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Adjuvant Chemotherapy May be Waived for Breast Cancer Nonresponders to Neoadjuvant Chemotherapy: A Population-Based Large Cohort Study

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ABSTRACT

Purpose: This study aimed to evaluate the efficacy of adjuvant chemotherapy (AC) in breast cancer patients who did not respond to neoadjuvant chemotherapy (NAC) following surgery.

Method: A retrospective analysis was performed using a large, population-based cohort to identify breast cancer patients who underwent radical surgery following NAC without achieving a response. Kaplan–Meier analysis and Cox regression models were employed to assess clinical outcomes and prognostic factors. Propensity score matching (PSM) was applied to compare outcomes between patients receiving AC vs. those who did not, followed by subgroup analyses.

Results: A total of 1866 patients were included, of whom 1030 received postoperative AC. The median follow-up time was 68.0 months. Patients receiving AC had a median overall survival (OS) of 124.0 months, compared to 93.0 months for those not receiving AC. However, multivariate analysis indicated that receiving postoperative AC was not an independent prognostic factor. Furthermore, PSM analysis indicated no improvement in long-term survival for patients receiving postoperative AC compared to those not receiving it. Subgroup analysis further supported these findings, revealing no significant differences in OS between AC and Non-AC cohorts across various subgroups.

Conclusion: These findings suggest that breast cancer patients unresponsive to NAC may derive limited benefit from subsequent AC. Therefore, the decision to administer AC should be carefully considered, and alternative therapeutic strategies should be explored for these patients.

1 | Introduction

Neoadjuvant chemotherapy (NAC) has emerged as a cornerstone in the management of locally advanced breast cancer, offering the potential to downstage tumors, improve surgical outcomes, and provide early insights into tumor biology and chemosensitivity. For patients who achieve a pathological complete response (pCR) following NAC, the prognosis is generally favorable, with reduced recurrence rates and improved survival outcomes. Multiple meta-analyses have validated pCR as a robust prognostic marker for relapse-free survival (RFS), disease-free survival (DFS), and overall survival (OS), establishing it as a surrogate endpoint for predicting long-term clinical benefit [1, 2].

However, approximately one-third of patients undergoing NAC exhibit no meaningful response, with disease either stabilizing (SD) or progressing (PD) during treatment [3]. These

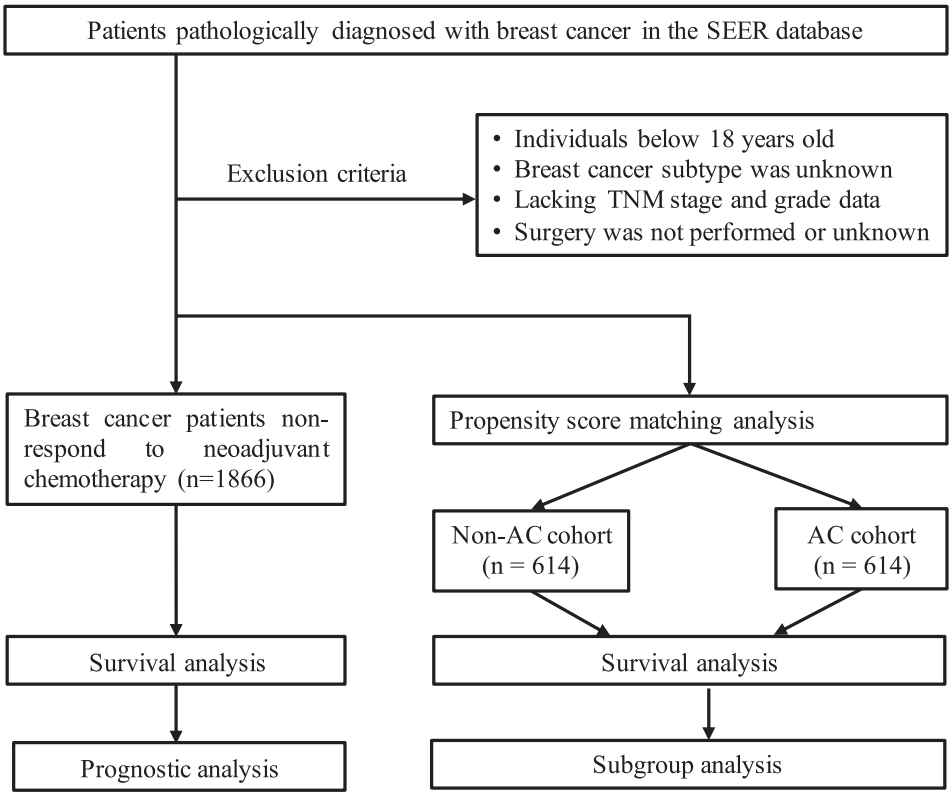

FIGURE 1 | Flowchart of patient selection. AC, adjuvant chemotherapy; Non-AC, nonadjuvant chemotherapy; SEER, surveillance, epidemiology, and end results program.

nonresponders are associated with poor prognoses, and the optimal management strategy for them remains contentious. Debate continues over whether adjuvant chemotherapy is necessary for these patients following curative surgery, as well as the selection of the most appropriate adjuvant treatment regimen.

