Postprint Study on the Prognostic Impact of Dapagliflozin in Elderly Breast Cancer Survivors with Heart Failure with Preserved Ejection Fraction and Type 2 Diabetes Mellitus

Authors: Yang Chen, Chen Tong, Zhang Lifang, Hongxu Zhang, Li Pengfei, Zhang Xuejuan, Xuejuan Zhang

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Abstract

Background With the advancement of tumor diagnosis and treatment technologies and the rapid development of antitumor drugs, the survival of cancer survivors has been significantly prolonged. Cardiovascular diseases induced by cancer therapy, particularly heart failure, have become an important concern. Dapagliflozin is a novel sodium-glucose cotransporter 2 inhibitor that has been proven to confer significant clinical benefits in the treatment of type 2 diabetes mellitus and heart failure. However, research on its prognostic impact in elderly breast cancer survivors with heart failure with preserved ejection fraction (HFpEF) complicated by type 2 diabetes mellitus remains scarce.

Objective To investigate the effect of dapagliflozin on the prognosis of elderly breast cancer survivors with HFpEF complicated by type 2 diabetes mellitus.

Methods A total of 93 elderly female breast cancer survivors with HFpEF complicated by type 2 diabetes mellitus admitted to The Affiliated Hospital of Qingdao University between January 2018 and August 2023 were selected as study subjects. According to the medication regimen, patients were divided into a dapagliflozin group (47 cases) and a control group (46 cases). Baseline data of enrolled patients were collected, and patients were followed up for 6 months with a cutoff date of April 2024. The primary endpoint event was rehospitalization due to heart failure during the follow-up period. Adverse reactions occurring during follow-up were also recorded. Survival function curves were plotted using the Kaplan-Meier method, with comparisons between groups performed using the Log-rank test. Multivariate Cox proportional hazards model was used to analyze factors influencing rehospitalization events.

Results The mean age of patients was (70.1$±$3.8) years, and there was no statistically significant difference in general characteristics between the two groups (P>0.05). After 6 months of treatment, fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels decreased, while estimated glomerular filtration rate (eGFR) increased in both the dapagliflozin and control groups (P<0.05). After 6 months of treatment, patients in the dapagliflozin group had lower FPG and HbA1c levels and higher eGFR levels compared with the control group (P<0.05). After 6 months of treatment, left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), ratio of early mitral inflow velocity to early mitral annular velocity (E/e'), left atrial volume index (LAVI), and left ventricular mass index (LVMI) decreased, while left ventricular ejection fraction (LVEF) increased compared with pre-treatment values in both the dapagliflozin and control groups (P<0.05). After 6 months of treatment, patients in the dapagliflozin group had lower LVEDD, IVST, LVPWT, LVMI, LAVI, and E/e' but higher LVEF compared with the control group (P<0.05). After 6 months of treatment, high-sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels decreased in both the dapagliflozin and control groups (P<0.05). After 6 months of treatment, patients in the dapagliflozin group had lower hs-cTnI and NT-proBNP levels compared with the control group (P<0.05). During the 6-month follow-up, 5 patients (10.6%) in the dapagliflozin group and 13 patients (28.3%) in the control group were rehospitalized due to heart failure. Kaplan-Meier survival analysis showed a statistically significant difference in cumulative rehospitalization-free survival rates between the two groups (P=0.0326). Multivariate Cox regression analysis revealed that dapagliflozin use (HR=0.325, 95%CI=0.116-0.912, P=0.033), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor (HR=0.562, 95%CI=0.236-0.949, P=0.035), and spironolactone (HR=0.836, 95%CI=0.710-0.985, P=0.037) were protective factors associated with reduced rehospitalization events, while increased age (HR=1.343, 95%CI=1.198-1.506, P<0.001), elevated BMI (HR=1.305, 95%CI=1.111-1.532, P=0.001), and anthracycline use (HR=1.197, 95%CI=1.035-1.384, P=0.023) were risk factors associated with increased rehospitalization events.

