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Adjuvant ovarian function suppression in premenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2–negative early breast cancer: a multi-center retrospective study

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Abstract

Purpose Based on SOFT and TEXT trials data, a composite recurrence risk score (CR-score) model was developed for early premenopausal women with hormone receptor -positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer using the subgroup treatment effect map (STEPP) method to guide ovarian function suppression (OFS) application. However, the CR-score model has yet to be validate in real-world settings.

Methods Our study included patients diagnosed between January 1, 2013, and December 31, 2021, from 42 breast centers in China. We utilized restricted cubic splines (RCS) to visualize continuous CR-score and hazard ratios for breast cancer recurrence. After adjusting for confounding factors via propensity score matching (PSM), Kaplan-Meier curves were used to compare disease-free survival (DFS) among premenopausal patients between the OFS and non-OFS groups.

Results The hazard ratio of recurrence consistently increased with higher CR-scores. Notably, 87.68% of patients who received OFS had a CR-score above 1.42. Following PSM, adjuvant OFS significantly improved DFS in the high CR-score group (CR-score above 1.42)(HR 0.571; 95% CI 0.403–0.809; $p = 0.001$). Among patients younger than 35 years old, those receiving OFS had significantly better DFS compared to those without OFS. After matching for age, grade, ER, PR, and lymph node status, OFS can significantly improve the DFS of those chemotherapy-treated patients with CR-score above 1.42 ($p = 0.006$). Furthermore, the group with high CR-score but ER expression below 50% did not benefit from OFS.

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Conclusion The CR-score model can effectively guide clinicians in making decisions regarding OFS for premenopausal patients with HR+/HER2- breast cancer.

Keywords Breast cancer, Ovarian function suppression, Composite recurrence risk score, Disease-free survival

Introduction

As early as 2000, in-depth molecular research ushered breast cancer into an era of classification and targeted treatment. Approximately 75% of early breast cancers are hormone receptor-positive (HR+) subtype, requiring adjuvant endocrine therapy [1]. Tamoxifen is the first adjuvant regimen for premenopausal women with HR + breast cancer [2]. Ovarian function suppression (OFS) is known to inhibit the production of estrogen in the ovaries, thereby preventing the proliferation of HR + breast cancer cells. In 2005, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) firstly reported that OFS could significantly reduce breast cancer mortality in the absence of other systemic treatments [3]. Since 2014, several trials have supported the use of OFS in combination with aromatase inhibitors (AI) or tamoxifen (TAM) in high-risk patients, showing improved outcomes compared to TAM alone [4, 5]. A large phase III clinical trial (SOFT) demonstrated that TAM or exemestane plus OFS significantly improved disease-free survival (DFS) in premenopausal women with HR-positive early breast cancer compared to TAM alone [6]. Therefore, both the St Gallen International Expert Consensus and the update of ASCO guideline in 2015 recommended the combination of OFS with tamoxifen or AI for high-risk premenopausal patients with HR-positive breast cancer.

However, it remains unclear which patients are considered at sufficiently high risk of recurrence to warrant OFS treatment. Regan and Pagani et al. conducted a retrospective analysis using data from the SOFT and TEXT trials and developed a composite recurrence risk score (CR-score) model for early premenopausal women with HR+, human epidermal growth factor receptor 2-negative (HER2-) breast cancer. This model was developed using subpopulation treatment effect pattern plot (STEPP) methodology [6, 7]. Patients with a CR-score above 1.42 are recommended to receive OFS. Notably, up to 94.5% of patients enrolled in the SOFT and TEXT trials had estrogen receptor (ER) expression exceeding 50%, indicating a better response to endocrine therapy. It is unknown whether patients with ER expression below 50% can benefit from OFS. However, these patients may have a high CR-score, indicating the need for OFS, which could conflict with actual clinical treatment decisions. Furthermore, the CR-score model has not been fully validated in real-world settings, leading to concerns among doctors when using this model for OFS decision-making.

Therefore, we aim to explore the value of OFS in premenopausal patients with HR+/ HER2- early breast cancer in real-world settings. More importantly, our study will further evaluate the effectiveness of the CR-score model in guiding OFS decisions for these patients.

Methods

Data source and study design

Data were gathered from Shanghai Jiaotong University-Breast cancer Database (SJTU-BCDB) (http://47.100.125.104:8080/), which includes information from 42 breast centers across China. The database used for this study is a centralized, multicenter repository that collects comprehensive clinical, pathological, and treatment-related information from all participating centers. Each center's data management team is responsible for entering and validating their respective data, which is then periodically audited to ensure quality control. The database includes detailed patient demographics, tumor characteristics (including ER/PR status), treatment modalities, and follow-up outcomes. All analysis was approved by independent Ethical Committees of all 42 hospitals. A waiver of informed consent was granted given the retrospective nature of the study. Authors complied with all relevant ethical regulations including the Declaration of Helsinki. We identified premenopausal women with HR+/HER2- breast cancer diagnosed during January 1, 2013 to December 31, 2021. Patients must undergo curative surgery and adjuvant endocrine therapy. In the present study, we excluded male breast cancer and who with a history of breast cancer or other invasive cancers. Patients who have distant metastasis or carcinoma in situ and bilateral breast cancer were also excluded. In addition, patients who lack of histological grade or missing information of endocrine therapy and follow-up were excluded from this study.