Current research has primarily focused on intensifying treatment for patients who do not achieve pCR, exploring novel agents and combination therapies to overcome residual disease [4, 5]. However, there is a relative paucity of studies specifically addressing the optimal post-surgical treatment strategy for those who exhibit no response to NAC at all. The potential of adjuvant chemotherapy to provide survival benefits in this high-risk group—or whether it merely adds toxicity without enhancing outcomes—remains largely unexplored [4, 6, 7].

In this study, we present the first large cohort analysis comparing the long-term outcomes of patients with nonresponse (NR) after NAC, with and without subsequent adjuvant chemotherapy (AC). Our goal is to provide evidence-based guidance to clinicians in determining the most appropriate treatment strategies for this challenging patients subgroup.

2 | Materials and Methods

2.1 | Data Collection

Patients initially diagnosed with breast cancer between January 2010 and December 2020 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. The inclusion criteria were as follows: (1) histopathologically confirmed cases of breast cancer; (2) patients receiving NAC followed by radical surgery; (3) absence of distant metastasis; and (4) clear documentation of neoadjuvant treatment efficacy, specifically indicating NR. In addition, the exclusion criteria were as follows: (1) duplicate patient IDs indicating inconsistent information; (2) unknown TNM staging or stage IV classification; (3) missing data on pathological grade, estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2) status; and (4) cases where surgery was either not performed or had unknown status. The patient screening process is illustrated in Figure 1. As all data were sourced from a publicly available database, ethical approval was waived due to the anonymized nature of the data and its public accessibility. Our study adhered to the Strengthening the Reporting of Cohort, Cross-Sectional, and Case-Control Studies in Surgery (STROCSS) criteria [8].

2.2 | Variable Retrieval

The clinicopathological characteristics and treatment strategies were retrieved and analyzed, including age at diagnosis, race, marital status, primary tumor site, TNM stage, T stage, N stage, ER status, PR status, HER2 status, molecular subtype, histological grade, type of surgery, administration of postoperative radiotherapy (PORT), AC administration, and survival outcome. In this study, NR refers to patients who do not achieve a pCR or partial response (PR) during NAC, including patients with SD as well as those with PD. This definition was used to ensure consistency in patient classification and to provide a clear distinction

between patients with varying responses to treatment. OS was defined as the time from breast cancer diagnosis to death from any cause or last follow-up.

2.3 | Statistical Analysis

Descriptive statistics for categorical data were reported as frequencies and percentages, while survival outcomes were summarized using median values and rates. Group comparisons utilized Pearson's Chi-Square and Fisher's exact tests (two-sided). Survival curves were depicted using the Kaplan–Meier methodology, with differences between groups assessed via log-rank tests. Independent prognostic factors were identified through multivariate Cox regression using stepwise forward analysis. To control comprehensively for treatment biases inherent in a retrospective design, propensity score matching (PSM) was employed. The covariates selected for matching included age at diagnosis, race, marital status, primary tumor site, tumor grade, breast cancer molecular subtype (e.g., HR-positive, HER2-positive, triple-negative), T stage, N stage, type of surgery, and administration of PORT. These covariates were selected based on their known clinical relevance in influencing both treatment decisions and survival outcomes in breast cancer patients. The goal of PSM was to create a balanced cohort with similar baseline characteristics, allowing for a more reliable comparison of treatment effects. This approach successfully balanced key differences between patients treated with AC and those who were not, addressing baseline covariate differences and selection biases. Additionally, forest plots were generated to visually represent the effects and outcomes. All statistical analyses were conducted using SPSS software (version 24.0), GraphPad Prism (version 9.0), and R software (version 3.6.4). A significance level of $p < 0.05$ was applied across all analyses.

3 | Result

3.1 | Clinicopathological Characteristics

A total of 1866 patients diagnosed with breast cancer who did not respond to NAC following radical surgery were identified from the SEER database. The baseline clinical characteristics of which are summarized in Table 1.

The mean age at diagnosis was approximately evenly distributed, with 58.9% of patients being under 60 years old and 41.1% being 60 years or older. Of the patients enrolled, the majority were White (73.5%), followed by Black (31.0%) and others (33.0%). The primary site of cancer varied among patients, with the upper-outer quadrant of the breast being the most common site (33.3%), followed by overlapping lesions (23.3%) and the breast not otherwise specified (14.0%). Other locations included lower-outer, upper-inner, and lower-inner quadrants, as well as the central portion and axillary tail of the breast, with no significant differences observed between groups ($p = 0.735$). Most patients were diagnosed at stage II (43.9%) and stage III (49.0%). Tumor grade distribution indicated that slightly more patients had lower-grade tumors (I–II) (53.3%) compared to higher-grade tumors (III–IV) (46.7%). The positive ratio of ER, PR, and HER2 status accounted for 71.6%, 60.3%, and 15.9%, respectively. HER2−/HR+ was the most common breast subtype (60.9%), with higher prevalence in the AC cohort (67.2%). Most patients underwent mastectomy (70.4%), with a slight preference for breast-conserving surgery in the AC group (31.5%, $p = 0.056$). A significant difference was also noted in PORT administration ($p < 0.001$), with more patients in the AC group receiving PORT (69.3% vs. 49.2% in the Non-AC cohort).