Conclusion In elderly breast cancer survivors with HFpEF complicated by type 2 diabetes mellitus, dapagliflozin not only effectively controls blood glucose and improves renal function, but also significantly improves cardiac function and enhances long-term prognosis.

Full Text

Prognostic Impact of Dapagliflozin in Elderly Breast Cancer Survivors with Heart Failure with Preserved Ejection Fraction and Type 2 Diabetes

YANG Chen, CHEN Tong, ZHANG Lifang, ZHANG Hongxu, LI Pengfei, ZHANG Xuejuan*

Department of General Medicine, Affiliated Hospital of Qingdao University, Qingdao 266000, China

*Corresponding author: ZHANG Xuejuan, Chief physician; E-mail: dzhangxue@126.com

Abstract

Background With advances in cancer diagnosis and treatment technologies, as well as the rapid development of anti-cancer drugs, the survival of cancer survivors has significantly improved. Cardiovascular diseases, particularly heart failure, resulting from cancer treatment have become a significant concern. Dapagliflozin, a novel sodium-glucose cotransporter 2 (SGLT2) inhibitor, has demonstrated significant clinical benefits in the treatment of type 2 diabetes and heart failure (HF). However, studies on its prognostic impact in elderly breast cancer survivors with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes remain scarce.

Objective To investigate the prognostic impact of dapagliflozin in elderly breast cancer survivors with HFpEF and type 2 diabetes.

Methods Ninety-three elderly female breast cancer survivors with HFpEF and type 2 diabetes admitted to the Affiliated Hospital of Qingdao University from January 2018 to August 2023 were enrolled. Based on the medication regimen, patients were divided into the dapagliflozin group (47 patients) and the control group (46 patients). Baseline data were collected, and patients were followed up for 6 months, with the follow-up period ending in April 2024. The primary endpoint was the occurrence of rehospitalization due to heart failure during the follow-up. Adverse reactions during the follow-up were also recorded. The Kaplan-Meier method was used to plot survival curves, and the Log-rank test was used for comparisons between groups. A multivariate Cox proportional hazards model was employed to analyze the factors influencing rehospitalization events.

Results The average age of the patients was (70.1$±$3.8) years. There were no statistically significant differences in baseline characteristics between the two groups (P>0.05). After 6 months of treatment, both the dapagliflozin group and the control group showed decreased levels of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), and increased estimated glomerular filtration rate (eGFR) (P<0.05). At 6 months post-treatment, the dapagliflozin

group had lower FPG and HbA1c levels and higher eGFR levels compared to the control group (P<0.05). Additionally, the left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), early diastolic mitral valve flow velocity (E)/early diastolic mitral annular peak velocity (e'), left atrial volume index (LAVI), and left ventricular mass index (LVMI) decreased in both groups, while the left ventricular ejection fraction (LVEF) increased compared to pre-treatment levels (P<0.05). At 6 months post-treatment, the dapagliflozin group had lower LVEDD, IVST, LVPWT, LVMI, LAVI, and E/e' , and higher LVEF compared to the control group (P<0.05). Levels of high-sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) decreased in both groups after 6 months of treatment (P<0.05). At 6 months post-treatment, the dapagliflozin group had lower hs-cTnI and NT-proBNP levels compared to the control group (P<0.05). During the 6-month follow-up, 5 patients (10.6%) in the dapagliflozin group and 13 patients (28.3%) in the control group were rehospitalized due to heart failure. Kaplan-Meier survival analysis showed a statistically significant difference in cumulative rehospitalization-free survival rates between the two groups (P=0.0326). Multivariate Cox regression analysis results indicated that the use of dapagliflozin (HR=0.325, 95%CI=0.116-0.912, P=0.033), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors (HR=0.562, 95%CI=0.236-0.949, P=0.035), and spironolactone (HR=0.836, 95%CI=0.710-0.985, P=0.037) were protective factors against rehospitalization events, while increasing age (HR=1.343, 95%CI=1.198-1.506, P<0.001), higher BMI (HR=1.305, 95%CI=1.111-1.532, P=0.001), and the use of anthracyclines (HR=1.197, 95%CI=1.035-1.384, P=0.023) were risk factors for increased rehospitalization events.