Definition

Premenopausal status for patients in our study was determined based on clinical criteria. Specifically, patients were considered premenopausal if they had regular menstrual cycles at the time of diagnosis or had experienced menstruation within the last 12 months. Additionally, serum hormone levels, including estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), were assessed to confirm premenopausal status when necessary. DFS, defined as the time interval from the date of radical breast surgery to the date of local recurrence, distant metastasis or death from breast cancer, was

end point of our study. ER or progesterone receptor (PR) positivity was defined if there was at least 1% staining in tumor nuclei. HER2-negative was defined as immunohistochemistry (IHC)+, or IHC + + but fluorescent in situ hybridization (FISH) negative. CR-score was calculated by summing the model parameter estimates corresponding to the observed clinicopathologic factor values. The weighting parameters used to derive the CR-score were obtained from the SOFT/TEXT trails. Patients with a CR-score above 1.42 are considered at high-risk for recurrence.

Statistical analysis

Chi-square tests were used to compare the differences in clinicopathological characteristics and treatment information between the OFS and non-OFS group. Restricted cubic splines (RCS) were used to visualize continuous CR-score and hazard ratios for breast cancer recurrence [8]. The confounding variables corrected for multivariate analysis include chemotherapy and radiotherapy. In this study, propensity score matching (PSM) was an important method for controlling confounding variables [9]. CR-score were matched by grouping them into quartiles. Matching factors included age, tumor size, node status, grade, ER, PR, Ki67 and chemotherapy in the PSM model. The matching ratio was 1:1 or 1:4 as needed. Difference in DFS was estimated using the Kaplan-Meier method. All analyses were perform using R version 4.2.3, with a two-tailed p value < 0.05 considered statistically significant.

Result

Patients and characteristics

A total of 4,724 premenopausal women with HR+/HER2- early breast cancer were enrolled for final analysis (Fig. 1). The median follow-up time was 45 months. The characteristics of patients in the OFS and non-OFS groups are summarized in Table 1. Significant differences were observed between patients receiving OFS and those who did not in terms of clinical and pathological characteristics. More patients with younger age (≤ 35), larger tumors (>2 cm), positive lymph node (≥ 1), later staging (Stage II&III), higher Ki67 index (≥ 26%), and higher histological grade (grade 3) received OFS as adjuvant endocrine treatment. Additionally, 89.54% of patients who received OFS also underwent chemotherapy. In this study, 94.17% of patients in the OFS group had ER expression exceeding 50%. Furthermore, 87.68% of patients who received OFS had a CR-score above 1.42. We further evaluated the relationship between the CR-score and recurrence risk using RCS. After adjusting for chemotherapy and radiation therapy, we found that the hazard ratio of recurrence increased monotonically with higher CR-scores (Fig. 2).

Effect of age on OFS decision-making

Women younger than 35 years old was considered as an independent risk factor for breast cancer. Therefore, we further estimated differences in DFS among patients under 35 with HR+/HER2- breast cancer who receiving OFS versus those who did not. Patients who receiving OFS showed a better trend in DFS benefits compared to the non-OFS group ($p = 0.088$, Fig. 3A). After 1:1 proportional propensity matching (Supplement Table 1), the addition of adjuvant OFS significantly improved DFS in patients under 35 ($p = 0.047$, Fig. 3B).

Effect of CR-score model on OFS decision-making

In this study, we investigate whether those with CR-score above 1.42 can benefit from OFS. In the overall population, the group receiving OFS in the high CR-score (CR-score above 1.42) cohort showed a trend towards improved DFS compared to the non-OFS group ($p = 0.058$, Fig. 4A). After dividing CR-score into four categories, we conducted survival analysis by matching CR-score and chemotherapy information between OFS groups and non-OFS groups (Supplement Table 2). After PSM, adjuvant OFS significantly improved DFS in the high CR-score group ($p = 0.001$, Fig. 4B). Before and after PSM (Supplement Table 3), OFS did not improve DFS in patients with low CR-score (CR-score equal or less than 1.42) compared to non-OFS group (Fig. 5A and B).

In our further analysis of the non-chemotherapy population, we evaluated the value of CR-score in guiding the use of OFS. In the high CR-score cohort, patients receiving OFS demonstrated improved DFS compared to those in the non-OFS group. However, in the low CR-score cohort, there was no statistically significant difference in DFS between the OFS and non-OFS groups (Fig. 6A and B). For those chemotherapy-treated patients with CR scores above 1.42, OFS did not result in an improvement in DFS (Fig. 7A). After matching for age, grade, ER, PR, and lymph node status, OFS can significantly improve the DFS of this cohort ($p = 0.006$, Fig. 7B).

Moreover, there was no statistically significant difference in DFS between the OFS and non-OFS groups in patients with a high CR-score but ER expression below 50% (Supplement Table 4; Fig. 8A and B).

