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Investigating cardiovascular diseases related to endocrine therapy in hormone receptor-positive early breast cancer: insights from a nationwide real-world study

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Abstract

Background Breast cancer (BC) patients face abnormal lipid metabolism and increased cardiovascular disease (CVD) risk due to endocrine therapies (ETs). This study evaluates CVD incidence and lipid abnormalities in Chinese patients with early-stage hormone receptor-positive (HR+) BC to inform personalized treatments.

Methods Data from female patients aged 18–80 years with stage I-III HR + BC registered in the National Cancer Center Oncology Information Database (NCCOID) (2013–2018) were analyzed. Outcomes included lipid profile changes, CVD incidence, and five-year survival rates.

Results Among 11,537 patients, ETs significantly disrupted lipid metabolism, increasing abnormal total cholesterol, triglycerides, LDL-C, and HDL-C levels. Nonsteroidal aromatase inhibitors (NSAI) ± ovarian function suppression (OFS) led to the largest increase in abnormal total cholesterol (10.26 to 17.32%), while selective estrogen receptor modulators (SERM) ± OFS caused the greatest rises in triglycerides (16.07 to 25.86%), LDL-C (12.11 to 23.34%), and HDL-C (10.86 to 17.23%). Only 3.82% of patients received lipid-lowering therapy. ETs were associated with higher CVD incidence, including hypertension, myocardial infarction, and atrial fibrillation, but five-year survival rates did not differ significantly across ET regimens ($P > 0.05$).

Conclusion ETs may be associated with alterations in lipid metabolism and a potential increase in CVD risk in early-stage HR + BC patients. These findings highlight the relevance of enhanced lipid monitoring and cardiovascular risk management to support optimized treatment outcomes in the Chinese population.

Keywords Breast cancer, Lipid, Endocrine therapy, Cardiovascular events

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Introduction

Breast cancer (BC) is one of the most common malignancies in women, with hormone receptor-positive (HR+) BC accounting for about 70% of all molecular subtypes [1–3]. For patients diagnosed with early-stage HR + BC, endocrine therapies (ETs) are the standard adjuvant treatment, most commonly using selective estrogen receptor modulators (SERMs), such as tamoxifen, or aromatase inhibitors (AIs) [1, 2]. These agents reduce tumor proliferation and metastasis by blocking or suppressing estrogen activity, significantly lowering the risk of recurrence and improving patient survival outcomes [4]. Despite the clear clinical benefits of ETs in reducing BC-specific mortality, its long-term use raises concerns about potential adverse effects. Cardiovascular complications and metabolic syndrome have all been associated with extended ETs use [5, 6]. These concerns highlight the need for ongoing surveillance and individualized management strategies to balance the benefits of therapy with the risks of side effects.

The relationship between ETs and cardiovascular diseases (CVDs) has become a significant focus of recent research. Some studies suggest that tamoxifen may lower cardiovascular risks in BC patients. For instance, a nationwide health data analysis indicated that tamoxifen significantly reduced the incidence of CVDs compared to patients who did not receive ETs, with a hazard ratio of 0.84 (95% confidence interval (CI): 0.74–0.97, $P = 0.014$) [7]. However, other findings, such as from the NSABP B-14 trial, showed no significant cardiovascular protective effect of tamoxifen compared to placebo [8]. Moreover, tamoxifen has been associated with an increased risk of venous thromboembolic events, including pulmonary embolism and stroke [9–13].

AIs, another widely used class of ETs, have been linked to an increased risk of adverse cardiovascular outcomes [14, 15]. Patients receiving AIs tend to experience a higher incidence of cardiovascular events compared to those treated with tamoxifen, including hypertension, atherosclerosis, myocardial infarction, and heart failure [15–19]. A recent real-world study based on the FDA Adverse Event Reporting System (FAERS) identified a significant association between letrozole and increased risks of arrhythmia (reporting odds ratio (ROR) = 2.2; 95% CI: 1.8–2.5) and myocardial infarction (ROR = 1.9; 95% CI: 1.4–2.6). Additionally, letrozole use was found to be significantly associated with an elevated risk of heart failure (ROR = 1.3; 95% CI: 1.1–1.6) [20]. However, current research on the CVDs of ETs in BC patients remains inconsistent, as most studies rely on data from clinical trials, which may not fully capture the long-term cardiovascular outcomes in diverse real-world populations, particularly in Chinese patients. This highlights the importance of further investigation into the cardiovascular risks associated with different ETs, particularly tamoxifen and AIs, in patients with early-stage HR + BC. Moreover, understanding how these risks manifest in real-world clinical settings is critical for guiding treatment choices. Therefore, it is essential to evaluate the cardiovascular risks associated with ETs in this patient population to support informed, personalized treatment decisions.

Building upon these prior findings, our study leverages a nationwide oncology database to provide a comprehensive real-world assessment of the impact of ETs on CVDs in a large cohort of Chinese patients with early-stage HR + BC patients. Additionally, we will investigate the dynamic effects of different endocrine regimens on lipid profiles. By providing comprehensive data on the long-term safety of ETs, this study aims to support clinicians in making informed, personalized treatment decisions, ultimately aiming to improve BC's survival while minimizing cardiovascular risks.

Materials and methods

Data source

This multi-center, observational cohort study aims to assess CVDs in patients with early-stage HR + BC following ETs. It employs a longitudinal design to track both patient survival and cardiovascular health over time. Data were obtained from the National Cancer Center Oncology Information Database (NCCOID) of China. The NCCOID is a longitudinal, electronic medical record (EMR)-based platform covering cancer-related data from 1,422 monitoring hospitals across 31 provinces in China, encompassing over 10 million cancer patients from 2013 to the present. It is the largest cancer database in China. The database is securely maintained in compliance with privacy regulations and has received approval from the Human Genetic Resources Administration of China (HGRAC). To protect patient privacy, all identifiable personal information, such as names and ID numbers, has been removed, ensuring confidentiality in compliance with ethical and legal standards. The NCCOID database contains 19 categories, 25 data tables, and 1,509 variables, including demographic and socioeconomic characteristics, clinical features, medical records, physician orders, laboratory test results, pathological findings, and molecular pathology reports. This study was approved by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital (Approval number: 21/369–3040). All procedure were performed in accordance with the Declaration of Helsinki and the International Conference for Harmonization/Good Clinical Practice guidelines.

Study design

Inclusion Criteria:1) Female patients diagnosed with early-stage BC (ICD-10: C50) confirmed via histopathological examination between January 1, 2013, and December 31, 2018, with clinical stages I, II, or III invasive carcinoma. 2) Age between 18 and 80 years [21]. 3) Patients confirmed as estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) through immunohistochemistry (≥ 1% of cells). 4) Baseline data must include at least one lipid profile test (including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) prior to initiating endocrine therapy, and at least two subsequent lipid tests within two years post-therapy initiation. Exclusion Criteria: (1) Pregnant or breastfeeding patients. (2) Patients with inflammatory BC. (3) Patients with metastatic BC. (4) Patients with a prior malignancy diagnosed within five years before their BC diagnosis or those who developed another malignancy within five years after diagnosis. The flowchart of the study is presented in Fig. 1.