Conclusion In elderly breast cancer survivors with HFpEF and type 2 diabetes, dapagliflozin not only effectively controls blood glucose and improves renal function but also significantly improves cardiac function, enhancing long-term prognosis.

Keywords Heart failure; Heart failure with reduced ejection fraction; Breast cancer; Breast cancer survivors; Type 2 diabetes mellitus; Dapagliflozin; Aged; Prognosis

Introduction

In recent years, with the rising incidence of cancer and continuous advances in early detection and treatment technologies, the number of cancer survivors has grown significantly. Despite these therapeutic advances, survivors remain highly vulnerable to cardiovascular diseases, particularly with an increased risk of heart failure (HF) [**?**]. Studies have shown that heart failure with preserved ejection fraction (HFpEF) is more common among breast cancer survivors and is

associated with significantly worse prognosis compared to HF from other causes [?],[?]. Dapagliflozin, as a sodium-glucose cotransporter 2 inhibitor (SGLT2i), has been proven to provide cardiovascular benefits beyond its glucose-lowering effects [?]. Multiple studies have demonstrated that dapagliflozin can attenuate cancer therapy-related cardiotoxicity and improve cardiovascular outcomes in cancer survivors [?],[?],[?],[?]. Elderly breast cancer survivors with HFpEF and type 2 diabetes represent a specific population with not only high cardiovascular event rates but also more complex prognosis due to cardiotoxicity from cancer treatment. The application of dapagliflozin in this context holds important clinical significance. Therefore, this study aims to investigate the prognostic impact of dapagliflozin in elderly breast cancer survivors with HFpEF and type 2 diabetes through retrospective analysis, providing new directions for clinical treatment.

Methods

Study Population

We selected 93 elderly female breast cancer survivors with HFpEF and type 2 diabetes admitted to the Affiliated Hospital of Qingdao University from January 2018 to August 2023. Breast cancer survivors were defined as "patients who have completed conventional treatment and entered the follow-up period" [?]. All patients' breast cancer staging was evaluated according to the 8th edition of the American Joint Committee on Cancer (AJCC) breast cancer staging criteria [?] and classified based on clinical and pathological data. The breast cancer patients in this study included early-stage breast cancer (Stage I, II) and locally advanced breast cancer (Stage III), and all patients were diagnosed with HF for the first time. The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFY WZLL 28871), and all patients provided informed consent.

Inclusion Criteria

1. Pathologically diagnosed breast cancer and having received standardized cancer treatment
2. Meeting the diagnostic criteria of the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017 Edition)" [?]
3. Age $\geq$ 65 years
4. Meeting the diagnostic criteria for HFpEF in the "Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018" : presence of HF symptoms and signs; left ventricular ejection fraction (LVEF) $\geq$ 50%; evidence of structural heart disease (left ventricular hypertrophy, left atrial enlargement) and/or diastolic dysfunction; N-terminal pro-B-type natriuretic peptide (NT-proBNP) $\geq$ 125 ng/L or B-type natriuretic peptide $\geq$ 35 ng/L [?]
5. Complete clinical data and good compliance

Exclusion Criteria

1. Type 1 diabetes
2. Renal insufficiency [estimated glomerular filtration rate (eGFR) < 45 mL $\cdot$ (min $\cdot$ 1.73m^2)$^{-1}$]
3. Acute or severe infection
4. Hypertrophic cardiomyopathy, valvular heart disease, or constrictive pericarditis
5. Other malignant tumors or hematological diseases
6. Old myocardial infarction
7. Incomplete clinical data or follow-up information