3.2 | Survival and Prognostic Factors Analysis

The median follow-up time for the cohort was 68 months, and the median OS was 111.0 months. The 1-, 3-, 5-, and 10-year OS rates for the entire cohort of patients with breast cancer receiving NAC following radical surgery were 94.6%, 76.2%, 65.4%, and 48.9%, respectively (Figure 2A). Additionally, we examined the long-term survival impact of AC compared to Non-AC in the unmatched cohort. Patients who received AC had a median OS of 124.0 months, whereas those who did not receive AC had a median OS of 93.0 months. This difference was statistically significant (hazard ratio [HR] 0.705, 95% confidence interval [CI] 0.608–0.818, $p < 0.001$) (Figure 2B). However, the results of *the* multivariate analysis, adjusted for other variables, indicate that receiving AC after surgery is not an independent prognostic factor.

In addition, univariate analysis identified several factors significantly associated with OS in breast cancer patients undergoing surgery after NAC. These factors included age, race, marital status, grade, breast cancer subtype, T stage, N stage, surgery method, and PORT (all p values < 0.05). Furthermore, multivariate Cox regression analysis also demonstrated significant poor prognostic factors. Patients aged ≥ 60 years had worse survival outcomes compared to those aged < 60 years (HR 1.290, 95% CI 1.105–1.505, $p = 0.001$). Race also played a role, with Black patients having worse outcomes compared to White patients (HR 1.345, 95% CI 1.114–1.623, $p = 0.002$). Unmarried patients had poorer survival compared to married patients (HR 1.255, 95% CI 1.078–1.462, $p = 0.003$). Higher tumor grade (III–IV vs. I–II) was associated with significantly worse OS (HR 2.34, 95% CI 1.946–2.815, $p < 0.001$). Breast cancer subtype also influenced survival, with HER2+/HR− and HER2−/HR− subtypes being associated with poorer outcomes compared to the HER2−/HR+ subtype (HR 1.429, 95% CI 1.005–2.033, $p = 0.047$ and HR 1.845, 95% CI 1.529–2.226, $p < 0.001$, respectively). However, patients with HER2+/HR+ have longer OS than those with HER2−/HR+ (HR 0.609, 95% CI 0.451–0.822, $p < 0.001$). Moreover, patients with T3 and T4 stages had worse survival compared to those with T1 stage (HR 1.624, 95% CI 1.197–2.205, $p = 0.002$ and HR 2.484, 95% CI 1.801–3.426, $p < 0.001$, respectively). Similarly, N stage was a significant prognostic factor, with N1, N2, and N3 stages associated with progressively worse OS compared to N0 stage (HR 1.705, 95% CI 1.379–2.108, $p < 0.001$, HR 2.429, 95% CI 1.914–3.082, $p < 0.001$, and HR 3.483, 95% CI 2.732–4.441, $p < 0.001$, respectively). Details of univariate and multivariate analysis results are shown in Table 2.

TABLE 1 | Clinicopathological characteristics of the study population.

Characteristics	Total ($n=1866$)	Non-AC ($n=836$)	AC ($n=1030$)	p
Age at diagnosis (year)				0.582
<60	1100 (58.9)	487 (58.3)	613 (59.5)	
≥60	766 (41.1)	349 (41.7)	417 (40.5)	
Race				<0.001
White	1372 (73.5)	597 (71.4)	775 (75.2)	
Black	289 (15.5)	160 (19.1)	129 (12.5)	
Others	615 (33.0)	79 (9.4)	126 (12.2)	
Marital status				0.194
Married	1002 (53.7)	435 (52.0)	567 (55.0)	
Unmarried	864 (46.3)	401 (48.0)	463 (45.0)	
Primary site				0.735
Upper-outer quadrant of breast	621 (33.3)	277 (33.1)	344 (33.4)	
Lower-outer quadrant of breast	129 (6.9)	54 (6.5)	75 (7.3)	
Upper-inner quadrant of breast	203 (10.9)	87 (10.4)	116 (11.3)	
Lower-inner quadrant of breast	94 (5.0)	37 (4.4)	57 (5.5)	
Central portion of breast, Nipple	113 (6.1)	52 (6.2)	61 (5.9)	
Axillary tail of breast	9 (0.5)	6 (0.7)	3 (0.3)	
Overlapping lesion of breast	435 (23.3)	201 (24)	234 (22.7)	
Breast, NOS	262 (14.0)	122 (14.6)	140 (13.6)	
Grade				<0.001
I–II	995 (53.3)	373 (44.6)	622 (60.4)	
III–IV	871 (46.7)	463 (55.4)	408 (39.6)	
Subtype				<0.001
HER2−/HR+	1137 (60.9)	445 (53.2)	692 (67.2)	
HER2+/HR+	230 (12.3)	78 (9.3)	152 (14.8)	
HER2+/HR−	66 (3.5)	28 (3.3)	38 (3.7)	
HER2−/HR−	433 (23.2)	285 (34.1)	148 (14.4)	
ER status				<0.001
Negative	530 (28.4)	326 (39)	204 (19.8)	
Positive	1336 (71.6)	510 (61)	826 (80.2)	
PR status				<0.001
Negative	740 (39.7)	417 (49.9)	323 (31.4)	
Positive	1126 (60.3)	419 (50.1)	707 (68.6)	
HER2 status				<0.001
Negative	1570 (84.1)	730 (87.3)	840 (81.6)	
Positive	296 (15.9)	106 (12.7)	190 (18.4)	

