

# Real-world data indicated that neoadjuvant chemotherapy alone was associated with a higher risk of tumor recurrence in high-risk breast cancer subgroup patients

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**Abstract.** Numerous clinical trials have reported equal effects of tumor control between neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) in patients with breast cancer (BC). However, this conclusion has not been verified in practice. The present retrospective study evaluated if there were different risk profiles for NAC, AC and their combinative modes on disease-free survival (DFS) in patients with BC using real-world data. All women with primary unilateral Stage I-III BC and first recurrence in 2008-2018 at The Fourth Hospital of Hebei Medical University were retrospectively identified for enrollment. The four modes of chemotherapy administered for primary BC were classified as 'None', 'NAC only', 'NAC+AC' and 'AC only'. One multivariate Cox model was

used to estimate the adjusted Hazard Ratio (HR) and P-value. Covariates included age, Easter Cooperative Oncology Group grade, T stage, N stage, pathology, grade, lymphovascular invasion (LVI), BC subtype, number of chemotherapy cycles and other therapies. Amongst 637 patients, who had a mean age of 48.2 years at BC diagnosis and 50.9 years at recurrence, the median DFS by the 'None' (n=27), 'NAC only' (n=47), 'NAC+AC' (n=118) and 'AC only' (n=445) modes were 31.4, 16.6, 22.6 and 28.4 months (P<0.001), respectively. Compared with the 'AC only', adjusted HR (P-value) of the 'None', 'NAC only' and 'NAC+AC' modes on tumor recurrence were 1.182 (0.551), 1.481 (0.037) and 1.102 (0.523), respectively. The adjusted HR of 'NAC only' vs. 'AC only' modes were 1.448 (P=0.157) for locoregional recurrence and 2.675 (P=0.003) for distant recurrence. Stratified analyses further indicated that the 'NAC only' mode was associated with a higher recurrence risk in T3-4, N2-3, LVI-positive, or HER2-negative subgroup patients. In conclusion, NAC alone was associated with a higher risk of tumor recurrence in high-risk BC subgroup patients in real-world data. Patient selection of chemotherapy mode was involved in practice but could not fully explain this finding. The 'inadequate' NAC was highly likely to have accounted for this observation.

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**Abbreviations:** AC, adjunct chemotherapy; ALND, axillary lymph node dissection; ANOVA, analysis of variance; BC, breast cancer; BCS, breast-conserving surgery; CI, confidence interval; DFS, disease-free survival; ECOG, Easter Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; LN, lymph node; LR, locoregional recurrence; LRR, locoregional recurrence rate; LVI, lymphovascular invasion; NAC, neoadjuvant chemotherapy; NCCN, National Comprehensive Cancer Network; OS, overall survival; pCR, pathologic complete response; RCT, randomized clinical trial; RR, relative risk; T-DM1, trastuzumab emtansine; TNBC, triple negative breast cancer

**Key words:** breast cancer, disease-free survival, neoadjuvant chemotherapy, adjuvant chemotherapy, real-world data

## Introduction

Neoadjuvant chemotherapy (NAC) is being increasingly used for operable breast cancer (BC) which is either locally advanced or has some risk factors (1-3). NAC benefits include increased rate of breast-conserving surgery (BCS), higher chance of tumor completion resection, and most importantly, providing valuable data about tumor response to chemotherapy (4-6). For example, randomized clinical trials (RCTs) have previously reported that human epidermal growth factor receptor 2 positive (HER2+) or triple negative BC (TNBC) patients had a better prognosis as a result of the changes to the chemotherapy strategy, based on the pathologic complete response (pCR) status after NAC (7-9). However, the routine use of NAC instead of adjunct chemotherapy (AC) in these patients with BC is still controversial (10,11). Although overall survival (OS) following NAC and AC were comparable in

these trials, certain concerns about NAC have been reported. For example, certain studies have reported that NAC is associated with higher risk of locoregional recurrence (LR), frequent inconsistent correlation between pCR status and OS, and increased complexity of surgery (4,6,12,13). Some researchers have hypothesized that NAC may delay tumor surgery and make it more conservative which can lead to a higher chance of tumor recurrence in certain subgroups of patients with BC, especially those with tumors insensitive to NAC (6,14).