Discussion

The results from TEXT and SOFT trials indicate that OFS can improve the survival of premenopausal women with HR-positive high-risk breast cancer. Based on data from these two trials, a CR-score model utilizing STEPP methodology has been developed as a clinical tool to aid physicians in OFS decision-making. Our study, incorporating data from multiple nationwide centers, revealed a positive correlation between increasing CR-scores and higher hazard ratios for recurrence. To our knowledge,

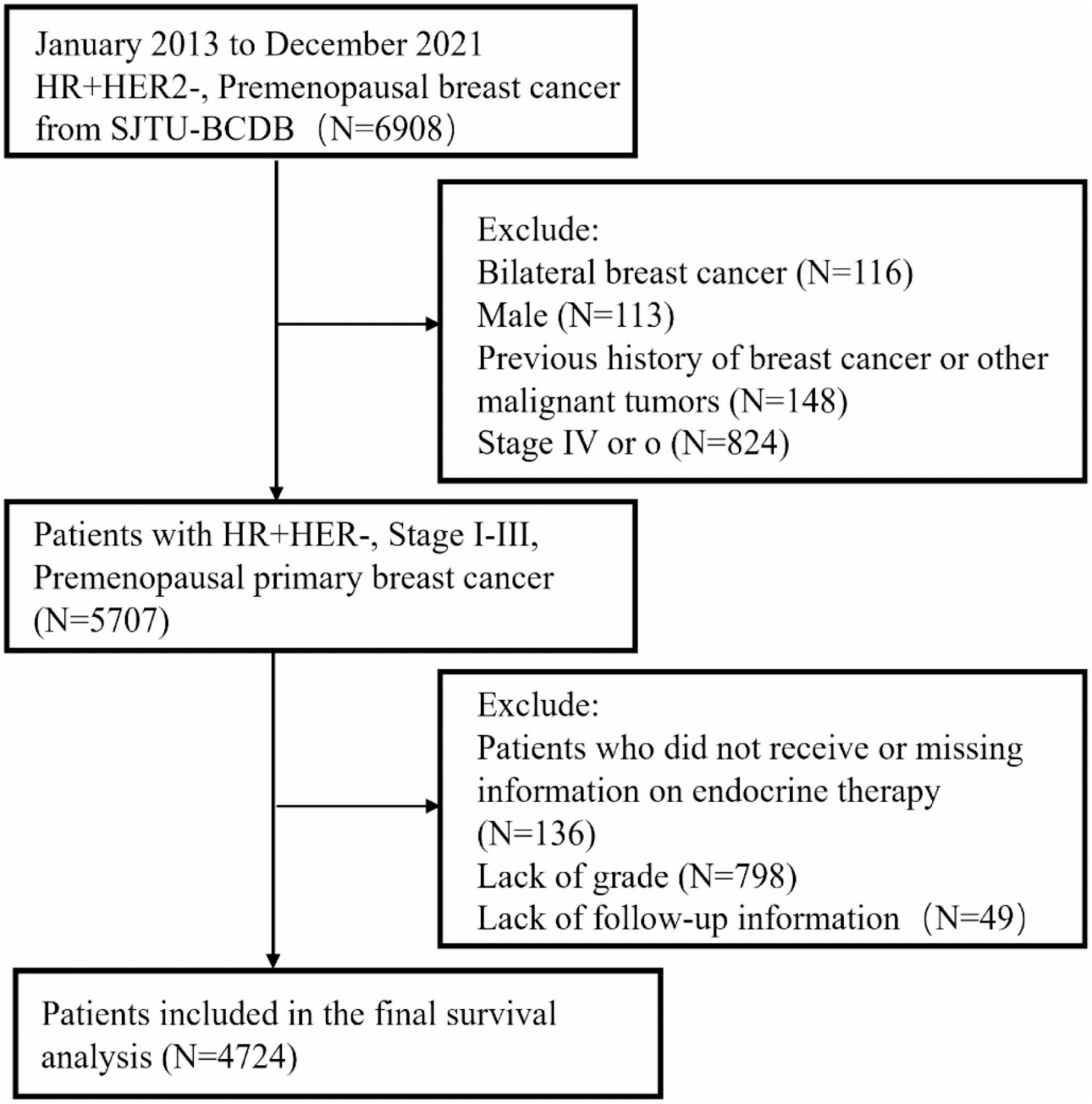

Fig. 1 Flow diagram of the 4724 patients with breast cancer included in the study. HR + HER2-, hormone receptor-positive human epidermal growth factor receptor 2-negative; SJTU-BCDB, Shanghai Jiaotong University-Breast cancer Database

this is the first study to validate CR-score model in real-world settings. Furthermore, our findings suggest that OFS could significantly improve DFS specifically among patients under 35 with HR+/HER2- breast cancer. For Chinese patients, those with a CR-score above 1.42 may particularly benefit from OFS, though this benefit does not extend to those with ER expression below 50%.

Currently, premenopausal women with HR+/HER2- breast cancer at high risk of recurrence are recommended to undergo OFS combined with selective estrogen receptor modulators (SERMs) or AI as adjuvant endocrine therapy [10]. In the SOFT and TEXT trials, patients who remained premenopausal after chemotherapy and received OFS showed improvements in BCFI. However, patients who did not undergo chemotherapy did not benefit from OFS. These findings suggest that premenopausal women with HR+/HER2- breast cancer requiring chemotherapy should receive OFS.