Definition of dyslipidemia

Dyslipidemia is defined based on the "2016 Chinese guidelines for the management of dyslipidemia in adults" and is operationally determined using the following biochemical thresholds: total cholesterol concentration (TC) ≥ 6.2 mmol/L, triglyceride concentration (TG) ≥ 2.3 mmol/L, low-density lipoprotein cholesterol(LDL-C)≥4.1 mmol/L, or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L [22].

The follow-up endpoint is defined as the last recorded lipid test performed during the post-ETs period. This ensures a final evaluation of lipid levels at the conclusion of the observation phase. The maximum follow-up period extends to 24 months, allowing for a comprehensive assessment of lipid profile changes. In cases where no lipid test was conducted within this period, the endpoint will default to the 24-month mark.

Variables

In this study, patient demographic characteristics (age, body mass index), as well as clinical data (smoking history, alcohol consumption history, menopausal status, tumor stage, number of lymph node metastases, and receptor status—ER, PR, and human epidermal growth factor receptor 2 [HER2]), were extracted from the NCCOID. All data were obtained following the predefined inclusion and exclusion criteria.

ET strategies for breast cancer patients in China primarily follow three major guidelines: the National Health Commission Breast Cancer Diagnosis and Treatment Guidelines, the China Anti-Cancer Association Committee of Breast Cancer Society (CACA-CBCS) Guidelines, and the Chinese Society of Clinical Oncology (CSCO) Guidelines. ET regimens administered to HR + BC patients included SERMs such as tamoxifen and toremifene, non-steroidal AIs (NSAIs) like anastrozole and letrozole, and steroidal AIs such as exemestane. Additionally, ovarian function suppressants (OFS), including goserelin and leuprolide, were incorporated into the treatment protocols when clinically indicated.

Data regarding the incidence of CVDs—hypertension, angina pectoris, myocardial infarction, heart failure, and atrial fibrillation—were recorded both pre- and post-endocrine therapy. Lipid profile parameters, including TC, TG, LDL-C, and HDL-C, were collected and compared before and after treatment.

Overall survival analysis

Overall survival (OS) was defined as the period from the initiation of the first endocrine therapy to death from any cause. For patients still alive at the time of analysis, the last known survival date was used for censoring. When the last known survival date was incomplete, imputation rules were applied to estimate the date of death.

A descriptive analysis of OS was performed for patients receiving different adjuvant endocrine therapy regimens. The Kaplan-Meier method was employed to estimate the survival function for each treatment group, with survival curves plotted to visually represent the data. Comparisons of OS between treatment groups were performed using the log-rank test.

Furthermore, assuming proportional hazards, a Cox proportional hazards model was utilized to estimate hazard ratios (HRs) and their respective 95% CIs between different groups. Survival rates were calculated at 6 months, 1 year, 2 years, and 5 years, offering a comprehensive overview of the treatment outcomes across time.

Statistical analysis

Statistical analyses were conducted by a dedicated biostatistics team with expertise in oncology epidemiology and clinical data analysis (Beijing Yiyong Technology Co., Ltd.). To ensure the accuracy and reliability of the results, the analyses were independently reviewed by a senior biostatistician prior to finalization. Statistical analysis was performed using R software (version 4.2.2). To address missing data, multiple imputation using chained equations (MICE) was applied for continuous variables to provide more robust and unbiased estimates. For categorical variables, missing values were managed using inverse probability weighting (IPW) to minimize potential bias. A two-sided significance level of 5% was applied throughout the study, and all CIs were calculated at a 95% confidence level. Continuous variables were summarized descriptively, reporting the number of subjects, mean, and standard deviation (SD). Chi-square test was used to