In China, the use of NAC in practice has been slow. Many Chinese patients with BC have low desire for BCS and are more concerned about how NAC could delay surgery and increase tumor progression (15). Furthermore, chemotherapy side effects such as fatigue, nausea, vomiting, leukopenia, emotional stress and unsatisfactory tumor reduction could discourage the patient or surgeon from continuing the NAC regime or completing the cycles as planned and then pursuing the necessary AC after the surgery done. The aforementioned issues indicate why the application of NAC in clinical practice is often different from that in trials. As a result, a retrospective study to characterize the possible different risk profiles of NAC vs. AC vs. their combinative chemotherapy modes, on disease-free survival (DFS) in patients with BC using real-world data was designed. After considering the history of NAC administration, an analysis was performed of all patients with BC at the first tumor recurrence over an 11-year time period.

## Patients and methods

**Patients and study design.** All women with unilateral primary TNM stage I-III BC (7th edition, AJCC/UICC) and first tumor recurrence in 2008-2018 at The Fourth Hospital of Hebei Medical University were enrolled in the present study (16). Patient inclusion criteria included: i) Age at diagnosis  $\geq 18$  years and diagnosed in 1997 or later; and ii) BC diagnosed pathologically as LR or presented clinically distant metastasis by computed tomography, magnetic resonance, bone scintigraphy or positron emission tomography imaging. In the present study, LR was defined as tumor recurrence at contralateral or ipsilateral breast, chest wall, or regional lymph node (LN) at axillary, supraclavicular, infraclavicular and internal mammary regions. Exclusion criteria included: i) Inflammatory BC; ii) contralateral BC diagnosed within 6 months following the primary BC diagnosis; iii) any recurrence diagnosed before the completion of chemotherapy or RT; and iv) any recurrence potentially from other cancers.

In the analysis, the primary BC diagnosis date was defined as the baseline. The earliest date of all tumor recurrences diagnosed in regular medical check-ups was regarded as the endpoint date. DFS in days was calculated as the number of days between the endpoint date and the baseline plus 1. Three time-to-event outcomes of; any tumor recurrence, LR and organ metastasis were analyzed.

The present study was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University (approval no. 2017-288). All participants provided written informed consent. All sensitive health information of participants was excluded from the study dataset.

**Chemotherapy mode and regimen.** While the National Comprehensive Cancer Network (NCCN) guidelines for BC treatments were followed, the actual timing and number of cycles of chemotherapy were at the discretion of the individual physician. The most common regimens of chemotherapy mainly consisted of the dose-dense doxorubicin and cyclophosphamide followed by paclitaxel; docetaxel and cyclophosphamide; cyclophosphamide, methotrexate and fluorouracil epirubicin and cyclophosphamide; or docetaxel, doxorubicin and cyclophosphamide. Trastuzumab was the only HER2 targeted therapy drug available to be administered. Due to the high out-of-pocket cost, trastuzumab was administered only in a small portion of HER2+ patients. Based on the timing of the chemotherapy cycles, patients were assigned to one of four modes, as follows: 'None', 'NAC only', 'NAC+AC' or 'AC only'.

**Statistical methods.** Continuous and categorical variables were analyzed using descriptive statistics. Analysis of variance (ANOVA),  $\chi^2$  or Fisher's exact tests, were used to perform statistical comparisons as appropriate. The Kaplan-Meier curve and log-rank test were used to analyze DFS rates. The Cox survival model was used to estimate the hazard ratio (HR), 95% confidence interval (CI) and P-value. Two-sided  $P < 0.05$  was considered to indicate a statistically significant difference. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Inc.).

## Results

**Characteristics at baseline.** Table I presented the 637 patients who were enrolled after reviewing all hospital admissions ( $n=16,891$ ) of patients with BC. Among the enrolled patients, 25.9% ( $n=165$ ) received NAC. Many variables at baseline were significantly associated with the choice of chemotherapy modes. Because the number of chemotherapy cycles was not normally distributed, its three-level category was created for analysis. While the proportion of '1-4 cycles' in 'AC only' patients was 23.1% (103/445), it was markedly lower, 7.9% (13/165) in combined NAC patients. Furthermore, the proportion of '1-4 cycles' was significantly higher in 'NAC only' patients than in 'NAC+AC' patients [14.9% (7/47) vs. 5.1% (6/118),  $P=0.035$ ]. The aforementioned results indicated that NAC patients had either less cycles of NAC alone or, more likely, did not attend for AC after surgery.