For HR+/HER2- breast cancer, results from the TAILORx trial indicate that the 21-gene assay can offer

Table 1 Patients' characteristics by OFS category

Characteristics	Total (*n* = 4,724)	OFS category		*p* value
		Non-OFS (*n* = 3,214)	OFS (*n* = 1,510)	
Age				< 0.001
<35	414 (8.76%)	125 (3.89%)	289 (19.14%)	
35–39	690 (14.61%)	314 (9.77%)	376 (24.90%)	
40–44	1,257 (26.61%)	852 (26.51%)	405 (26.82%)	
45–49	1,610 (34.08%)	1,313 (40.85%)	297 (19.67%)	
≥50	753 (15.94%)	610 (18.98%)	143 (9.47%)	
Tumor size, cm				< 0.001
≤2	2,942 (62.28%)	2,161 (67.24%)	781 (51.72%)	
>2	1,782 (37.72%)	1,053 (32.76%)	729 (48.28%)	
No. of positive nodes				< 0.001
0	2,842 (60.16%)	2,275 (70.78%)	567 (37.55%)	
1–3	1,254 (26.55%)	699 (21.75%)	555 (36.75%)	
≥4	628 (13.29%)	240 (7.47%)	388 (25.70%)	
ER expression, %				< 0.001
<50	370 (7.83%)	282 (8.77%)	88 (5.83%)	
≥50	4,354 (92.17%)	2,932 (91.23%)	1,422 (94.17%)	
PR expression, %				< 0.001
<20	743 (15.73%)	472 (14.69%)	271 (17.95%)	
20–49	484 (10.25%)	306 (9.52%)	178 (11.79%)	
≥50	3,497 (74.03%)	2,436 (75.79%)	1,061 (70.26%)	
TNM Stage				< 0.001
I	2,132 (45.13%)	1,758 (54.70%)	374 (24.77%)	
II	1,923 (40.71%)	1,197 (37.24%)	726 (48.08%)	
III	669 (14.16%)	259 (8.06%)	410 (27.15%)	
Ki67 index, %				< 0.001
<14	1,834 (38.82%)	1,402 (43.62%)	432 (28.61%)	
14–19	368 (7.79%)	273 (8.49%)	95 (6.29%)	
20–25	840 (17.78%)	556 (17.30%)	284 (18.81%)	
≥26	1,682 (35.61%)	983 (30.58%)	699 (46.29%)	
Tumor grade				< 0.001
1	579 (12.26%)	474 (14.75%)	105 (6.95%)	
2	3,253 (68.86%)	2,230 (69.38%)	1,023 (67.75%)	
3	892 (18.88%)	510 (15.87%)	382 (25.30%)	
Chemotherapy				< 0.001
No	1,192 (25.23%)	1,034 (32.17%)	158 (10.46%)	
Yes	3,532 (74.77%)	2,180 (67.83%)	1,352 (89.54%)	
Radiotherapy				< 0.001
No	2,032 (43.01%)	1,608 (50.03%)	424 (28.08%)	
Yes	2,692 (56.99%)	1,606 (49.97%)	1,086 (71.92%)	
CR-score				< 0.001
≤ 1.42	1,795 (38%)	1,609(50.06%)	186 (12.32%)	
>1.42	2,929 (62%)	1,605(49.94%)	1,324 (87.68%)	

clinicians precise guidance regarding adjuvant chemotherapy [11]. However, this approach is not applicable in China. Therefore, there is a need for a simpler and more feasible method to assess recurrence risk and guide decisions regarding chemotherapy or OFS. The CR-score model, as analyzed through STEPP methodology, integrates clinical and pathological factors relevant to prognosis and assigns weights based on their impact. Our study confirmed that the CR-score model effectively predicts recurrence risk, with higher CR-scores correlating significantly with increased recurrence risk.

Age less than 35 years old is defined as young breast cancer (YBC) in this study. YBC patients present with more aggressive pathological features than elder [12, 13]. In the SOFT and TEXT trials, the majority of YBC patients (94% and 82%, respectively) received adjuvant