(Continues)

TABLE 1 | (Continued)

Characteristics	Total ($n=1866$)	Non-AC ($n=836$)	AC ($n=1030$)	p
TNM stage				0.211
I	133 (7.1)	59 (7.1)	74 (7.2)	
II	819 (43.9)	349 (41.7)	470 (45.6)	
III	914 (49.0)	428 (51.2)	486 (47.2)	
T stage				0.008
T1	235 (12.6)	91 (10.9)	144 (14)	
T2	833 (44.6)	359 (42.9)	474 (46)	
T3	523 (28)	241 (28.8)	282 (27.4)	
T4	275 (14.7)	145 (17.3)	130 (12.6)	
N stage				0.009
N0	580 (31.1)	286 (34.2)	294 (28.5)	
N1	682 (36.5)	282 (33.7)	400 (38.8)	
N2	344 (18.4)	164 (19.6)	180 (17.5)	
N3	260 (13.9)	104 (12.4)	156 (15.1)	
Surgery method				0.056
Breast-conserving Surgery	553 (29.6)	229 (27.4)	324 (31.5)	
Mastectomy	1313 (70.4)	607 (72.6)	706 (68.5)	
PORT				<0.001
No	741 (39.7)	425 (50.8)	316 (30.7)	
Yes	1125 (60.3)	411 (49.2)	714 (69.3)	

Note: The table presents the distribution of patient characteristics across the total cohort ($n=1866$), and compares patients who received adjuvant chemotherapy (AC) vs. those who did not (Non-AC). Data are shown as frequencies (percentages) with comparisons made between groups using Pearson's Chi-Square or Fisher's exact tests, as appropriate. Variables include demographic and clinical characteristics such as age at diagnosis, race, marital status, tumor grade, molecular subtype, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, TNM staging, T stage, N stage, surgery method, and postoperative radiotherapy (PORT) administration. Statistical significance is indicated where appropriate (p values).
Abbreviations: AC: adjuvant chemotherapy; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; Non-AC: nonadjuvant chemotherapy; PORT: postoperative radiotherapy; PR: progesterone receptor.

3.3 | PSM and Subgroup Analysis

To reduce bias, PSM was employed, resulting in all Chi-Squared test p values being greater than 0.05 and decreased absolute values of standardized differences, indicating improved balance. The resulting PSM cohort was comprised of 1228 patients, with 614 receiving AC and 614 not receiving AC. Previously observed differences between cohorts with respect to race, grade, breast subtype, ER status, PR status, HER2 status, and PORT administration were successfully balanced after matching (Supporting Information Table 1).

After matching, the OS of patients treated with AC vs. those not treated with AC was examined by Kaplan–Meier estimates, and the survival curves are shown in Figure 2C. No survival advantage was observed for patients who received AC compared with those in *the* Non-AC cohort (HR = 0.973, 95% CI = 0.815–1.163, $p=0.767$).

Furthermore, subgroup analysis based on age, race, marital status, tumor grade, breast cancer subtype, ER status, PR status, HER2 status, TNM stage, T stage, N stage, and type of surgery did not demonstrate any significant differences in the hazard ratios for OS between the Non-AC and AC cohorts (Figure 3). This indicates that AC did not confer a survival benefit across various subgroups, suggesting the need for more personalized treatment strategies to improve outcomes for those patients.

4 | Discussion

This large-scale study provides compelling evidence that breast cancer patients who exhibit NR to NAC derive no significant benefit from subsequent AC, a conclusion that holds true across all molecular subtypes. These findings are particularly impactful as they challenge the prevailing assumption that AC could potentially improve outcomes in nonresponders. This conclusion is particularly important as it addresses a critical gap in current clinical practice, where AC is often continued without a clear evidence base for its efficacy in nonresponders, thereby potentially exposing patients to unnecessary side effects without therapeutic benefit. It underscores the importance of avoiding