Grouping

All study subjects were breast cancer survivors who had completed standardized breast cancer treatment protocols, and none received subsequent breast cancer-related treatment during the study period. Based on medication regimens, patients were divided into the dapagliflozin group (47 cases) and the control group (46 cases). After admission, all patients first received lifestyle improvement interventions upon confirmed diagnosis, followed by conventional anti-HF treatment. The control group received standard anti-HF therapy with dose adjustments based on clinical status. The dapagliflozin group received additional dapagliflozin (trade name: Forxiga, AstraZeneca Pharmaceuticals Ltd., specification 10 mg/tablet, national drug approval number J20170040) at a dose of 10 mg once daily in the morning, on top of the control group treatment.

Data Collection

Baseline data were collected from the enrolled patients, including age, BMI, systolic blood pressure, diastolic blood pressure, previous chemoradiotherapy status, clinical medications, echocardiographic parameters, blood biochemical indicators [fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), eGFR, NT-proBNP, high-sensitivity cardiac troponin I (hs-cTnI)], and blood lipids [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)].

Biochemical indicators: All patients had 5 mL of fasting venous blood drawn in the morning and tested by the clinical laboratory.

Echocardiographic parameters: Experienced cardiac sonographers used the Philips EPIQ5 ultrasound system with Simpson's method to measure left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular mass index (LVMI), left atrial volume index (LAVI), early diastolic mitral valve flow velocity (E)/early diastolic mitral annular peak velocity (e'), and related indicators, which were reviewed by associate senior-level or higher ultrasound physicians.

Follow-up

This study conducted a 6-month follow-up by reviewing electronic medical records, with the follow-up period ending in April 2024. The primary endpoint was the occurrence of rehospitalization due to heart failure during the follow-up period. Adverse reactions during follow-up were also recorded to comprehensively evaluate treatment safety.

Statistical Methods

Data analysis was performed using SPSS 26.0 statistical software, and GraphPad Prism 9.5 software was used for graphing. Normally distributed continuous data were expressed as ($\bar{x}\pm s$), with independent samples t-test for between-group comparisons and paired t-test for before-after treatment comparisons. Non-normally distributed data were expressed as $M(P_{25}, P_{75})$, with non-parametric tests for between-group comparisons and paired rank-sum tests for before-after comparisons. Categorical data were expressed as cases (%) and compared using ^{2} test. The Kaplan-Meier method was used to plot survival curves, with Log-rank test for between-group comparisons. Multivariate Cox proportional hazards model was used to analyze factors influencing rehospitalization events. $P<0.05$ was considered statistically significant.

Results

Comparison of General Patient Data

The average age of patients was (70.1$±$3.8) years. There were no statistically significant differences between the two groups in age, BMI, blood pressure, laboratory indicators, chemoradiotherapy status, clinical medications, and comorbidities ($P>0.05$) .

Comparison of Indicators Before and After Treatment

Comparison of FPG, HbA1c, and eGFR Levels Between Groups There were no statistically significant differences in FPG, HbA1c, and eGFR between the dapagliflozin and control groups before treatment ($P>0.05$). After 6 months of treatment, both groups showed decreased FPG and HbA1c levels and increased eGFR levels ($P<0.05$). At 6 months post-treatment, the dapagliflozin group had lower FPG and HbA1c levels and higher eGFR levels compared to the control group ($P<0.05$) .

Comparison of Cardiac Function Parameters Between Groups There were no statistically significant differences in LVEF, LVEDD, IVST, LVPWT, E/e' , LAVI, and LVMI between the dapagliflozin and control groups before treatment ($P>0.05$). After 6 months of treatment, both groups showed decreased LVEDD, IVST, LVPWT, E/e' , LAVI, and LVMI, and increased LVEF compared to pre-treatment levels ($P<0.05$). At 6 months post-treatment, the

dapagliflozin group had lower LVEDD, IVST, LVPWT, LVMI, LAVI, and E/e' , and higher LVEF compared to the control group (P<0.05) .