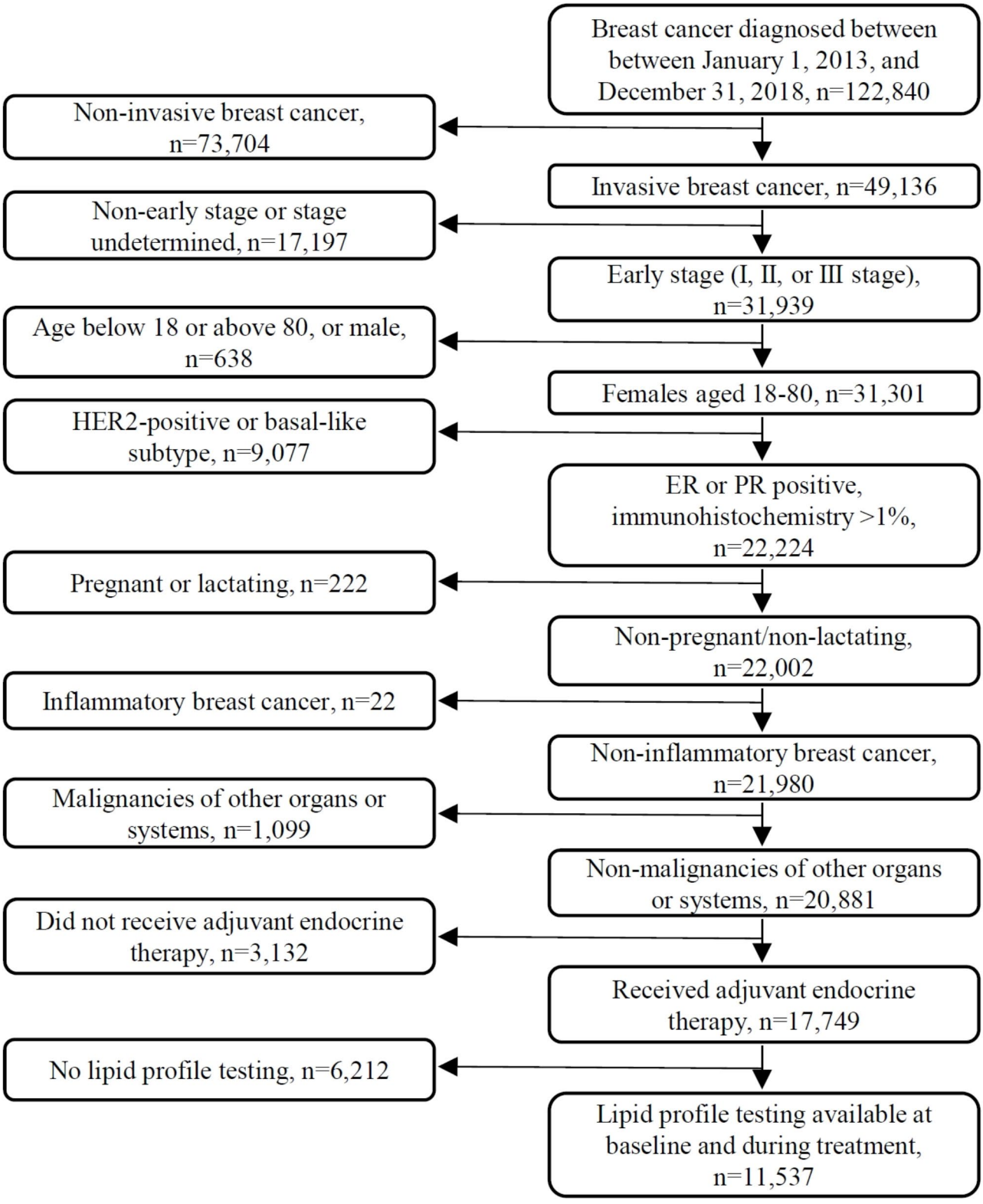

Fig. 1 Cohort flowchart

compare the differences of categorical variables. Specifically, associations were examined between cardiovascular-related comorbidities before and after treatment, as well as between lipid profiles before and after treatment. For matched pairs with expected frequencies less than 5, Fisher's exact test was applied to ensure statistical accuracy. Categorical variables were presented as frequencies and percentages.

Results

Demographic and other baseline characteristics

All participants were female, with a mean age of 49.3 (ranging from 19 to 80 years). Most participants were aged 40–59 years (67.19%), with only 1.77% under 30. Tumor staging was primarily stage II (51.43%, 5,934 cases), while stage I and III comprised 23.89% (2,756 cases) and 24.68% (2,847 cases), respectively. The predominant pathological type was invasive BC (74.92%, 4,591 cases), with HR+/HER2- being the most common molecular subtype (54.25%, 6,259 cases) and HR+/HER2 + at 26.94% (3,108 cases). Patients received various adjuvant ET regimens, including SERM ± OFS (46.10%, 5,319 cases), NSAI ± OFS (39.19%, 4,521 cases), AI ± OFS (11.82%, 1,364 cases), OFS (2.70%, 311 cases), and others (0.19%, 22 cases).

Statins emerged as the most commonly prescribed lipid-lowering medication, utilized by 390 patients (88.44%). At baseline, the mean TC level was 4.912 (SD: 1.1748) mmol/L, with 22.12% (1,669 patients) exhibiting abnormal levels. The mean TG concentration was 1.696 (SD: 1.1678) mmol/L, with 35.46% (3,513 patients) classified as abnormal. The mean LDL-C level was 3.001 (SD: 0.8970) mmol/L, with 29.36% (2,543 patients) falling outside the normal range. Meanwhile, the mean HDL-C level was 1.320 (SD: 0.5708) mmol/L, with 24.07% (2,098 patients) presenting as abnormal.

The baseline characteristics of the study participants are summarized in Table 1.

Cardiovascular events incidence pre- and post-adjuvant ETs

Among 2913 patients who developed hypertension post-ETs, 6.5% (188 individuals) were newly diagnosed, indicating a potential risk associated with the therapy. For angina, 60.7% of the 28 patients experienced symptoms for the first time after ETs, suggesting that it may contribute to new cases. In terms of myocardial infarction, 40.9% (27 patients) developed the condition post-ETs without prior history. Additionally, among 26 patients with heart failure, 65.4% (17 patients) reported new onset after ETs, while in the 3213 patients with atrial fibrillation, 11.2% (361 patients) were newly diagnosed (Table 2).

These findings collectively indicate a potential association between ETs and an increased incidence of various

Table 1 Patients' baseline characteristics and treatment information

Variables	Total (N = 11537)
Mean age (SD), years	49.3 (10.04)
Age group, n/N (%)	
< 30 years	204/11537 (1.77)
30–39 years	1699/11537 (14.73)
40–49 years	4259/11537 (36.92)
50–59 years	3492/11537 (30.27)
≥ 60 years	1883/11537 (16.32)
Female, n/N (%)	11537/11537 (100.00)
Mean height (SD), cm	159.7 (5.73)
Mean Weight (SD), kg	61.1 (8.98)
Mean BMI (SD), kg/m^2	24.10 (3.386)
Smoking history, n/N (%)	
Ex-smoker	6/7597 (0.08)
Current smoker	59/7597 (0.78)
Non-smoker	7532/7597 (99.14)
Alcohol history, n/N (%)	
Ex-drinker	36/7595 (0.47)
Current drinker	27/7595 (0.36)
Non-drinker	7532/7595 (99.17)
Hypertension, n/N (%)	4455/11528 (38.65)
Diabetes, n/N (%)	7862/11528 (68.20)
Menopausal status, n/N (%)	
Premenopausal	3828/6413 (59.69)
Postmenopausal	2585/6413 (40.31)
Tumor site, n/N (%)	
Bilateral breasts	152/6093 (2.49)
Right breast	2951/6093 (48.43)
Left breast	2990/6093 (49.07)
Tumor staging, n/N (%)	
Stage I	2756/11537 (23.89)
Stage II	5934/11537 (51.43)
Stage III	2847/11537 (24.68)
Number of lymph node metastases, n/N (%)	
1–3	21/62 (33.87)
4–9	23/62 (37.10)
≥ 10	18/62 (29.03)
ER status, n/N (%)	
Positive	381/11434 (3.33)
Negative	11053/11434 (96.67)
PR status, n/N (%)	
Positive	1374/11224 (12.24)
Negative	9850/11224 (87.76)
HER2 status, n/N (%)	
Positive	5971/9367 (63.75)
Negative	3108/9367 (33.18)
Low expression	288/9367 (3.07)
Molecular type, n/N (%)	
$HR^+/HER2^-$	6259/11537 (54.25)
$HR^+/HER2^+$	3108/11537 (26.94)
Others	2170/11537 (18.81)
Total cholesterol	
Mean (SD), mmol/L	4.912 (1.1748)

Table 1 (continued)

Variables	Total (N = 11537)
Abnormal, n/N (%)	1669/7545 (22.12)
Normal, n/N (%)	5876/7545 (77.88)
Triglyceride	
Mean (SD), mmol/L	1.696 (1.1678)
Abnormal, n/N (%)	3513/9907 (35.46)
Normal, n/N (%)	6394/9907 (64.54)
LDL cholesterol	
Mean (SD), mmol/L	3.001 (0.8970)
Abnormal, n/N (%)	2543/8661 (29.36)
Normal, n/N (%)	6118/8661 (70.64)
HDL cholesterol	
Mean (SD), mmol/L	1.320 (0.5708)
Abnormal, n/N (%)	2098/8718 (24.07)
Normal, n/N (%)	6620/8718 (75.93)
Adjuvant endocrine therapy, n/N (%)	
SERM ± OFS	5319/11537 (46.10)
NSAI ± OFS	4521/11537 (39.19)
AI ± OFS	1364/11537 (11.82)
Hypolipidemic therapy, n/N (%)	
Statins	390/441 (88.44)
Fenofibrate	25/441 (5.67)
Fenofibrate + statins	3/441 (0.68)
Fenofibrate + others	2/441 (0.45)
Cholesterol absorption inhibitors + statins	2/441 (0.45)
Statins + others	1/441 (0.23)
others	18/441 (4.08)

Abbreviation: AI, aromatase inhibitor; ER, estrogen receptor; BMI, body mass index; HDL, high density lipoprotein; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LDL, low density lipoprotein; NSAI, nonsteroidal aromatase inhibitors; OFS, ovarian function suppression; PR, progesterone receptor; SD, standard deviation; SERM, selective estrogen receptor modulator

cardiovascular diseases in HR + BC patients. Table 2 presents important data regarding the incidence of cardiovascular diseases in patients undergoing ETs.