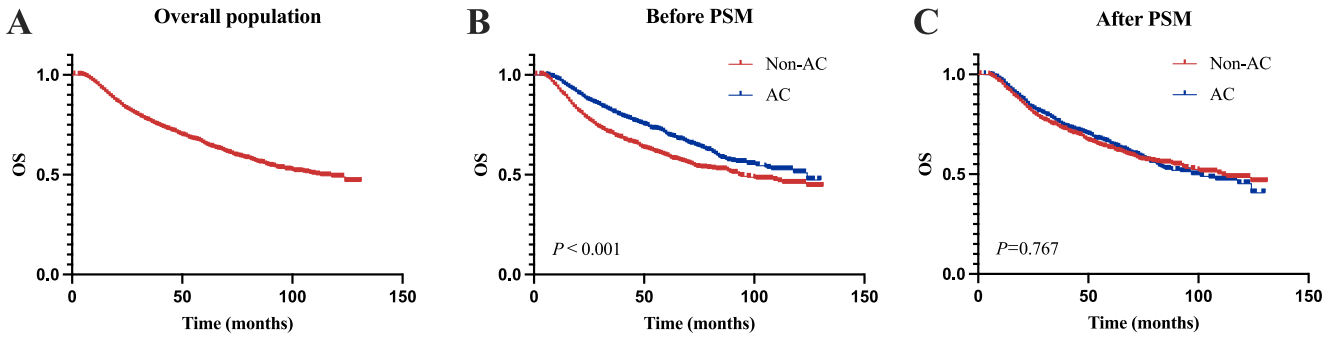

FIGURE 2 | Survival curves of the overall population and different cohorts. (A) Kaplan–Meier survival curves for the overall cohort of breast cancer patients who did not respond to neoadjuvant chemotherapy following radical surgery. (B) Comparison of survival curves between patients receiving AC and those not receiving AC before PSM. (C) Comparison of survival curves between patients receiving AC and those not receiving AC after PSM. AC, adjuvant chemotherapy; PSM, propensity score matching.

unnecessary treatments that not only fail to improve prognosis but also expose patients to avoidable treatment-related adverse effects, ultimately supporting a more personalized and evidence-based approach to breast cancer management.

Patients who achieve a pCR after NAC typically demonstrate favorable prognoses, while those who do not achieve a pCR often face a higher risk of recurrence and poorer outcomes [1, 2], particularly in triple-negative breast cancer (TNBC) and HER2-positive breast cancer [9, 10]. For patients who do not achieve a pCR, adjuvant intensified therapy—characterized by increased drug dosages, extended treatment durations, the addition of novel agents, or the combination of multiple therapies—may help further reduce the risk of recurrence and prolong OS. Numerous clinical trials have explored adjuvant intensified treatment strategies for various molecular subtypes of breast cancer, particularly targeting populations with Non-pCR after neoadjuvant therapy and those at high risk of postoperative recurrence [4, 11, 12]. However, despite the promising results of some intensified therapies in specific subgroups, our study reinforces the notion that for patients who are Non-pCR to NAC, conventional AC regimens offer no survival benefit, and alternative treatment strategies should be explored. A brief comparison of these pivotal trials with our study could further highlight the unique contributions of our findings. For instance, the CREATE-X trial, a phase III randomized controlled trial, evaluated the efficacy of capecitabine in improving DFS in patients with TNBC who did not achieve a pCR after standard NAC [4]. The results indicated that capecitabine significantly improved DFS and OS rates compared to the control group receiving a placebo [4]. In addition, the KATHERINE trial demonstrated that in patients with HER2-positive breast cancer who did not achieve a pCR after NAC, the use of T-DM1 instead of trastuzumab significantly improved DFS [11]. While these trials highlight the potential benefits of specific adjuvant therapies, they also underline the importance of selecting the right treatment based on the patient's response to NAC. Our study, however, suggests that AC regimens, particularly those not incorporating novel agents, do not improve survival in patients who are NR to NAC, regardless of the specific molecular subtype. For HER2-negative patients with BRCA mutations who do not achieve a pCR after neoadjuvant therapy, treatment with olaparib for 1 year may be considered [5]. For patients with ER-positive HER2-negative breast cancer who have high-risk factors such as lymph node metastasis, consideration may be given to extending the duration of endocrine therapy [13–15] or combining endocrine therapy with CDK4/6 inhibitors [16, 17]. However, all these adjuvant intensified treatments have strict indications and are not suitable for all patient populations. The above trials both highlight the significance of tailored adjuvant therapy in nonresponders, but our study found that AC regimens, particularly those not incorporating novel agents, do not improve survival in patients who are NR to NAC, regardless of the specific molecular subtype. This underscores the need to move beyond conventional AC regimens in nonresponder populations and explore personalized treatment options that better align with individual patient characteristics and disease biology.

An increasing number of clinical studies, along with a growing number of clinicians in practice, are focusing on the "add-on" approach during the adjuvant treatment phase for patients who did not achieve a pCR or exhibited poor response to NAC [4, 7, 11]. However, there remains considerable variability in clinical practice regarding the optimal adjuvant strategy for nonresponders. This aligns with our research, which found that over half of the nonresponders received AC postsurgery. However, there remains controversy regarding the necessity of postoperative AC and the selection of treatment regimens for this patient population. Despite the widespread use of AC, our study clearly demonstrates its lack of efficacy in this patient population. More tailored, biomarker-driven strategies need to be integrated into clinical decision-making. Through PSM analysis, we explored the impact of AC on survival benefits in patients who underwent radical surgical resection after NAC and did not achieve a pCR. Our findings indicated that NR patients who received AC postsurgery did not experience an extension in survival compared to those who did not receive AC. Notably, consistent results were observed across different subgroups, including varying molecular subtypes, lymph node metastasis status, and tumor sizes. These findings provide critical clinical guidance by avoiding unnecessary additional treatments and thereby reducing associated treatment-related adverse effects. Currently, there is no clinical trial evidence demonstrating that postoperative AC reduces the risk of recurrence or prolongs survival in patients who have undergone a full course of NAC, regardless of whether they are classified as Non-pCR or NR.