Comparison of NT-proBNP and hs-cTnI Levels Between Groups
There were no statistically significant differences in hs-cTnI and NT-proBNP between the dapagliflozin and control groups before treatment (P>0.05). After 6 months of treatment, both groups showed decreased hs-cTnI and NT-proBNP levels (P<0.05). At 6 months post-treatment, the dapagliflozin group had lower hs-cTnI and NT-proBNP levels compared to the control group (P<0.05) .

Follow-up Results

During the 6-month follow-up, 5 patients (10.6%) in the dapagliflozin group and 13 patients (28.3%) in the control group were rehospitalized due to heart failure. Kaplan-Meier survival analysis showed a statistically significant difference in cumulative rehospitalization-free survival rates between the two groups (P=0.0326) [Figure 1: see original paper]. No severe adverse reactions such as hypoglycemia, hypotension, allergy, or ketoacidosis occurred in either group during follow-up. Two cases (4.3%) of urinary tract infection were observed in the dapagliflozin group, which resolved after anti-infective treatment.

Multivariate Cox Regression Analysis of Factors Influencing Rehospitalization Events

In this study, univariate Cox regression analysis was performed with rehospitalization events during follow-up (assignment: no=0, yes=1) as the dependent variable and dapagliflozin use (assignment: no=0, yes=1), age (assignment: actual value), BMI (assignment: actual value), comorbidities (assignment: no=0, yes=1), ACEI/ARB/ARNI use (assignment: no=0, yes=1), spironolactone (assignment: no=0, yes=1), and anthracycline use (assignment: no=0, yes=1) as independent variables. Variables with statistically significant differences were included in multivariate Cox regression analysis. The results showed that dapagliflozin use (HR=0.325, 95%CI=0.116~0.912, P=0.033), ACEI/ARB/ARNI use (HR=0.562, 95%CI=0.236~0.949, P=0.035), and spironolactone (HR=0.836, 95%CI=0.710~0.985, P=0.037) were protective factors against rehospitalization events, while increasing age (HR=1.343, 95%CI=1.198~1.506, P<0.001), higher BMI (HR=1.305, 95%CI=1.111~1.532, P=0.001), and anthracycline use (HR=1.197, 95%CI=1.035~1.384, P=0.023) were risk factors for increased rehospitalization events .

Discussion

Cardiovascular disease is the leading cause of non-cancer death among cancer survivors [**?**],[**?**]. Breast cancer, as one of the most common cancer types, has survivors who face significantly increased short-term and long-term cardiovascular mortality and morbidity. Previous research has primarily focused on heart

failure with reduced ejection fraction (HFrEF), but recent studies indicate that HFpEF is more common among breast cancer survivors [?]. The pathophysiological mechanisms of HFpEF are complex, involving systemic inflammation, myocardial microvascular dysfunction, metabolic disorders, epicardial fat accumulation, and myocardial fibrosis [?]. In breast cancer survivors, the observed increased risk of HFpEF may be associated with many shared risk factors, such as age, lifestyle factors, comorbidities, cancer-related inflammation, and iatrogenic effects of treatment [?]. Therefore, adverse cardiovascular outcomes in cancer survivors remain a major challenge to improving cancer outcomes.

In recent years, cardio-oncology research has received increasing attention. The "2022 ESC Guidelines on Cardio-Oncology" [?] comprehensively elaborated on the diagnosis and management strategies for various types of cancer therapy-related cardiovascular toxicity (CTR-CVT). Subsequently, the updated "CSCO Guidelines for Cardio-Oncology 2023" [?] expanded from focusing on cardiovascular toxicity prevention and treatment to cardio-oncology, adding two new cardioprotective therapeutic drugs (angiotensin receptor neprilysin inhibitors and SGLT2i).

