining a favorable safety profile.

In this study, all patients were prescribed the guideline-recommended quadruple therapy; however, four patients - one in the control group and three in the dapagliflozin group - did not receive aldosterone antagonists due to concerns over hypotension or hyperkalemia. Such adjustments align with clinical practice standards and showed no statistically significant difference in drug utilization between groups, thus exerting minimal impact on overall therapeutic outcomes. The combination of dapagliflozin with standard HFrEF treatments - including diuretics, β-blockers, ACE inhibitors, and aldosterone antagonists - was not only safe but also appeared to enhance patient prognosis through multi-targeted mechanisms involving diuresis, neurohormonal inhibition, and metabolic regulation. Nonetheless, close monitoring of blood glucose and blood pressure is particularly essential in elderly and diabetic patients.

Overall, this study suggests that dapagliflozin may offer a novel therapeutic approach for HFrEF by improving cardiac function and modulating inflammation and energy metabolism, highlighting the need for further validation in larger patient populations. Given the limited sample size and absence of long-term follow-up data, these findings should be interpreted cautiously. Further large-scale studies with extended follow-up are needed to confirm and expand upon these results.

Acknowledgements

This work was supported by Jilin Province Health and Wellness Science and Technology Capability Enhancement Project (2021LC097).

Disclosure of conflict of interest

None.

Address correspondence to: Qingbo Li, Department of Clinical Pharmacy, Jilin Province FAW General Hospital, No 2643 Dongfeng Street, Changchun 130013, Jilin, China. Tel: +86-15044032909; E-mail: lqb15044032909@163.com

References

[1] Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M and Langkilde AM; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022; 387: 1089-1098.

[2] Redfield MM and Borlaug BA. Heart failure with preserved ejection fraction: a review. JAMA 2023; 329: 827-838.

[3] Peikert A, Martinez FA, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Shah SJ, Katova T, Merkely B, Vardeny O, Wilderäng U, Lindholm D, Petersson M, Langkilde AM, McMurray JJV and Solomon SD. Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: the DELIVER trial. Circ Heart Fail 2022; 15: e010080.

[4] Song XY, Han JM and Ma YL. Effect and Mechanism of Dapagliflozin in the Treatment of Cardiovascular Diseases [J]. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease 2024; 32: 1-5.

[5] Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W and Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020; 396: 819-829.

[6] Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, Vaduganathan M, Gasparyan SB, Bengtsson O, Lindholm D, Petersson M, Langkilde AM, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Køber L, Lam CSP, Martinez FA, Sabatine MS, Shah SJ, Solomon SD and McMurray JJV. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nat Med 2022; 28: 1956-1964.

[7] Working Group for Formulating the Chinese Expert Consensus on the Diagnosis and Treatment of Heart Failure with Preserved ejection Fraction Chinese Expert Consensus on Diagno-

sis and Treatment of Heart Failure with Preserved Ejection Fraction 2023. Chin J Circ 2023; 38: 375-393.
[8] Wang ZY, Chen C, Lyu Q, Du X and Dong JZ. Interpretation of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Chin J Cardiol 2021; 49: 1252-1255.
[9] Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Lindholm D, Wilderäng U, Öhrn F, Claggett B, Langkilde AM, Petersson M and McMurray JJV. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail 2021; 23: 1217-1225.
[10] Butt JH, Dewan P, Merkely B, Belohlávek J, Drożdż J, Kitakaze M, Inzucchi SE, Kosiborod MN, Martinez FA, Tereshchenko S, Ponikowski P, Bengtsson O, Lindholm D, Langkilde AM, Schou M, Sjöstrand M, Solomon SD, Sabatine MS, Chiang CE, Docherty KF, Jhund PS, Køber L and McMurray JJV. Efficacy and safety of dapagliflozin according to frailty in heart failure with reduced ejection fraction: a post hoc analysis of the DAPA-HF trial. Ann Intern Med 2022; 175: 820-830.
[11] Adamson C, Docherty KF, Heerspink HJL, de Boer RA, Damman K, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Petrie MC, Ponikowski P, Sabatine MS, Schou M, Solomon SD, Verma S, Bengtsson O, Langkilde AM, Sjöstrand M, Vaduganathan M, Jhund PS and McMurray JJV. Initial Decline (Dip) in estimated glomerular filtration rate after initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: insights from DAPA-HF. Circulation 2022; 146: 438-449.
[12] Inzucchi SE, Claggett BL, Vaduganathan M, Desai AS, Jhund PS, de Boer RA, Hernandez AF, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Verma S, Han Y, Kerr Saraiva JF, Bengtsson O, Petersson M, Langkilde AM, McMurray JJV and Solomon SD. Efficacy and safety of dapagliflozin in patients with heart failure with mildly reduced or preserved ejection fraction by baseline glycaemic status (DELIVER): a subgroup analysis from an international, multicentre, double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2022; 10: 869-881.
[13] Banerjee M, Pal R, Nair K and Mukhopadhyay S. SGLT2 inhibitors and cardiovascular outcomes in heart failure with mildly reduced and preserved ejection fraction: a systematic review and meta-analysis. Indian Heart J 2023; 75: 122-127.
[14] Withaar C, Meems LMG, Markousis-Mavrogenis G, Boogerd CJ, Silljé HHW, Schouten EM, Dokter MM, Voors AA, Westenbrink BD, Lam CSP and de Boer RA. The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction. Cardiovasc Res 2021; 117: 2108-2124.
[15] Blair HA. Dapagliflozin: a review in symptomatic heart failure with reduced ejection fraction. Am J Cardiovasc Drugs 2021; 21: 701-710.
[16] Bao LW, Liu RC, Yan FY, Gao XF, Xie K, Bao LL, Zhuang XY, Shi HM and Li Y. Research progress on sodium-glucose co-transporter 2 inhibitors for the treatment of cardiovascular diseases. Chin J Cardiol 2020; 48: 339-343.
[17] Mc Causland FR, Claggett BL, Vaduganathan M, Desai A, Jhund P, Vardeny O, Fang JC, de Boer RA, Docherty KF, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Saraiva JFK, McGrath MM, Shah SJ, Verma S, Langkilde AM, Petersson M, McMurray JJV and Solomon SD. Decline in estimated glomerular filtration rate after dapagliflozin in heart failure with mildly reduced or preserved ejection fraction: a prespecified secondary analysis of the DELIVER randomized clinical trial. JAMA Cardiol 2024; 9: 144-152.
[18] Zhang X, Wang N, Fu P, An Y, Sun F, Wang C, Han X, Zhang Y, Yu X and Liu Y. Dapagliflozin attenuates heart failure with preserved ejection fraction remodeling and dysfunction by elevating β-hydroxybutyrate-activated citrate synthase. J Cardiovasc Pharmacol 2023; 82: 375-388.
[19] Peikert A, Goyal P, Vaduganathan M, Claggett BL, Kulac IJ, Miao ZM, Vardeny O, Kosiborod MN, Desai AS, Jhund PS, Lam CSP, Inzucchi SE, Martinez FA, de Boer RA, Hernandez AF, Shah SJ, Petersson M, Langkilde AM, McMurray JJV and Solomon SD. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to polypharmacy status. JACC Heart Fail 2023; 11: 1380-1393.
[20] Mohammadnezhad G, Azadmehr B, Mirheidari M and Yousefi N. Cost-effectiveness analysis of dapagliflozin in the management of heart failure with reduced ejection fraction (HFrEF): a systematic review. Cost Eff Resour Alloc 2022; 20: 62.