**Characteristics of tumor recurrence.** The overall median DFS was 25.9 months (Table II). The DFS rates were significantly different among chemotherapy mode ( $P < 0.001$ , Fig. 1A) and cycle ( $P=0.002$ , Fig. 1B) subgroups. Patients who had 'NAC only' or had  $\geq 5$  chemotherapy cycles had the lowest DFS. Given the selection of chemotherapy mode varied by factors such as tumor size, LN status and BCS pursuit, as considered by the oncologist, multivariate analysis was performed to verify the independence of these observed links.

**Cox survival models.** Table III shows the analysis results. The covariates were determined based on the model building process and literature review. Compared with the 'AC only' patients, the 'NAC only' patients were significantly associated

Table I. Baseline characteristics of patients.

Characteristic	All	Chemotherapy mode				P-value <sup>a</sup>
		None	NAC only	NAC+AC	AC only	
Patients (n, %)	637 (100)	27 (4.2)	47 (7.4)	118 (18.5)	445 (69.9)	
Mean age $\pm$ SD, years	48.2 $\pm$ 10.4	54.8 $\pm$ 13.8	48.5 $\pm$ 10.2	48.8 $\pm$ 10.1	47.6 $\pm$ 10.1	0.005
Diagnosis year <sup>b</sup> , n (%)						<0.001
1997-2010	251 (39.4)	10 (4.0)	5 (2.0)	41 (16.3)	195 (77.7)	
2011-2016	386 (60.6)	17 (4.4)	42 (10.9)	77 (19.9)	250 (64.8)	
ECOG grade, n (%)						0.040
0	617 (96.5)	25 (4.0)	46 (7.5)	117 (19.0)	429 (69.5)	
1-2	20 (3.5)	2 (10.0)	1 (5.0)	1 (5.0)	16 (80.0)	
Tumor laterality, n (%)						0.230
Left	351 (55.1)	14 (4.0)	24 (6.8)	75 (21.4)	238 (67.8)	
Right	286 (44.9)	13 (4.5)	23 (8.0)	43 (15)	207 (72.4)	
Tumor surgery, n (%)						0.053
Lumpectomy	22 (3.5)	3 (13.6)	0 (0.0)	2 (9.1)	17 (77.3)	
Mastectomy	615 (96.5)	24 (3.9)	47 (7.6)	116 (18.9)	428 (69.6)	
LN procedure, n (%)						
ALND	579 (90.9)	16 (2.8)	47 (8.1)	113 (19.5)	403 (69.6)	<0.001
SLND	22 (3.5)	0 (0.0)	3 (13.6)	14 (63.6)	5 (22.7)	<0.001
IMLND	17 (2.7)	0 (0.0)	4 (23.5)	5 (29.4)	8 (47.1)	0.134
T stage, n (%)						<0.001
T1	141 (22.1)	6 (4.3)	7 (5.0)	10 (7.1)	118 (83.7)	
T2	338 (53.1)	16 (4.7)	10 (3.0)	51 (15.1)	261 (77.2)	
T3-4	114 (17.9)	0 (0.0)	30 (26.3)	55 (48.2)	29 (25.4)	
Unknown	44 (6.9)	5 (11.4)	0 (0.0)	2 (4.5)	37 (84.1)	
N stage, n (%)						<0.001
N0	236 (37)	16 (6.8)	3 (1.3)	14 (5.9)	203 (86.0)	
N1	167 (26.2)	6 (3.6)	9 (5.4)	26 (15.6)	126 (75.4)	
N2	74 (11.6)	1 (1.4)	8 (10.8)	14 (18.9)	51 (68.9)	
N3	141 (22.1)	1 (0.7)	27 (19.1)	63 (44.7)	50 (35.5)	
Unknown	19 (3.0)	3 (15.8)	0 (0.0)	1 (5.3)	15 (78.9)	
Tumor pathology, n (%)						0.345
IDC	529 (83.0)	21 (4.0)	42 (7.9)	102 (19.3)	364 (68.8)	
Other	108 (17.0)	6 (5.6)	5 (4.6)	16 (14.8)	81 (75.0)	
Tumor grade, n (%)						0.070
I	8 (1.3)	0 (0.0)	0 (0.0)	1 (12.5)	7 (87.5)	
II	393 (61.7)	17 (4.3)	34 (8.7)	86 (21.9)	256 (65.1)	
III	140 (22.0)	4 (2.9)	8 (5.7)	15 (10.7)	113 (80.7)	
Not reported	96 (15.1)	6 (6.3)	5 (5.2)	16 (16.7)	69 (71.9)	
LVI, n (%)						<0.001
Positive	152 (23.9)	3 (2.0)	5 (3.3)	43 (28.3)	101 (66.4)	
Negative	164 (25.7)	4 (2.4)	8 (4.9)	21 (12.8)	131 (79.9)	
Not reported	321 (50.4)	20 (6.2)	34 (10.6)	54 (16.8)	213 (66.4)	
Subtype, n (%)						0.036
Luminal A	258 (40.5)	11 (4.3)	14 (5.4)	43 (16.7)	190 (73.6)	
Luminal B	132 (20.7)	6 (4.5)	16 (12.1)	21 (15.9)	89 (67.4)	
HER2-enriched	97 (15.2)	2 (2.1)	9 (9.3)	21 (21.6)	65 (67.0)	
TNBC	86 (13.5)	2 (2.3)	8 (9.3)	22 (25.6)	54 (62.8)	
Unclassified	64 (10.0)	6 (9.4)	0 (0.0)	11 (17.2)	47 (73.4)	