SGLT2i is a novel class of hypoglycemic agents that has been shown to reduce oxidative stress, improve inflammation, and provide cardiovascular benefits. Meta-analyses have demonstrated that SGLT2i is safe in patients with heart disease or malignant tumors [?],[?]. Meta-analyses of mouse models have shown that SGLT2i can prevent anthracycline-induced left ventricular dysfunction [?]. Systematic reviews by CHONG et al. [?] and KUO et al. [?] also support the cardioprotective potential of SGLT2i in cancer therapy-related cardiac dysfunction. In our study results, dapagliflozin effectively reduced FPG and HbA1c while improving eGFR levels, with superior outcomes compared to the control group. This further confirms the significant effects of dapagliflozin as an SGLT2i in metabolic and renal function management, providing important evidence for future treatment optimization and new hope for improving cardiac health and quality of life in breast cancer survivors, while further expanding the application of SGLT2i in the field of cardio-oncology.

SGLT2i offers dual advantages in metabolic and renal protection: it improves metabolic status not only by lowering blood glucose but also by enhancing renal function protection, thereby reducing cardiovascular and renal disease risks in diabetic patients. SGLT2i can reduce left ventricular load, slow the progression of cardiac fibrosis and inflammatory responses, effectively improve myocardial energy metabolism, and exert varying degrees of improvement on cardiac structure and function in heart failure patients at different clinical stages [?]. Our study results showed that the dapagliflozin group demonstrated significant improvements in all cardiac function parameters, superior to the control group. This is consistent with the research report by GIANGIACOMI et al. [?], indicating that dapagliflozin has significant advantages in improving cardiac function in elderly breast cancer survivors, can ameliorate heart failure status, and improve quality of life.

Patients enrolled in this study underwent testing for cardiac biomarkers NT-proBNP and hs-cTnI. These markers are used to assess cardiovascular disease risk, monitor responses to cardioprotective therapy, and predict prognosis in patients receiving cardiotoxic anticancer therapy [**?**]. Additionally, NT-proBNP can independently reflect cardiac function and evaluate long-term prognosis of heart failure [**?**]. In our study, NT-proBNP and hs-cTnI levels significantly improved after treatment in the dapagliflozin group, indicating that it not only reduces cardiac load and improves myocardial injury but also has positive effects on cardiac function. The Kaplan-Meier survival analysis results further demonstrated that dapagliflozin can significantly improve the long-term prognosis of HFpEF patients among breast cancer survivors. This is consistent with the observation by CHIANG et al. [**?**] that SGLT2i users had lower heart failure hospitalization rates and improved overall survival.

In the multivariate Cox regression analysis, we evaluated factors associated with rehospitalization risk in breast cancer survivors. The results showed that dapagliflozin, age, BMI, ACEI/ARB/ARNI use, spironolactone use, and anthracycline chemotherapy regimens were all significantly associated with rehospitalization events. Specifically, dapagliflozin significantly reduced rehospitalization risk, demonstrating its protective role in heart failure management. Additionally, anthracycline chemotherapy regimens significantly increased rehospitalization risk, likely related to their cardiotoxicity. Traditional cardiovascular risk factors such as age and BMI were also significantly associated, emphasizing the importance of individualized management. ACEI/ARB/ARNI and spironolactone use showed potential benefits in reducing cardiac burden and improving prognosis.

This study has several limitations: it is a retrospective observational study with a limited sample size and short follow-up duration, which may introduce certain biases and errors. Future larger-scale, long-term prospective multicenter studies are needed to obtain more reliable evidence. Further exploration of SGLT2i application in survivors of other cancer types, evaluation of its long-term efficacy and safety, and investigation of its potential in combination therapy are warranted to maximize cardiovascular health and quality of life in cancer survivors.

In summary, dapagliflozin demonstrates significant advantages in improving cardiac function, metabolism, and renal function in elderly female breast cancer survivors. Overall, this study highlights the importance of SGLT2i application in cancer survivors, particularly in those with cardiovascular risk. Dapagliflozin not only shows excellent performance in glycemic control and renal function improvement but also provides cardiac protection and heart failure management benefits.

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