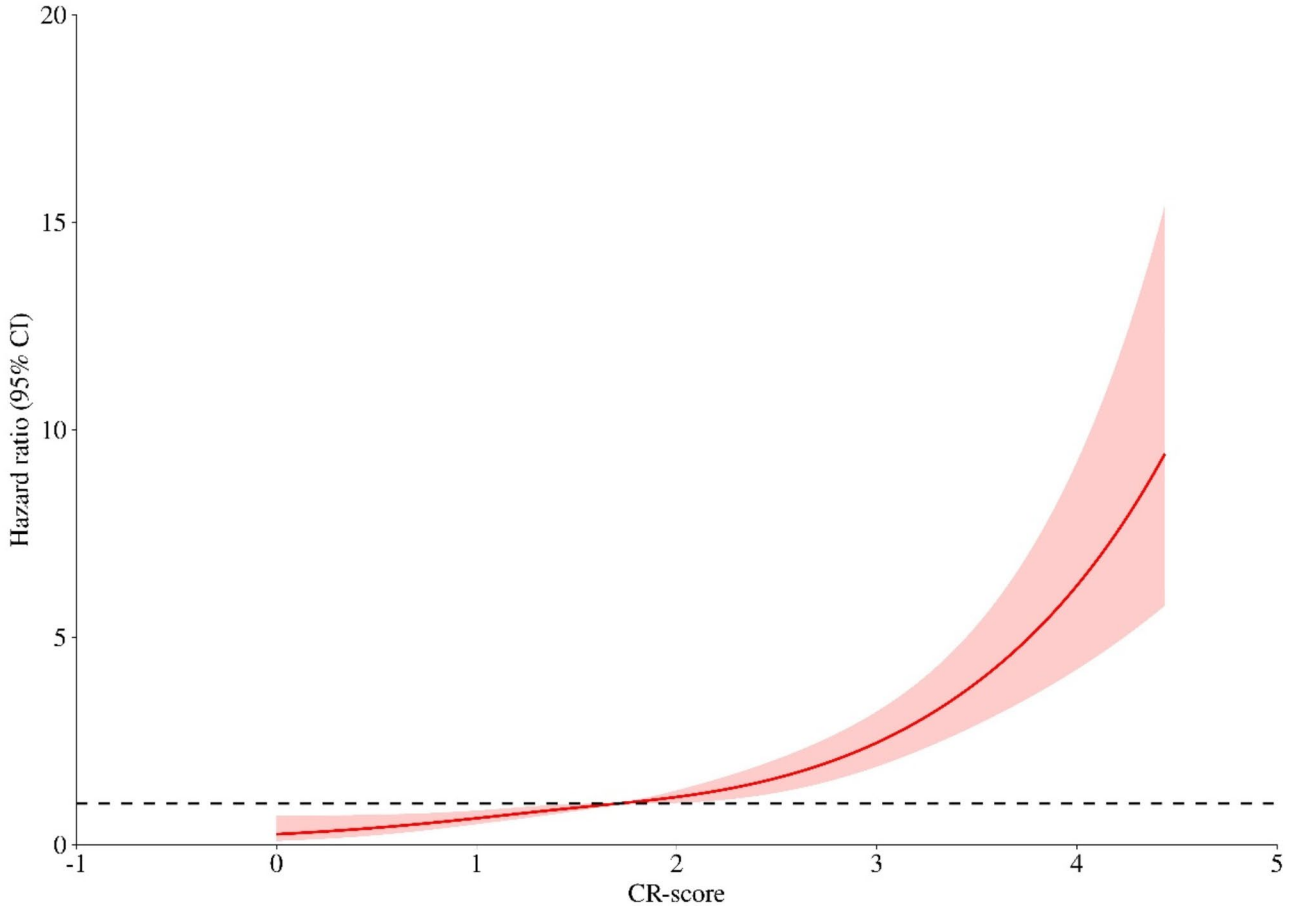

Fig. 2 Restricted Cubic Splines (RCS) of the relationship between composite recurrence risk score (CR-score) and breast cancer disease-free survival

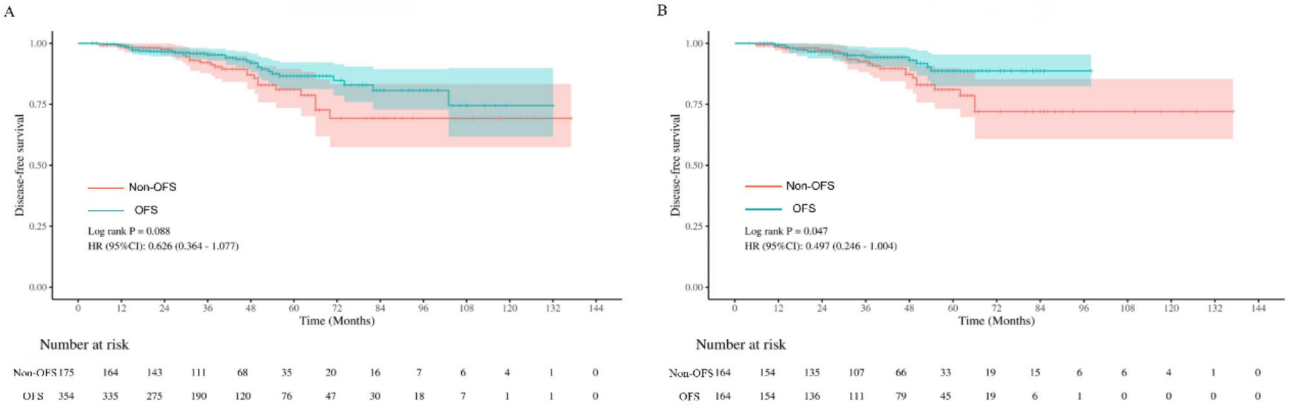

Fig. 3 Disease-free survival difference between underwent OFS or non-OFS among age under 35 women with HR + HER2- breast cancer. **(A)** Disease-free survival difference between underwent OFS or non-OFS among age under 35 women with HR + HER2- breast cancer before PSM. **(B)** Disease-free survival difference between underwent OFS or non-OFS among age under 35 women with HR + HER2- breast cancer after 1:1 PSM. PSM, propensity score matching; HR + HER2-, hormone receptor-positive human epidermal growth factor receptor 2-negative; OFS, ovarian function suppression

chemotherapy, as did 85.6% of patients in this study (Supplementary Table 1). Compared to patients aged 35 years and older, the YBC subgroup demonstrated a higher risk of breast cancer recurrence and distant metastasis according to the SOFT and TEXT trials. Therefore, YBC patients often require more aggressive treatment. Combined analysis of the SOFT and TEXT trials demonstrated that patients under the age of 35 who received OFS along with TAM/AI as adjuvant endocrine therapy experienced significant survival benefits. Similarly, a