Table I. Continued.

Characteristic	All	Chemotherapy mode				P-value <sup>a</sup>
		None	NAC only	NAC+AC	AC only	
Chemotherapy, cycles, n (%)						<0.001
0	27 (4.2)	27 (100)	0 (0.0)	0 (0.0)	0 (0.0)	
1-4	116 (18.2)	0 (0.0)	7 (6.0)	6 (5.2)	103 (88.8)	
≥5	494 (77.6)	0 (0.0)	40 (8.1)	112 (22.7)	342 (69.2)	
Systemic therapy, n (%)						
ET	232 (36.4)	7 (3.0)	12 (5.2)	33 (14.2)	180 (77.6)	0.015
RT	264 (41.4)	1 (0.4)	25 (9.5)	75 (28.4)	163 (61.7)	<0.001
Trastuzumab	12 (1.9)	0 (0.0)	0 (0.0)	5 (41.7)	7 (58.3)	0.158

<sup>a</sup>Calculated using ANOVA,  $\chi^2$  or Fisher's Exact test, on non-missing values, as appropriate. <sup>b</sup>Use of Trastuzumab was started in 2011. NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; ALND, axillary lymph node dissection; SLND, supraclavicular lymph node dissection; IMLND, internal mammary lymph node dissection; IDC, invasive ductal carcinoma; LVI, lymphovascular invasion; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; ET, endocrine therapy; RT, radiotherapy; T, tumor; N, node.

Table II. Characteristics of tumor recurrence (n=637).