TABLE 2 | Univariate and multivariate survival analysis on OS for the entire population.

	OS univariate		Multivariate	
Characteristics	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age at diagnosis (year)				
< 60	1			
≥ 60	1.194 (1.029–1.386)	0.019	1.290 (1.105–1.505)	0.001
Race				
White	1		1	
Black	1.670 (1.393–2.002)	< 0.001	1.345 (1.114–1.623)	0.002
Others	0.800 (0.612–1.047)	0.104	0.840 (0.640–1.103)	0.209
Marital status				
Married	1		1	
Unmarried	1.364 (1.176–1.582)	< 0.001	1.255 (1.078–1.462)	0.003
Primary site				
Upper-outer quadrant of breast	11		1	
Lower-outer quadrant of breast	0.898 (0.653–1.234)	0.506	1.017 (0.738–1.402)	0.918
Upper-inner quadrant of breast	0.789 (0.602–1.034)	0.086	0.987 (0.749–1.299)	0.923
Lower-inner quadrant of breast	1.138 (0.812–1.597)	0.453	1.373 (0.973–1.937)	0.072
Central portion of breast, Nipple	0.726 (0.507–1.039)	0.080	0.655 (0.454–0.943)	0.023
Axillary tail of breast	0.786 (0.252–2.456)	0.679	0.796 (0.252–2.516)	0.697
Overlapping lesion of breast	0.846 (0.689–1.038)	0.109	0.811 (0.658–0.999)	0.049
Breast, NOS	1.337 (1.078–1.659)	0.008	1.275 (1.02–1.594)	0.033
Grade				
I–II	1		1	
III–IV	3.031 (2.589–3.548)	< 0.001	2.34 (1.946–2.815)	< 0.001
Breast subtype				
HER2−/HR+	1		1	
HER2+/HR+	0.69 (0.513–0.927)	0.014	0.609 (0.451–0.822)	0.001
HER2+/HR−	1.981 (1.412–2.778)	< 0.001	1.429 (1.005–2.033)	0.047
HER2−/HR−	2.508 (2.134–2.948)	< 0.001	1.845 (1.529–2.226)	< 0.001
T stage				
T1	1		1	
T2	1.506 (1.124–2.017)	0.006	1.217 (0.906–1.635)	0.191
T3	1.966 (1.457–2.651)	< 0.001	1.624 (1.197–2.205)	0.002
T4	3.932 (2.893–5.343)	< 0.001	2.484 (1.801–3.426)	< 0.001
N stage				
N0	1		1	
N1	1.55 (1.259–1.907)	< 0.001	1.705 (1.379–2.108)	< 0.001
N2	2.217 (1.767–2.781)	< 0.001	2.429 (1.914–3.082)	< 0.001
N3	3.387 (2.701–4.247)	< 0.001	3.483 (2.732–4.441)	< 0.001

(Continues)

TABLE 2 | (Continued)

Characteristics	OS univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Surgery method				
Breast-conserving surgery	1			
Mastectomy	1.652 (1.378–1.979)	< 0.001		
PORT				
No	1			
Yes	0.853 (0.735–0.991)	0.038		
AC				
No	1			
Yes	0.705 (0.608–0.818)	< 0.001		

Abbreviations: AC: adjuvant chemotherapy; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PORT: postoperative radiotherapy; PR: progesterone receptor.

NAC not only reduces tumor size and stages the disease but also provides insights into drug sensitivity. In populations that do not respond to NAC, it indicates potential resistance to the regimen. Although a few studies, such as CREATE-X, have reported positive results for the addition of treatments in patients with Non-pCR, the distinction between Non-pCR and NR *remains unclear*. The Non-pCR group includes patients who may have reached a PR on imaging or are close to achieving pCR, indicating sensitivity to NAC. In contrast, NR patients are generally insensitive or resistant to chemotherapy. Current guidelines and consensus recommend AC for different molecular subtypes of breast cancer, typically favoring regimens that include anthracyclines and/or taxanes [18, 19]. Clearly, these treatment regimens demonstrate varying degrees of cross-resistance with NAC regimens. Additionally, most patients in the neoadjuvant therapy phase have already undergone a change in their chemotherapy regimen based on efficacy assessments [20–22]. This suggests that this group of nonresponders may exhibit resistance to chemotherapy agents with more than two different mechanisms of action. This phenomenon likely contributes to the challenges faced by most clinical trials investigating additional postoperative AC in demonstrating significant benefits.