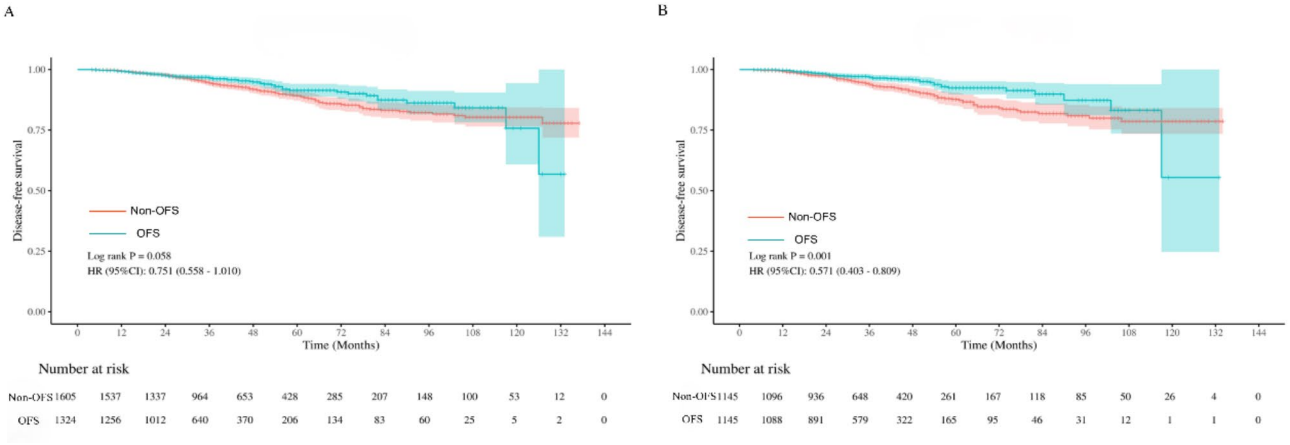

Fig. 4 Disease-free survival difference between underwent OFS or non-OFS among CR-score>1.42 premenopausal women with HR + HER2- breast cancer. **(A)** Disease-free survival difference between underwent OFS or non-OFS among CR-score>1.42 premenopausal women with HR + HER2- breast cancer before PSM. **(B)** Disease-free survival difference between underwent OFS or non-OFS among CR-score>1.42 premenopausal women with HR + HER2- breast cancer after 1:1 PSM. PSM, propensity score matching; HR + HER2-, hormone receptor-positive human epidermal growth factor receptor 2-negative; OFS, ovarian function suppression; CR-score, composite recurrence risk score

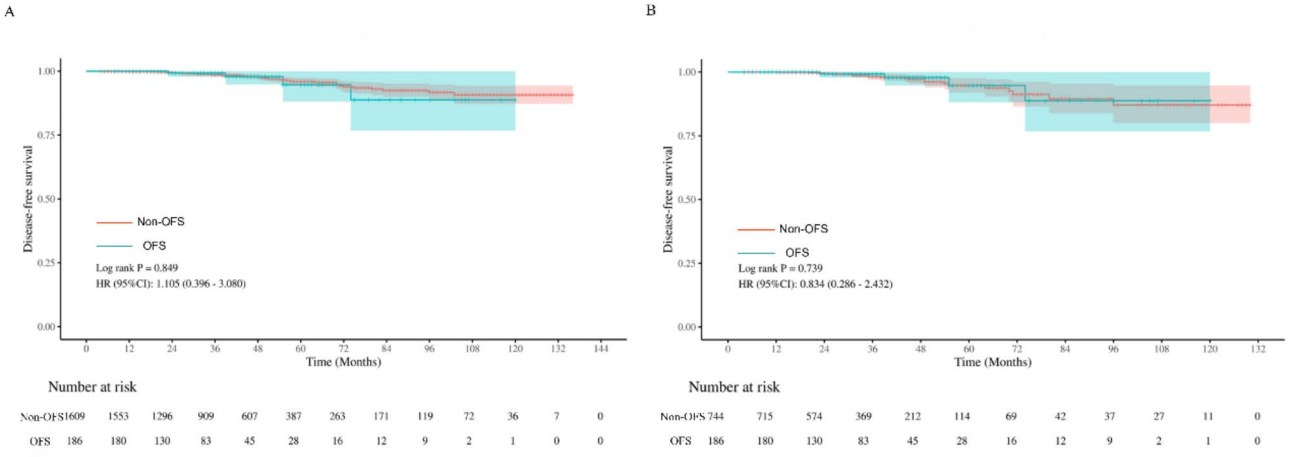

Fig. 5 Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score ≤ 1.42. **(A)** Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score ≤ 1.42 before PSM. **(B)** Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score ≤ 1.42 after 1:4 PSM. PSM, propensity score matching; OFS, ovarian function suppression; CR-score, composite recurrence risk score

phase III clinical trials from Korea (ASTRRA) indicated that addition of OFS to tamoxifen for premenopausal breast cancer (age ≤ 45 years) significantly improved disease-free survival [14]. Our study reported similar results. After matching CR-score and chemotherapy, YBC patients who received OFS combined with SERM/AI have better DFS than those receiving SERM alone ($p = 0.047$). In this case, while the p-value suggests some evidence against the null hypothesis, the result remains on the edge of statistical significance, which may raise concerns about the value of OFS in YBC patients. In addition, the small sample size of this subgroup in this study leads to reduced statistical power and increases the likelihood of type II error. However, research has showed that the inferior outcome of YBC patients who only received TAM may result from tamoxifen resistance [15]. Furthermore, compliance with endocrine therapy is also an important factor affecting prognosis. Many studies have shown that YBC patients have poorer compliance than elder [16, 17]. The non-compliance of OFS is significantly higher in the younger subgroup than elder [18]. Nevertheless, YBC patients who received OFS as part of their adjuvant endocrine therapy remain significant survival benefits.