Characteristic	All	Chemotherapy mode				P-value <sup>a</sup>
		None	NAC only	NAC+AC	AC only	
Mean age ± SD, years	50.9±10.6	57.9±13.2	50.1±10.1	51.0±10.1	50.5±10.4	0.001
Median DFS, months (95%CI)	25.9 (24.1-27.8)	31.4 (13.3-39.4)	16.6 (13.2-19.3)	22.6 (19.7-24.7)	28.4 (26.1-31.2)	<.001
Recurrence site, n (%)						
Ipsilateral region	321 (50.4)	16 (5.0)	23 (7.2)	51 (15.9)	231 (72.0)	0.293
Contralateral region	123 (19.3)	4 (3.3)	18 (14.6)	26 (21.1)	75 (61.0)	0.004
Any organ	453 (71.1)	20 (4.4)	34 (7.5)	82 (18.1)	317 (70.0)	0.959
Recurrence organ, n (%)						
Bone	254 (39.9)	11 (4.3)	19 (7.5)	37 (14.6)	187 (73.6)	0.218
Liver	156 (24.5)	3 (1.9)	12 (7.7)	33 (21.2)	108 (69.2)	0.331
Lung	154 (24.2)	9 (5.8)	10 (6.5)	30 (19.5)	105 (68.2)	0.652
Brain	35 (5.5)	1 (2.9)	3 (8.6)	9 (25.7)	22 (62.9)	0.675
Other	107 (16.8)	5 (4.7)	5 (4.7)	25 (23.4)	72 (67.3)	0.379
Recurrence type, n (%)						
Region only	137 (21.5)	6 (4.4)	4 (2.9)	23 (16.8)	104 (75.9)	0.074
Organ only	315 (49.5)	10 (3.2)	24 (7.6)	67 (21.3)	214 (67.9)	
Region and organ	185 (29.0)	11 (5.9)	19 (10.3)	28 (15.1)	127 (68.6)	

<sup>a</sup>P-value from ANOVA,  $\chi^2$  test or log-rank test on non-missing values, as appropriate. NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; DFS, disease-free survival; CI, confidence interval.

with higher risks of any recurrence (HR 1.452,  $P=0.037$ ) and organ metastasis (HR 2.675,  $P=0.003$ ) after the adjustment of covariates. No significant difference in the risk of any recurrence, LR and organ metastasis were demonstrated among the 'NAC+AC' patients and the 'AC only' patients (all HR 0.945-1.141,  $P=0.523$ -0.765). No difference in the risks linked to the '1-4 cycles' (vs. '≥5 cycles') of events was demonstrated by multivariate analyses for any recurrence (HR 0.811,

$P=0.062$ ), LR (HR 0.824,  $P=0.207$ ), and organ metastasis (HR 0.817,  $P=0.439$ ) (data not shown).

**Stratified Cox analysis.** Fig. 2 demonstrated that the significantly higher risk of any recurrence linked to the 'NAC only' mode compared with the 'AC only' mode was particularly presented in certain subgroups of patients. Specifically, it was present in patients with BC characterized by diagnosis

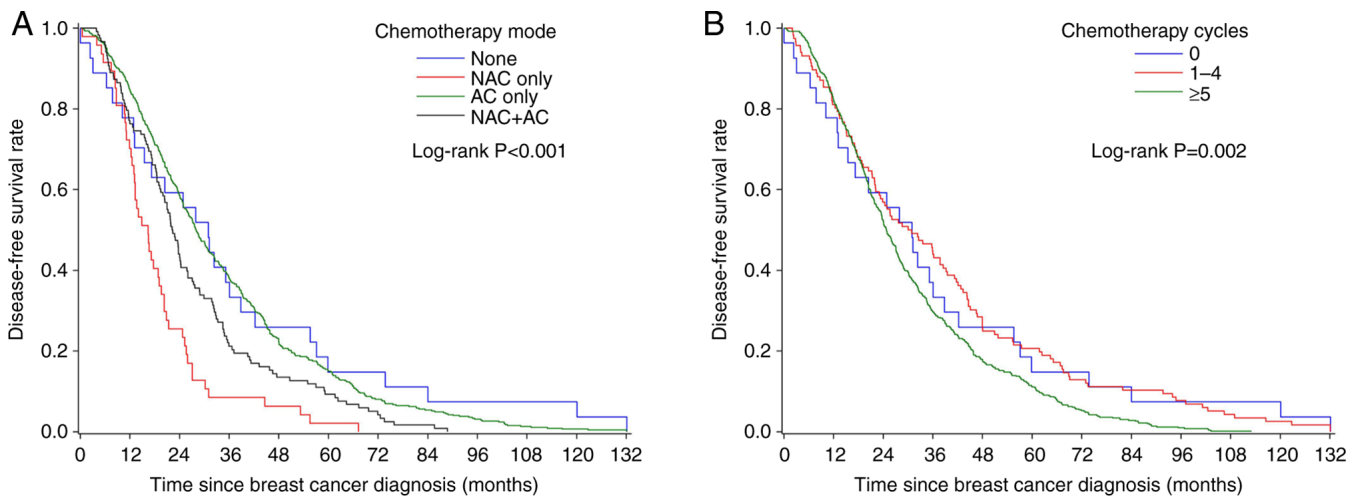


Figure 1. Kaplan-Meier disease-free survival curves for patients grouped by chemotherapy (A) mode and (B) number of cycles used. AC, adjunct chemotherapy; NAC, neoadjuvant chemotherapy.