Consequently, some studies have explored the potential of switching treatment regimens for these patients. A prospective study compared AC with an anthracycline-based regimen (VACP) vs. a noncross-resistant regimen without anthracyclines (VbMF) in breast cancer patients who had poor pathological responses after neoadjuvant treatment. The results indicated that VbMF improved RFS and OS, although the differences between the two groups did not reach statistical significance [7]. The NSABP B-27 study found that adding docetaxel to the preoperative doxorubicin and cyclophosphamide regimen in breast cancer patients did not improve DFS or OS [6]. Similarly, the EA1131 study explored the use of carboplatin or cisplatin in a noninferiority design against capecitabine over four cycles, focusing on invasive disease-free survival (iDFS). Despite preclinical models supporting the antitumor activity of platinum-based drugs in TNBC, the results indicated that platinum agents did not improve outcomes compared to capecitabine and were associated with an increase in adverse reactions [23]. These findings add weight to our study's argument that AC regimens, particularly those based on older chemotherapy agents, have limited benefit in this group of patients. Additionally, the phase II clinical trial BRE12-158 compared genomics-based personalized treatment for residual disease in TNBC after NAC with physician's choice treatment (TPC) [24]. The results indicated that genomics-directed therapy did not demonstrate superiority over TPC [24]. These findings suggest that even when using alternative regimens to avoid cross-resistance, adding chemotherapy during the postoperative adjuvant phase still fails to improve survival outcomes.

Based on our research findings, routine postoperative AC is not recommended for patients who show nonresponse after completing a full course of NAC, whether they continue with the original regimen or switch to an alternative. Currently, for breast cancer patients who do not achieve pCR (including nonresponse) after NAC, evidence-based studies on adjuvant intensified treatment include CREATE-X, KATHERINE, and OlympiA. We found that both capecitabine and other clinical trial drugs that have shown positive results for Non-pCR patients, such as the PARP inhibitor olaparib and the antibody-drug conjugate T-DM1, do not exhibit cross-resistance with the currently recommended neoadjuvant treatment regimens. In other words, the neoadjuvant treatment regimens do not include drugs with similar mechanisms of action. Furthermore, all of these agents require prolonged administration, with chemotherapy typically necessitating a treatment duration of 6 months, while other therapeutic agents may require even longer treatment periods, often exceeding 1 year.

Capecitabine is currently the only approved chemotherapeutic agent for adjuvant intensification therapy in breast cancer patients who do not achieve a pCR after NAC. We seek to explain the reasons behind the success of capecitabine as an adjuvant intensification treatment from multiple perspectives. As an oral