A CR-score greater than 1.42 is considered indicative of a high risk of recurrence and necessitates treatment with OFS. To our knowledge, it remains unknown whether a CR-score of 1.42 is a suitable threshold for the Chinese population. After matching CR-scores and chemotherapy, patients with CR-score greater than 1.42

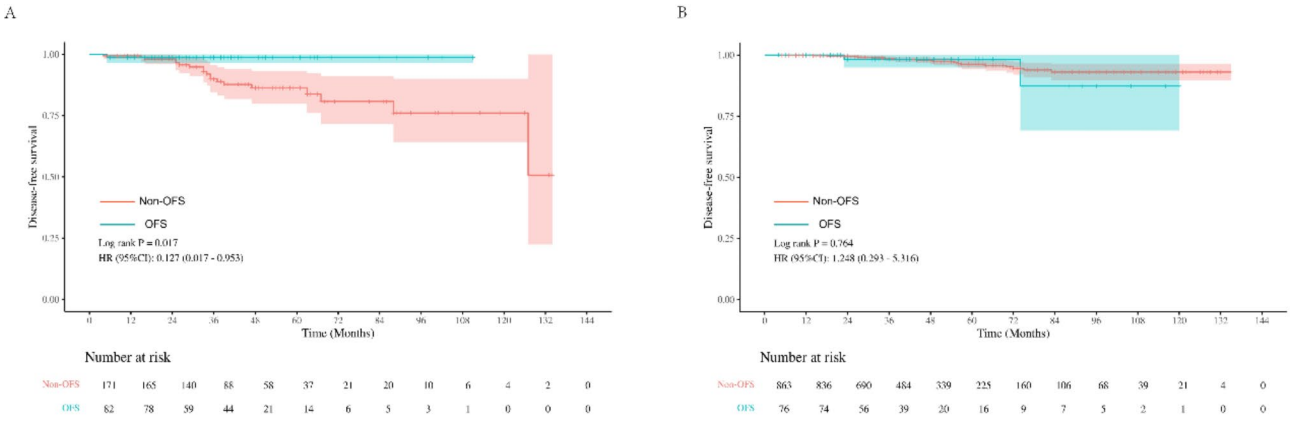

Fig. 6 Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with non-chemotherapy cohort. **(A)** Disease-free survival difference between underwent OFS or non-OFS among patients with CR-score>1.42. **(B)** Disease-free survival difference between underwent OFS or non-OFS among patients with CR-score ≤ 1.42. OFS, ovarian function suppression; CR-score, composite recurrence risk score

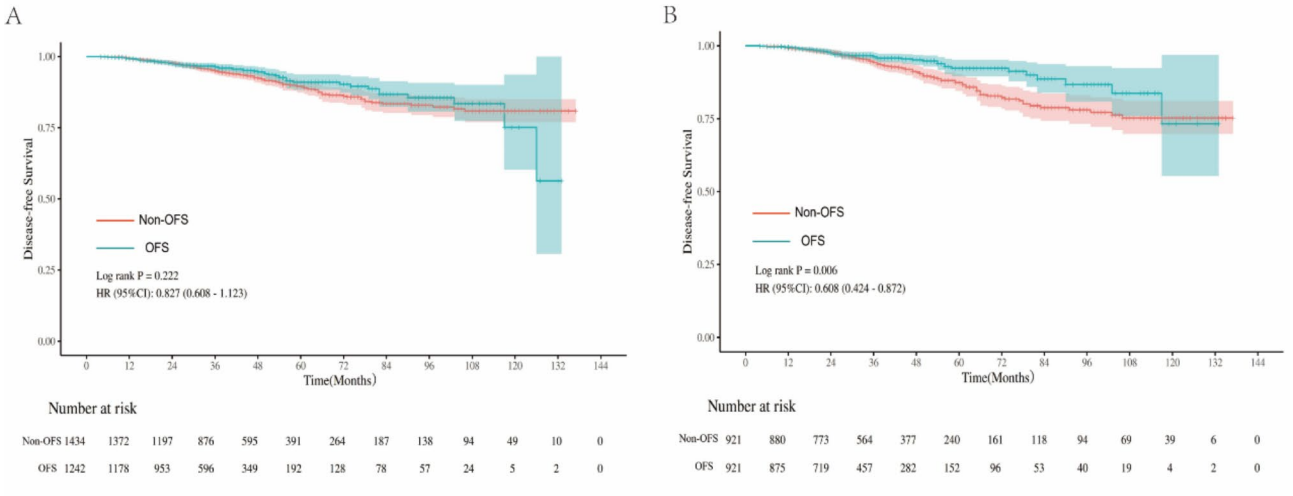

Fig. 7 Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score>1.42 and chemotherapy-treated. **(A)** Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score>1.42 and receiving chemotherapy before PSM. **(B)** Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score>1.42 and receiving chemotherapy after 1:1 PSM. OFS, ovarian function suppression; CR-score, composite recurrence risk score; PSM, propensity score matching

who received OFS combined with SERM/AI exhibited better DFS than those who received SERM alone. In our study, we further analyzed the value of CR-score in guiding the use of ovarian function suppression (OFS) among patients who did not receive chemotherapy. Our results demonstrate that, consistent with findings from the SOFT trial [6], patients with a low CR-score did not experience a significant improvement in DFS with OFS. This alignment with the SOFT trial reinforces the notion that OFS may not be necessary for patients with low CR-scores, as their prognosis tends to be favorable regardless of OFS treatment. However, our study provides novel insights into the high CR-score cohort. The SOFT trial had a limited number of patients in this subgroup, and no results were specifically reported for high CR-scores without chemotherapy. Our findings reveal that, even in the absence of chemotherapy, OFS significantly improves DFS in patients with high CR-scores. This underscores the potential of OFS as an effective treatment option for high-risk patients who are unable or unwilling to receive chemotherapy, offering a viable alternative to improve their prognosis. Our results identified that CR-score model can be a valuable tool in identifying patients who could benefit from OFS, even when chemotherapy is not an option.