and treatment in earlier years of the study period (HR 3.638,  $P=0.015$ ), stage T3-4 (HR 3.441,  $P<0.001$ ), stage N2-3 (HR 1.741,  $P=0.022$ ), lymphovascular invasion positive (LVI+) (HR 5.155,  $P=0.005$ ) or HER2-negative (HR 1.697,  $P=0.039$ ). There were similar results from the stratified Cox analysis of organ metastasis (data not shown).

## Discussion

For numerous reasons, such as different populations and interventions, real-world data could provide risk profiles of variables on tumor recurrence different to those generated in RCTs. Through adjusted and stratified analyses, this retrospective study demonstrated that, compared with the most commonly used 'AC only' mode, the 'NAC only' mode was associated with a significantly higher risk of tumor recurrence, especially at distant organ. These links were more specifically presented in high-risk BC subgroup patients characterized by stage T3-4, stage N2-3, LVI+ or HER2-negative. It could be hypothesized that the 'inadequate' total cycles of chemotherapy in BC patients who had NAC could have played a role. Another factor could possibly be the circumstances-these 'NAC+AC' patients would become 'NAC only' patients if they abandoned the planned AC. Given the potential clinical value of chemotherapy modes, more studies on the real-world data are needed to confirm and explain this finding.

Many factors can influence the decision-making for initiation, elongation, and termination of NAC in BC patients in clinical practice. Under the NCCN guidelines, NAC is usually recommended to patients with operable BC with larger tumors, more metastatic LN, HER2+, TNBC or stronger desire for BCS (17). For most early TNBC patients, NAC is currently used as the standard treatment while AC is only used for some patients opting for upfront surgery (18,19). The present study focused on patients with BC with first tumor recurrence in the past. It was noted that, different from the current guideline, the AC mode was demonstrated to be administered markedly more often than the NAC mode 62.8% (54/86) compared with 9.3% (8/86)

in TNBC patients (Table I, Fig. 2). Furthermore, a previous meta-analysis (9 studies, 2,109 patients) reported that the inclusion of platinum in NAC regimens led to a significantly higher rate of pCR (51.2% vs. 37.0%; OR 1.96, 95%CI 1.46-2.62) in TNBC patients, but no significant improvement in OS (HR 0.86, 95%CI 0.46-1.63) (20). Many factors are involved the decision-making of NAC against AC. Based on the results of the present study, the tumor recurrence risk profiles of chemotherapy modes should consider factors such as patient age, performance status, tumor feature, tumor response, adverse effects of prior chemotherapy and others. In the present study, data for pCR and adverse effects of chemotherapy were lacking for additional analysis. However, the consistent results of multivariate analyses indicated that the covariates assessed could not fully account for the study's results.

NAC and AC may have different drug mechanisms for reducing risk of tumor recurrence in BC patients (6). While surgery can cure the primary tumor, systemic treatments of NAC or AC are reported to be required to eliminate the occult tumor cells (6,21). Previous studies demonstrated that the effectiveness of AC varies with BC subtypes, metastatic LN status, dosage and number of cycles of chemotherapy regimens (22-25). For example, only patients with estrogen receptor-positive (ER+) and LN-negative BC with high 21-gene recurrence scores have been reported to benefit from adding chemotherapy to ET based on prognosis (26-28). In patients with ER-negative (ER-) or HER2+ BC, only having AC over a certain dosage of its regimens and number of cycles has been reported to lead to improved DFS and OS (23,29). The present study was not able to exclude the possibility that NAC and AC may have different mechanisms and effectiveness in reducing the tumor recurrence risk in certain BC subgroups.