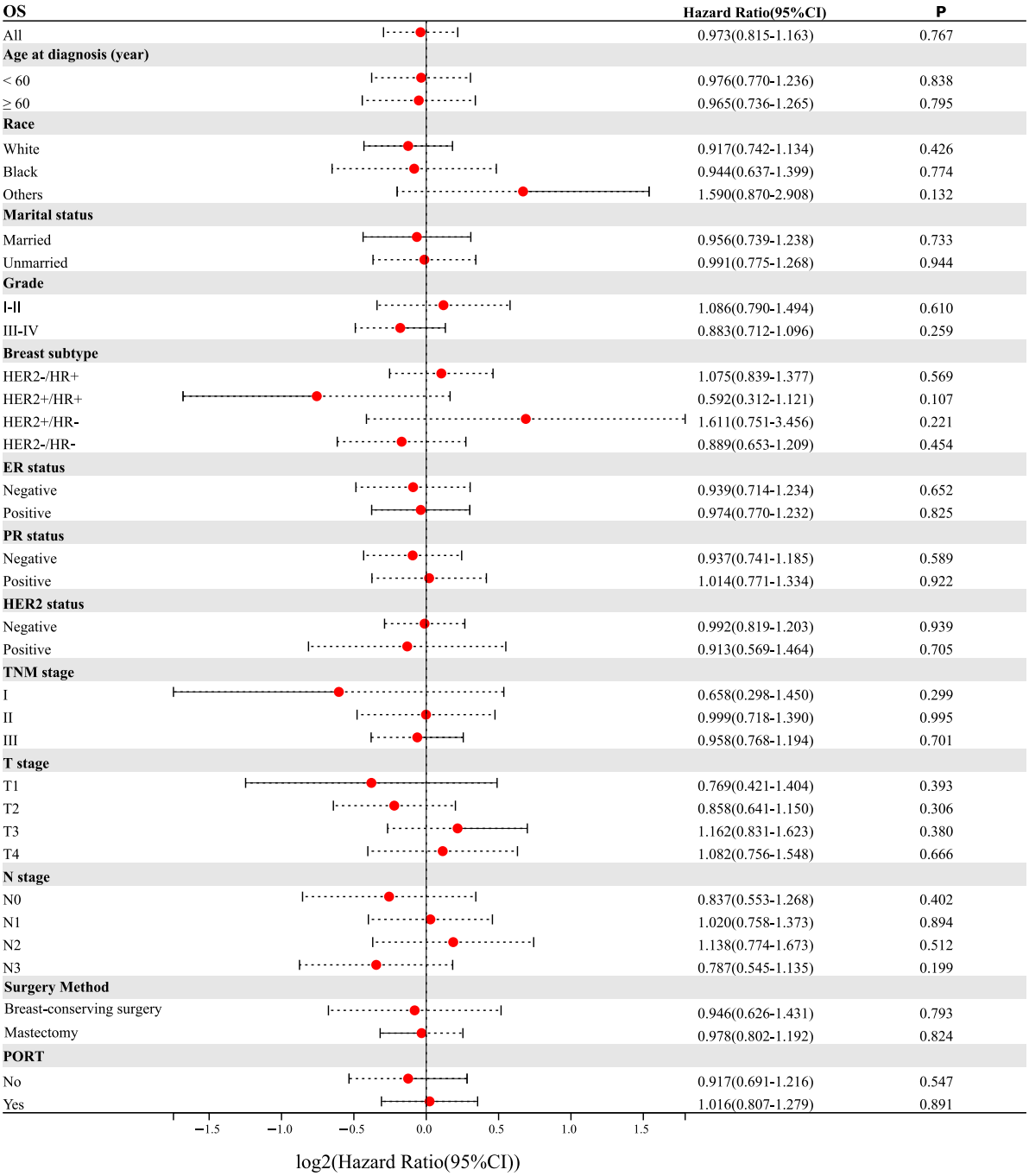

FIGURE 3 | Forest plot demonstrating the benefit or lack thereof of adjuvant chemotherapy across subgroups after propensity score matching.

chemotherapeutic drug, capecitabine has been shown in multiple clinical trials to significantly improve outcomes for patients with TNBC. Whether used in combination with standard treatment or as a consolidation therapy following standard treatment completion, capecitabine demonstrates potential for reducing recurrence risk and enhancing survival rates [4, 25, 26]. NAC primarily involves anthracyclines and taxanes, which can upregulate the expression of thymidine phosphorylase (TP). TP subsequently facilitates the conversion of capecitabine into its active form, 5-fluorouracil, thereby enhancing the efficacy of capecitabine [25]. Fluoropyrimidine-based antimetabolites have a short half-life and exhibit time-dependent effects, making continuous intravenous infusion or oral administration more effective for antitumor action. Moreover, patients undergoing NAC rarely receive antimetabolite treatments, with few having prior exposure to capecitabine. This can partly explain why continuous capecitabine as an adjuvant therapy can further improve the prognosis of high-risk, Non-pCR TNBC patients. When considering antitumor efficacy, it is also essential to address the safety of the medication, particularly with long-term use. In the CREATE-X study, the incidence of hand-foot syndrome associated with capecitabine was as high as 73.4%, with hematological adverse events exceeding 40% [4]. To reduce the incidence of adverse reactions, some studies have explored the efficacy of metronomic

dosing of capecitabine in high-risk TNBC [25]. Metronomic chemotherapy involves administering low doses at high frequency with short intervals between doses [27]. In the SYSUCC-001 study, the metronomic dosing regimen of capecitabine enabled over 90% of patients to complete the planned 1-year treatment course as scheduled [25]. Moreover, the incidence of adverse reactions was significantly lower compared to traditional dosing methods. The primary adverse event observed was hand-foot syndrome, which occurred in 45.2% of patients, with most cases classified as grade 1 or 2 [25]. Therefore, for patients who do not achieve a pCR after NAC and for those at high risk of postoperative recurrence, adopting a scheduling approach for adjuvant intensified chemotherapy may help ensure treatment efficacy while also preserving the patients' quality of life.

This study has several limitations that should be considered when interpreting the findings. First, the retrospective design may introduce selection bias and limit our ability to control for confounding factors, potentially affecting the validity of the results. Additionally, we lacked access to detailed information on the specific regimens, dosages, and cycles of both neoadjuvant and adjuvant chemotherapy, which prevented us from conducting more granular subgroup analyses. Furthermore, an important factor that could not be analyzed is the duration of NAC, which may influence patient outcomes. Unfortunately, due to limitations in the available data, we were unable to explore this aspect. However, we recognize that treatment duration is a critical variable and suggest that future studies investigate its impact on survival and response rates. Despite these limitations, this study is significant as it addresses a critical gap in understanding the optimal management strategy for breast cancer patients who do not respond to NAC, providing valuable insights that could guide future clinical practice and research.

5 | Conclusion

Our study found that breast cancer patients who did not respond to NAC did not exhibit improved OS with subsequent AC. These findings suggest that AC might not provide additional benefit for this subset of patients. Further research is needed to identify more effective treatment strategies for breast cancer patients unresponsive to NAC.

Author Contributions

FM served as the corresponding author and guarantor of the study. LXL conceived and designed the study. DZ conducted the initial literature search and data analysis. DZ responsible for the preparation of figures and tables, while LXL interpreted the results and drafted the manuscript. SNL and CZ provided technical support and critical suggestions. YLQ contributed to manuscript writing and revision. FM provided critical revisions and finalized the manuscript. All authors made substantial contributions to the study, reviewed and approved the final version, and consented to its submission.

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Ethics Statement

All data were extracted from the public SEER database, which contains de-identified information. Ethical approval was deemed unnecessary for this study.

Consent

Secured.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets utilized in this study can be accessedupon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.