Dyslipidemia incidence among different adjuvant ETs' regimens

Among 2,485 patients with elevated TC post-treatment, 1,332 (53.6%) had normal baseline levels (Table 3). Similarly, 2,346 out of 4,882 patients (48.1%) with abnormal TC concentrations, 1,332 out of 4,132 (53.6%) with abnormal LDL-C, and 1,410 out of 2,786 (50.6%) with abnormal HDL-C also started with normal levels (Table 3). These findings indicate that ETs may induce lipid disturbances in HR + BC patients.

Further analysis in Supplementary Tables 1 and Fig. 2 reveals significant increases in abnormal lipid levels post-treatment. After SERM ± OFS, abnormal TC rose from 8.52 to 14.88%, while NSAI ± OFS increased from 10.26 to 17.32%, and AI ± OFS from 2.90 to 4.90%, with NSAI ± OFS showing the largest increase (7.06%). For TG concentrations, rates after SERM ± OFS rose from 16.07 to 25.86%, NSAI ± OFS from 14.64 to 22.40%, and AI ± OFS from 4.19 to 5.86%, with SERM ± OFS leading to a 9.79% increase. Regarding LDL-C, rates increased from 12.11 to 23.34% after SERM ± OFS, 12.53 to 22.45% after NSAI ± OFS, and 4.21 to 7.27% after AI ± OFS, with the largest rise from SERM ± OFS at 11.23%. Finally, HDL rates increased from 10.86 to 17.23% after SERM ± OFS, 9.08 to 14.64% after NSAI ± OFS, and 3.62 to 5.50% after AI ± OFS, with SERM ± OFS showing the most significant rise of 6.37%. Overall, SERM ± OFS treatment has the most substantial impact on TG, LDL-C, and HDL-C, while NSAI ± OFS primarily affects TGs.

Survival outcomes of patients with normal vs. abnormal lipid levels on adjuvant ETs

Patients receiving NSAI + OFS and AI alone had the highest 5-year survival rates at 98.78% (95% CI: 97.91–99.65%) and 98.33% (95% CI: 96.76–99.92%), respectively. The AI + OFS regimen followed with a rate of 97.57% (95% CI: 94.66–100.00%). The 5-year survival rates for SERM + OFS, NSAI, and SERM alone were similar, ranging from 96.40 to 96.65%, while the OFS regimen had the lowest rate at 93.26% (95% CI: 83.51–100.00%). Supplementary Tables 2 and Fig. 3 summarize the OS outcomes for patients receiving different adjuvant endocrine therapy regimens. There were no significant differences in median OS among patients treated with SERM + OFS, AI + OFS, and NSAI + OFS compared to those receiving AI alone, NSAI alone, SERM alone, or OFS alone (all $P > 0.05$). Currently, the median OS has not been reached for any group (Supplementary Tables 3 and Fig. 4), with 5-year survival rates of 96.88% (95% CI: 95.92–97.85%) for those with abnormal lipid levels and 97.53% (95% CI: 96.63–98.44%) for those with normal lipid levels.

There was minimal difference in median OS between patients with abnormal and normal lipid levels at baseline ($P = 0.6389$), with 5-year survival rates of 96.88% for those with abnormal levels and 97.53% for those with normal levels. No significant differences in overall survival were found among patients with abnormal and normal lipid levels receiving various adjuvant ETs (all $P > 0.05$).

Among patients with baseline dyslipidemia, those receiving OFS monotherapy exhibited the highest 5-year OS rate at 100.00% (95% CI: 100.00–100.00%). This was followed by NSAI+OFS (98.90%, 95% CI: 97.82–99.98%), AI monotherapy (98.20%, 95% CI: 95.99–100.00%), SERM+OFS (97.44%, 95% CI: 95.16–99.78%), and AI+OFS (97.30%, 95% CI: 92.21–100.00%). In contrast, patients treated with NSAI or SERM monotherapy showed slightly lower 5-year OS rates of 96.42% (95% CI: 94.96–97.89%) and 96.68% (95% CI: 94.96–98.42%), respectively (Supplementary Table 2). Among patients with normal baseline lipid levels, those treated with SERM monotherapy had the highest 5-year OS rate at

Table 2 Cardiovascular-related comorbidities before and after treatment (*N* = 11537)

Baseline comorbidities	Post-treatment comorbidities			χ2	*P* value
	Yes	No	Unknown		
Hypertension, n (%)				4952.60	0.000
Yes	2722 (93.4)	1694 (19.9)	39 (30.5)		
No	188 (6.5)	6796 (80.0)	89 (69.5)		
Unknown	3 (0.1)	6 (0.1)	0(0.0)		
Angina pectoris, n (%)				1319.2	0.000
Yes	10 (35.7)	22 (0.2)	0(0.0)		
No	17 (60.7)	11,351 (99.7)	128 (100.0)		
Unknown	1 (3.6)	8 (0.1)	0		
Myocardial infarction, n (%)				2231.2	0.000
Yes	38 (57.6)	73 (0.6)	1 (0.8)		
No	27 (40.9)	11,262 (99.3)	127 (99.2)		
Unknown	1 (1.5)	8 (0.1)	0		
Heart failure, n (%)				1319.6	0.000
Yes	9 (34.6)	18 (0.2)	0		
No	17 (65.4)	11,356 (99.8)	128 (100.0)		
Unknown	0	9 (0.1)	0		
Atrial fibrillation, n (%)				3270.1	0.000
Yes	2851 (88.7)	2410 (29.4)	57 (44.5)		
No	361 (11.2)	5778 (70.5)	71 (55.5)		
Unknown	1 (0.03)	8 (0.1)	0		