International guidelines defined ER ≥ 1% as ER positive in 2010, and ER 1–9% was defined as ER-low expression. A Swedish Study showed that patients with ER low, HER2-negative breast cancer have similar characteristics and prognosis to triple-negative breast cancer [19]. Patients with ER-low expression has limited benefit from endocrine therapy. A higher expression level of ER may

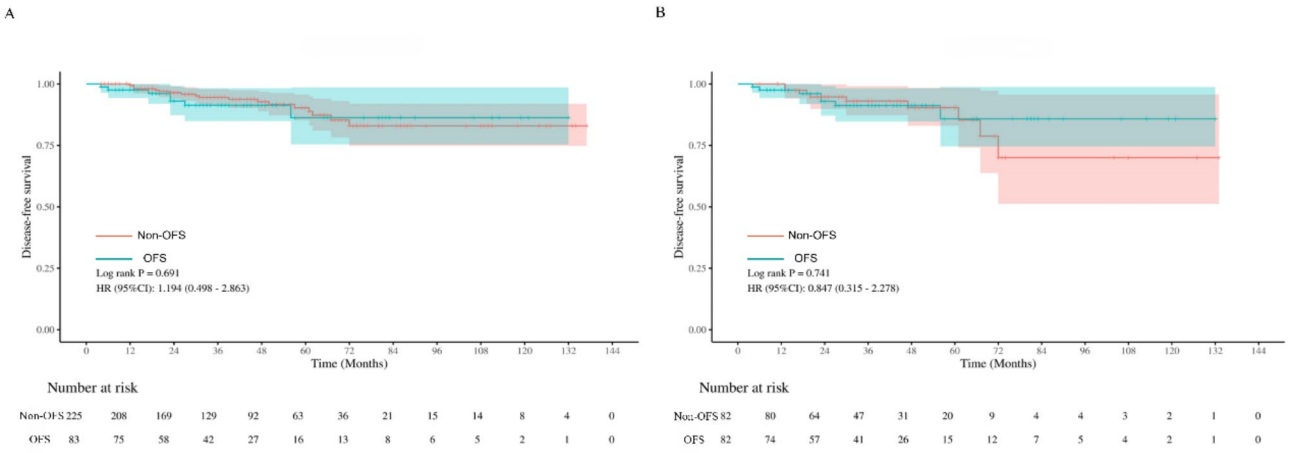

Fig. 8 Disease-free survival difference between underwent OFS or non-OFS among premenopausal patients with CR-score>1.42 and ER expression below 50%. **(A)** Disease-free survival difference between underwent OFS or non-OFS among patients with CR-score>1.42 and ER expression below 50% before PSM. **(B)** Disease-free survival difference between underwent OFS or non-OFS among patients with CR-score>1.42 and ER expression below 50% after 1:1 PSM. PSM, propensity score matching; ER, estrogen receptor; OFS, ovarian function suppression; CR-score, composite recurrence risk score

indicate a better response to endocrine therapy. Due to 94.5% of patients enrolled in SOFT and TEXT trials having ER ≥ 50%, we are interested in whether ER expression below 50% can benefit from OFS. We found that patients with a CR-score greater than 1.42 but ER expression below 50% rarely benefit from OFS. Certainly, the number of cases in the enrolled cohort was limited, and the results still need to be interpreted with caution.

Limitations and strengths

The strengths of our study include multi-center cohort patients with long-term follow-up. Certainly, there are some limitations in this study. Firstly, selection bias and confounding factors are major concerns in our observational studies. Reassuringly, we used propensity score models to adjust for confounding factors, which largely controlled for potential selection bias [20]. Secondly, chemotherapy-induced menopause can potentially impact the prognosis of breast cancer patients, and we recognize that the lack of specific information on this aspect in our study may influence the results. Moreover, we lack information of adherence to endocrine therapy, which may affect outcome. Finally, we have not obtained specific medication duration for endocrine therapy. Future research needs to focus on the duration of OFS medication.

Conclusion

In summary, the CR-score model can effectively guide clinicians in making decisions regarding OFS for premenopausal patients with HR+/HER2- breast cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14120-0.

Supplementary Material 1

Acknowledgements

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Author contributions

WL, CH and DC contributed to the study conception and design, analysis of data was contributed by WL and LL, WL prepared all the figures and tables, WL drafted the manuscript, WL, CH and DC discussed and edited the paper. All authors read and approved the manuscript.

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Data availability

The data supporting all tables and figures in this published article are not publicly available to protect patient privacy but can be accessed from the corresponding author on request.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Ethics Committee of Quanzhou First Hospital, affiliated with Fujian Medical University.

Consent to participate

Formal consent was not required for this type of study.

Consent for publish

Not applicable.

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