Table 3 Lipid profiles before and after treatment in patients

Baseline variables	Total	Post-treatment variables		χ2	*P* value
		Abnormal	Normal		
Total cholesterol, n (%)	6768			1373.8	0.000
Abnormal		1153 (46.4)	330 (7.7)		
Normal		1332 (53.6)	3953 (92.3)		
Triglyceride, n (%)	8738			1335.5	0.000
Abnormal		2536 (51.9)	551 (14.3)		
Normal		2346 (48.1)	3305 (85.7)		
LDL cholesterol, n (%)	7436			937.25	0.000
Abnormal		1816 (43.9)	375 (11.3)		
Normal		2316 (56.1)	2929 (88.7)		
HDL cholesterol, n (%)	7506			1580.3	0.000
Abnormal		1376 (49.4)	418 (8.9)		
Normal		1410 (50.6)	4302 (91.1)		

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein

99.08% (95% CI: 98.34–99.83%), followed by NSAI+OFS (97.28%, 95% CI: 94.68–99.96%) and AI monotherapy (97.22%, 95% CI: 93.47–100.00%). The 5-year OS rates for patients receiving SERM+OFS, AI+OFS, and NSAI monotherapy were 96.75% (95% CI: 94.52–99.03%), 96.48% (95% CI: 91.81–100.00%), and 96.35% (95% CI: 93.89–98.87%), respectively (Supplementary Table 2).Overall, these findings indicate minimal differences in survival between patients with abnormal and normal lipid levels receiving various adjuvant endocrine therapy regimens (all $P > 0.05$).

Discussion

The findings of this study highlight a potential increase in the incidence of cardiovascular diseases following ET in patients with HR + early-stage BC. Specifically, there was a rise in the occurrence of conditions such as hypertension, angina, myocardial infarction, and heart failure after treatment. While some patients had pre-existing cardiovascular issues, others developed these conditions for the first time during or after ET. The incidence rates of hypertension (6.5%) and atrial fibrillation (11.2%) post-therapy are of particular concern, suggesting that ET may exacerbate cardiovascular risk through hormone modulation or by inducing metabolic disturbances. Previous studies have emphasized the differential cardiovascular

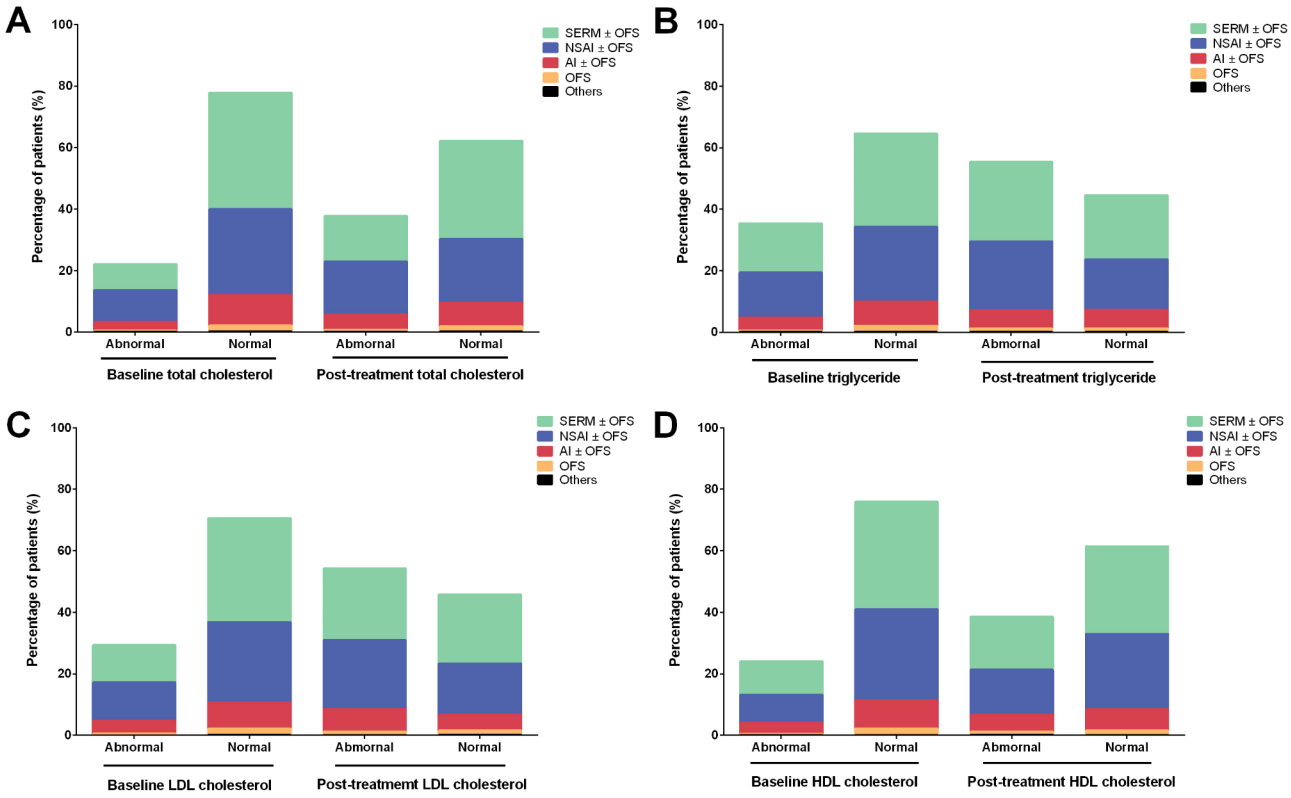

Fig. 2 Adjuvant endocrine therapy of patients in subgroups of baseline and post-treatment lipid profiles. (**A**) Total cholesterol concentration; (**B**) triglyceride concentration; (**C**) LDL cholesterol and (**D**) HDL cholesterol levels

effects of tamoxifen and AIs. Tamoxifen has been shown to improve lipid profiles but is associated with an increased risk of venous thromboembolism (VTE) [9–13, 23–25]. In contrast, AIs have been linked to adverse cardiovascular outcomes, including a higher incidence of hypertension, atherosclerosis, myocardial infarction, and heart failure [15–19]. The current study supports these findings, underscoring the need for regular cardiovascular monitoring, especially for patients with pre-existing conditions undergoing long-term ET [8]. Therefore, patients undergoing these therapies, particularly those with pre-existing cardiovascular conditions, should be monitored regularly and provided with tailored interventions. Notably, our dataset does not systematically record disease recurrence status or subsequent treatment modifications, which may introduce potential confounding in the observed associations. This limitation constrains our ability to fully account for the impact of recurrence-related therapies on cardiovascular outcomes. Future studies incorporating longitudinal data on recurrence and treatment adjustments are necessary to provide a more comprehensive understanding of these effects.

In addition to cardiovascular complications, our study revealed a significant increase in dyslipidemia following ET. Patients treated with SERM ± OFS and NSAI ± OFS regimens exhibited the highest rates of lipid abnormalities, with substantial increases in total cholesterol, triglycerides, LDL-C, and HDL-C. Notably, patients receiving SERM ± OFS experienced marked elevations in LDL-C (+ 11.23%) and triglycerides (+ 9.79%), suggesting that these therapies may disrupt lipid metabolism by blocking estrogen receptors or inhibiting estrogen synthesis. These findings emphasize the importance of incorporating routine lipid monitoring into clinical practice for patients undergoing ET. Importantly, only 3.82% of patients with baseline dyslipidemia received appropriate lipid management during the study, highlighting a critical gap in patient care. More personalized lipid-lowering strategies should be employed to prevent metabolic disorders and reduce cardiovascular risks during BC treatment.

To further contextualize our findings, it is important to acknowledge that additional factors beyond ET may influence cardiovascular outcomes and lipid metabolism. While our study primarily focused on ET-associated risks, other pharmacological interventions, including medications for managing lifestyle-related diseases such as hypertension, diabetes, and hyperlipidemia, could also play a role in modifying cardiovascular risk. However, due to database limitations, we were unable to systematically capture information on concurrent medication use, which may have influenced our results.

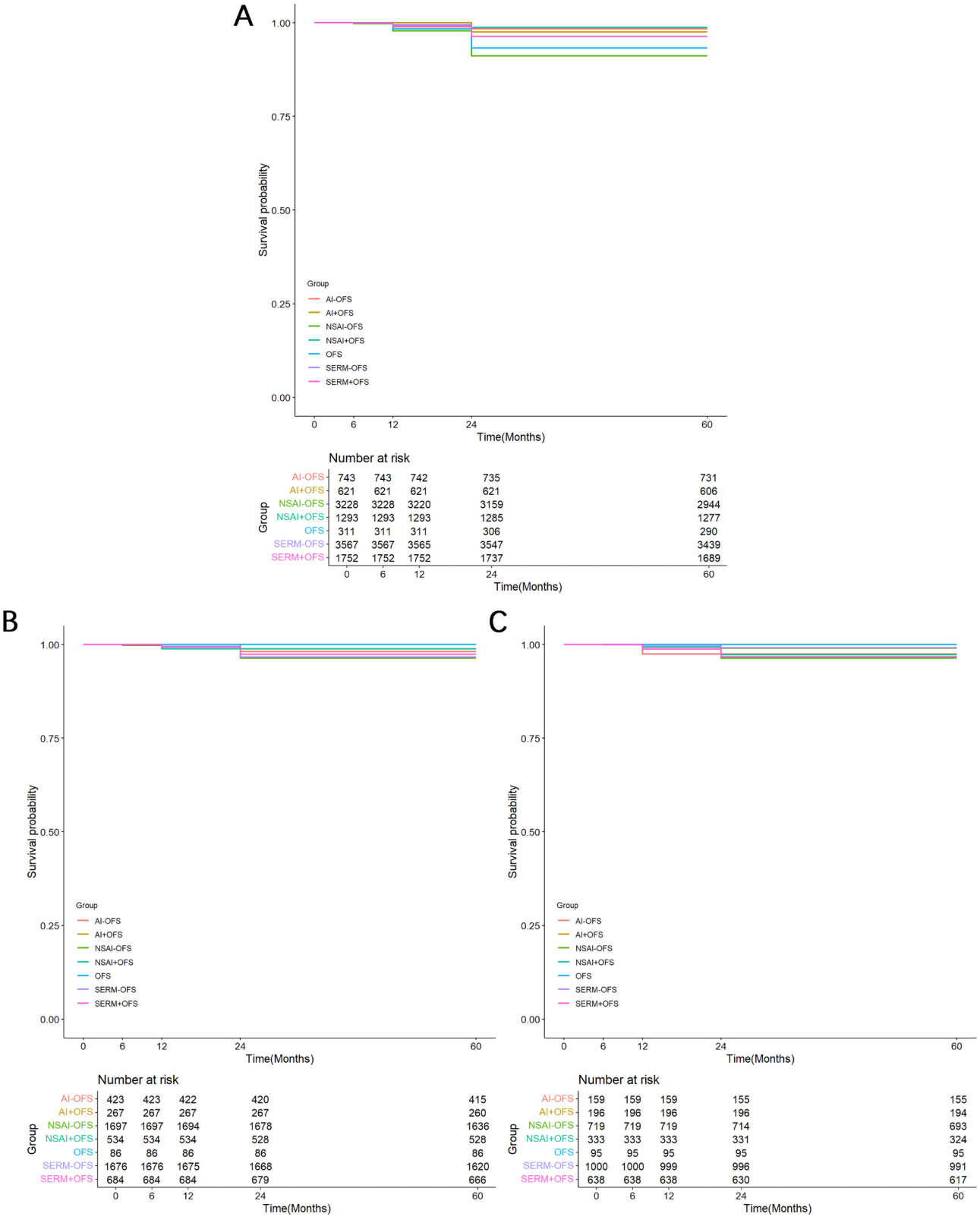

Fig. 3 Overall survival of patients with different adjuvant endocrine regimens in (**A**) overall populations and in subgroups with (**B**) baseline normal and (**C**) dyslipidemia lipids. Note: Due to incomplete follow-up data, only five time points—0, 6, 12, 24, and 60 months—have been documented, without specific records of deaths or censoring events. Consequently, this figure serves solely as a reference

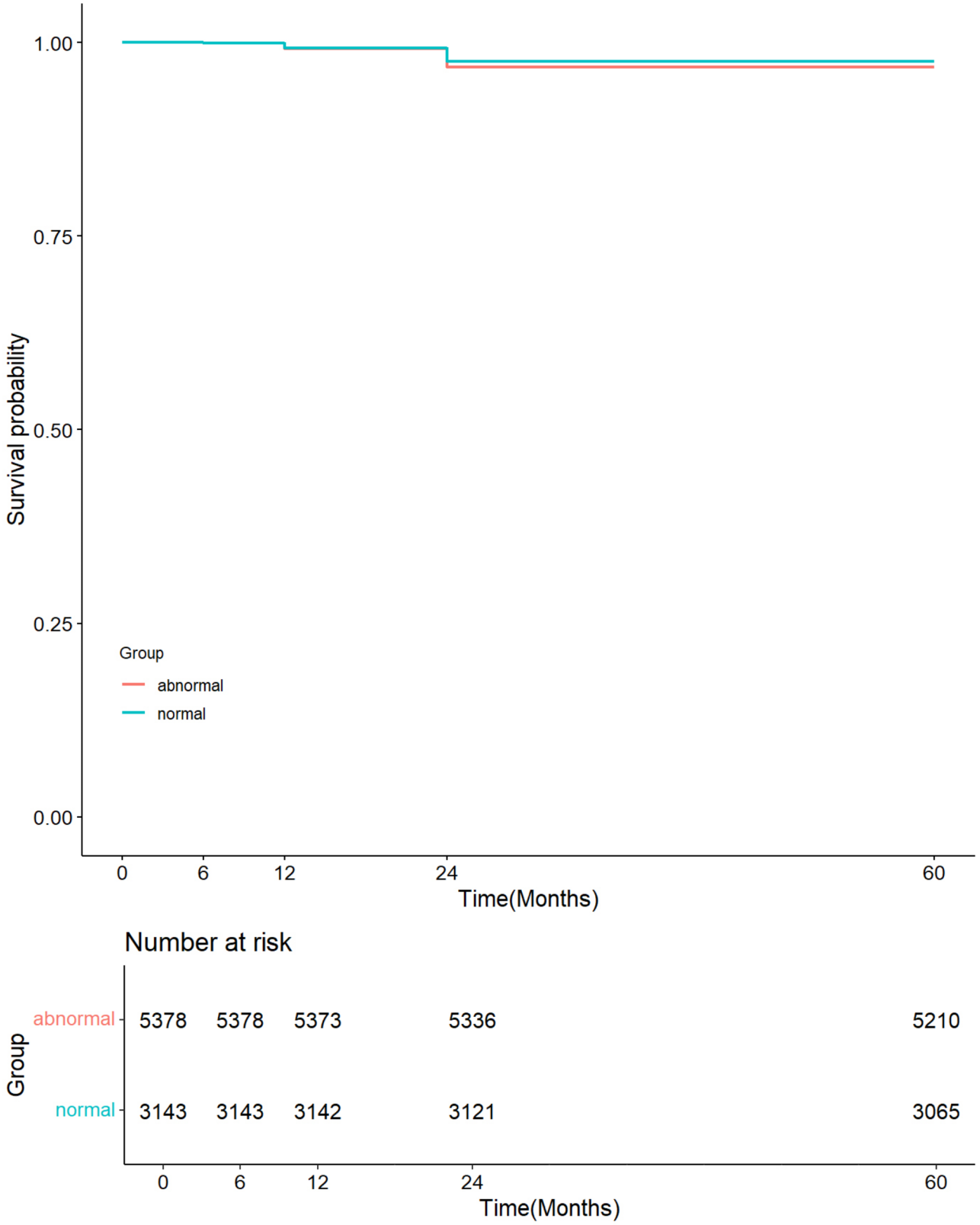

Fig. 4 Overall survival of patients in subgroups with baseline dyslipidemia and normal lipids. Note: Due to incomplete follow-up data, only five time points—0, 6, 12, 24, and 60 months—have been documented, without specific records of deaths or censoring events. Consequently, this figure serves solely as a reference

Additionally, while the study population was derived from hospitals practicing Western medicine, and oncologists in these institutions do not typically prescribe traditional Chinese medicine (TCM), we cannot completely exclude the possibility that some patients may have independently used TCM. Given that certain TCM formulations have been reported to influence lipid metabolism and cardiovascular health [26, 27], their potential effects on study outcomes remain uncertain. Future studies incorporating more comprehensive data on concurrent medication use, including both conventional and complementary therapies, may help provide a more precise assessment of ET-related cardiovascular risks.

Interestingly, despite the observed increases in cardiovascular and metabolic risks, no significant differences in 5-year survival rates were found among patients receiving different ET regimens. This suggests that ET remains effective in providing long-term survival benefits, irrespective of dyslipidemia status. Even among patients with baseline dyslipidemia, the 5-year survival rate was not significantly impacted, indicating that ET efficacy remains stable despite lipid profile alterations. However, it is noteworthy that patients receiving OFS monotherapy exhibited a slightly lower 5-year survival rate (93.26%), which may suggest reduced efficacy compared to combination therapies. This finding underscores the importance of selecting appropriate ET regimens and conducting regular monitoring to ensure optimal outcomes.

From a clinical perspective, these results have important implications. Healthcare providers should be aware of the potential cardiovascular and metabolic complications associated with ETs in HR + BC patients, particularly with respect to hypertension, atrial fibrillation, and lipid abnormalities. For patients with pre-existing cardiovascular risk factors, the initiation of ETs may exacerbate these risks, necessitating comprehensive cardiovascular assessments prior to treatment. Regular monitoring of relevant cardiovascular indicators during ETs is crucial, and interventions, such as the introduction of lipid-lowering agents or other cardioprotective strategies, should be considered. Moreover, lifestyle modifications, including dietary changes and exercise, could further enhance the therapeutic efficacy of ETs while minimizing its complications.

This study possesses several strengths, including its multicenter real-world design, which enhances the representativeness and applicability of the findings. Data collection from diverse medical institutions reflects a broader patient population and real clinical scenarios. Furthermore, systematic monitoring of CVDs and dyslipidemia occurrences in patients undergoing endocrine therapy provides a rich dataset for analysis. Examining the impact of various endocrine therapy regimens on lipid levels can also inform clinical practices.

However, several limitations must be acknowledged. As an observational cohort study, the potential for selection bias and unmeasured confounding factors cannot be fully eliminated. The influence of lifestyle factors, such as diet, exercise, and baseline cardiovascular health, may not have been adequately controlled, thus affecting the results. Additionally, the retrospective nature of the study and reliance on real-world data introduce challenges related to data completeness and accuracy, with potential biases arising from missing follow-up records or inconsistencies in medical documentation. Moreover, due to database constraints, detailed information regarding patient adherence to specific ET guidelines and the precise reasons for treatment discontinuation was not systematically captured. While the OS analysis employed a Cox proportional hazards model with adjustments for key baseline characteristics, the possibility of unmeasured confounding remains. Furthermore, our findings are based on descriptive associations rather than causal inferences. Future prospective studies with more rigorous control of confounding variables are warranted to validate these findings and provide clearer guidance on cardiovascular risk management in patients receiving ET for BC.

Conclusion

This study indicates a potential association between ETs and an increased risk of CVDs and dyslipidemia in early-stage HR + BC patients within the Chinese population, highlighting the need for systematic monitoring and proactive management to support optimal patient outcomes.

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors contributed to the conception and design of the study. Fei Ma and Jiani Wang led the protocol and project development. Material preparation was handled by Cheng Zeng, Hong Li, Wenna Wang, Lixi Li, and Binliang Liu. Data collection and analysis were conducted by Cheng Zeng, Bo Lan, Qing Li, and Wenjing Yang. Cheng Zeng wrote the first draft of the manuscript. All authors provided feedback on manuscript drafts and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital (Approval number: 21/369–3040). All procedure were performed in accordance with the Declaration of Helsinki and the International Conference for Harmonization/Good Clinical Practice guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Lloyd MR, Jhaveri K, Kalinsky K, Bardia A, Wander SA. Precision therapeutics and emerging strategies for HR-positive metastatic breast cancer. Nat Rev Clin Oncol. 2024;21:743–61. https://doi.org/10.1038/s41571-024-00935-6
2. Harbeck N, Gnant M. Breast cancer. Lancet (London. England). 2017;389:1134–50. https://doi.org/10.1016/S0140-6736(16)31891-8
3. Zhai J, Wu Y, Ma F, Kaklamani V, Xu B. Advances in medical treatment of breast cancer in 2022. Cancer Innov. 2023;2. https://doi.org/10.1002/cai2.46
4. Patel HK, Bihani T. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment. Pharmacol Ther. 2018;186. https://doi.org/10.1016/j.pharmthera.2017.12.012
5. Cucciniello L, Garufi G, Di Rienzo R, Martinelli C, Pavone G, Giuliano M, et al. Estrogen deprivation effects of endocrine therapy in breast cancer patients: incidence, management and outcome. Cancer Treat Rev. 2023;120:102624. https://doi.org/10.1016/j.ctrv.2023.102624
6. Ramchand SK, Cheung Y-M, Yeo B, Grossmann M. The effects of adjuvant endocrine therapy on bone health in women with breast cancer. J Endocrinol. 2019;241:R111. https://doi.org/10.1530/JOE-19-0077
7. Choi SH, Kim K-E, Park Y, Ju YW, Jung J-G, Lee ES, et al. Effects of tamoxifen and aromatase inhibitors on the risk of acute coronary syndrome in elderly breast cancer patients: an analysis of nationwide data. Breast. 2020;54:25–30. https://doi.org/10.1016/j.breast.2020.08.003
8. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the national surgical adjuvant breast and bowel project B-14 randomized trial. J Natl Cancer Inst. 2001;93:684–90. https://doi.org/10.1093/jnci/93.9.684
9. Decensi A, Maisonneuve P, Rotmensz N, Bettega D, Costa A, Sacchini V, et al. Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. Circulation. 2005;111:650–6. https://doi.org/10.1161/01.CIR.0000154545.84124.AC
10. Hernandez RK, Sørensen HT, Pedersen L, Jacobsen J, Lash TL. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer. 2009;115:4442–9. https://doi.org/10.1002/cncr.24508
11. Pérez-Jacoiste Asín MA, Blanco Molina Á, Gómez-Cuervo C, Díaz-Pedroche MDC, Pedrajas JM, López-Núñez JJ, et al. Venous thromboembolism in women with hormone-dependent breast cancer. To continue or discontinue hormonal treatment? Insights from the RIETE registry. Thromb Res. 2024;241:109087. https://doi.org/10.1016/j.thromres.2024.109087
12. Geiger AM, Fischberg GM, Chen W, Bernstein L. Stroke risk and tamoxifen therapy for breast cancer. J Natl Cancer Inst. 2004;96:1528–36. https://doi.org/10.1093/jnci/djh285
13. Marto JP, Strambo D, Livio F, Michel P. Drugs associated with ischemic stroke: a review for clinicians. Stroke. 2021;52:e646–59. https://doi.org/10.1161/STROKEAHA.120.033272
14. Foglietta J, Inno A, de Iuliis F, Sini V, Duranti S, Turazza M, et al. Cardiotoxicity of aromatase inhibitors in breast cancer patients. Clin Breast Cancer. 2017;17:11–7. https://doi.org/10.1016/j.clbc.2016.07.003
15. Zhao F, Ren D, Shen G, Ahmad R, Dong L, Du F, et al. Toxicity of extended adjuvant endocrine with aromatase inhibitors in patients with postmenopausal breast cancer: a systemtic review and meta-analysis. Crit Rev Oncol/Hematol. 2020;156:103114. https://doi.org/10.1016/j.critrevonc.2020.103114
16. Abboud K, Umoru G, Trachtenberg B, Ajewole V. Real-world data of cardio-oncologic interventions for cardiovascular adverse events with oral oncolytics. Cardiooncology. 2024;10:22. https://doi.org/10.1186/s40959-024-00221-5
17. Abdel-Qadir H, Amir E, Fischer HD, Fu L, Austin PC, Harvey PJ et al. The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer. European Journal of Cancer (Oxford, England: 1990). 2016; 68: 11–21. https://doi.org/10.1016/j.ejca.2016.08.022
18. Yu Q, Xu Y, Yu E, Zheng Z. Risk of cardiovascular disease in breast cancer patients receiving aromatase inhibitors vs. tamoxifen: a systematic review and meta-analysis. J Clin Pharm Ther. 2022;47:575–87. https://doi.org/10.1111/jcpt.13598
19. Khosrow-Khavar F, Filion KB, Bouganim N, Suissa S, Azoulay L. Aromatase inhibitors and the risk of cardiovascular outcomes in women with breast cancer: a population-based cohort study. Circulation. 2020;141:549–59. https://doi.org/10.1161/CIRCULATIONAHA.119.044750
20. Elshafie S, Villa-Zapata L, Tackett RL, Zaghloul IY, Young HN. Cardiovascular and metabolic adverse events of endocrine therapies in women with breast cancer: a disproportionality analysis of reports in the FDA adverse event reporting system. Cancer Med. 2025;14:e70548. https://doi.org/10.1002/cam4.70548
21. Bach L, Kostev K, Schiffmann L, Kalder M. Association between thyroid gland diseases and breast cancer: a case-control study. Breast Cancer Res Treat. 2020;182:207–13. https://doi.org/10.1007/s10549-020-05675-6
22. 2016 Chinese guidelines for the management of dyslipidemia in adults. J Geriatr Cardiol. 2018; https://doi.org/10.11909/j.issn.1671-5411.2018.01.011
23. Alomar SA, Găman M-A, Prabahar K, Arafah OA, Almarshood F, Baradwan S, et al. The effect of tamoxifen on the lipid profile in women: a systematic review and meta-analysis of randomized controlled trials. Exp Gerontol. 2022;159:111680. https://doi.org/10.1016/j.exger.2021.111680
24. Hozumi Y, Suemasu K, Takei H, Aihara T, Takehara M, Saito T, et al. The effect of exemestane, anastrozole, and tamoxifen on lipid profiles in Japanese postmenopausal early breast cancer patients: final results of National surgical adjuvant study BC 04, the TEAM Japan sub-study. Annals Oncology: Official J Eur Soc Med Oncol. 2011;22:1777–82. https://doi.org/10.1093/annonc/mdq707
25. Kang Y-K, Wang X, Hu N-L, Yue J, Si Y-R, Ju J, et al. The effects of endocrine therapies on lipid profiles in Chinese young women with early breast cancer. Front Oncol. 2021;11:759595. https://doi.org/10.3389/fonc.2021.759595
26. Zhang Y, Kishi H, Kobayashi S. Add-on therapy with traditional Chinese medicine: an efficacious approach for lipid metabolism disorders. Pharmacol Res. 2018;134:200–11. https://doi.org/10.1016/j.phrs.2018.06.004
27. Hao P, Jiang F, Cheng J, Ma L, Zhang Y, Zhao Y. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. J Am Coll Cardiol. 2017;69:2952–66. https://doi.org/10.1016/j.jacc.2017.04.041

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