Numerous recent studies have reported that the pCR status after a certain number of cycles of NAC could provide valuable guidance to the application of AC (9,30). For example, the KATHERINE trial included 1,486 patients with early HER2+ BC who had non-pCR after NAC and were randomized into the trastuzumab armor T-DM1

Table III. Cox proportional hazard regression analysis of recurrence type.

A, Any recurrence						
Chemotherapy	Univariate			Multivariate <sup>a</sup>		
	HR	95% CI	P-value	HR	95% CI	P-value
None	0.835	(0.56-1.245)	0.376	1.182	(0.682-2.047)	0.551
NAC only	2.378	(1.752-3.228)	<0.001	1.452	(1.022-2.062)	0.037
NAC + AC	1.388	(1.131-1.703)	0.002	1.085	(0.845-1.394)	0.523
AC only	1.000		ref.	1.000		ref.
B, regional recurrence						
Chemotherapy	Univariate			Multivariate <sup>a</sup>		
	HR	95% CI	P-value	HR	95% CI	P-value
None	0.915	(0.539-1.553)	0.742	1.060	(0.507-2.216)	0.878
NAC only	2.278	(1.474-3.522)	<0.001	1.448	(0.867-2.419)	0.157
NAC + AC	1.161	(0.855-1.575)	0.339	0.945	(0.652-1.369)	0.765
AC only	1.000		ref.	1.000		ref.
C, Organ metastasis						
Chemotherapy	Univariate			Multivariate <sup>a</sup>		
	HR	95% CI	P-value	HR	95% CI	P-value
None	0.679	(0.244-1.893)	0.460	1.090	(0.273-4.345)	0.903
NAC only	5.960	(3.510-10.122)	<0.001	2.675	(1.392-5.139)	0.003
NAC + AC	1.880	(1.197-2.951)	0.006	1.141	(0.656-1.983)	0.641
AC only	1.000		ref.	1.000		ref.

<sup>a</sup>The final covariates included diagnosis age at diagnosis of primary BC, ECOG, T stage, N stage, tumor pathology, tumor grade, LVI, subtype, ET, RT, Trastuzumab, if calendar year of primary BC diagnosis was after 2010, number group of chemotherapy cycles administered. HR hazard ratio, CI confidence interval, NAC neoadjuvant chemotherapy, AC adjuvant chemotherapy, ref. reference, BC breast cancer, ET endocrine therapy, RT radiotherapy; ECOG, Easter Cooperative Oncology Group; LVI, lymphovascular invasion; ET, endocrine therapy; RT, radiotherapy; T, tumor; N, node.

arm in AC (9). The trial reported that there was an 11.3% absolute gain in 3-year DFS (HR 0.50; 95%CI 0.39-0.64) in the T-DM1 arm, compared to the trastuzumab arm (9). The CREATE-X trial included 910 patients with early HER2-negative BC who had non-pCR after NAC reported that adding capecitabine for 6-8 cycles significantly improved the 5-year DFS (HR 0.70, 95%CI 0.53-0.92) and 5-year OS (HR 0.59, 95%CI 0.39-0.90) (7). This benefit was larger in the TNBC subgroup patients (n=286) with 5-year DFS (HR 0.58, 95% CI 0.39-0.87) and 5-year OS (HR 0.52, 95% CI 0.30-0.90) (7). Given these results, the adapted strategy of modifying AC based on the pCR status after NAC has become more widely used in recent years (18). In the present study, trastuzumab, being the only anti-HER2 target agent used, was administered to only a few HER2+ patients. As stated previously, how the AC was discontinued

or changed after NAC and surgery could not be summarized for any possible analysis in the study. The 'NAC only' patients had significantly less cycles of chemotherapy compared with the 'NAC+AC' patients. Since the chemotherapy cycle number was not normally distributed, the three levels were used one covariate in subsequent analysis.

There are a limited number of published studies that explore the relationship of NAC and AC with DFS and OS (6,13,14,31). In 2008, one combined analysis of two RCTs [National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, B-27] reported that the NAC and AC approaches did not have different tumor recurrence rates and OS in BC patients (13). However, a 2005 meta-analysis of 9 RCTs (n=3,946) reported that compared with the AC, the NAC approach was associated with a higher LR [relative risk (RR) 1.22, P=0.015] and had similar rates of any recurrence and

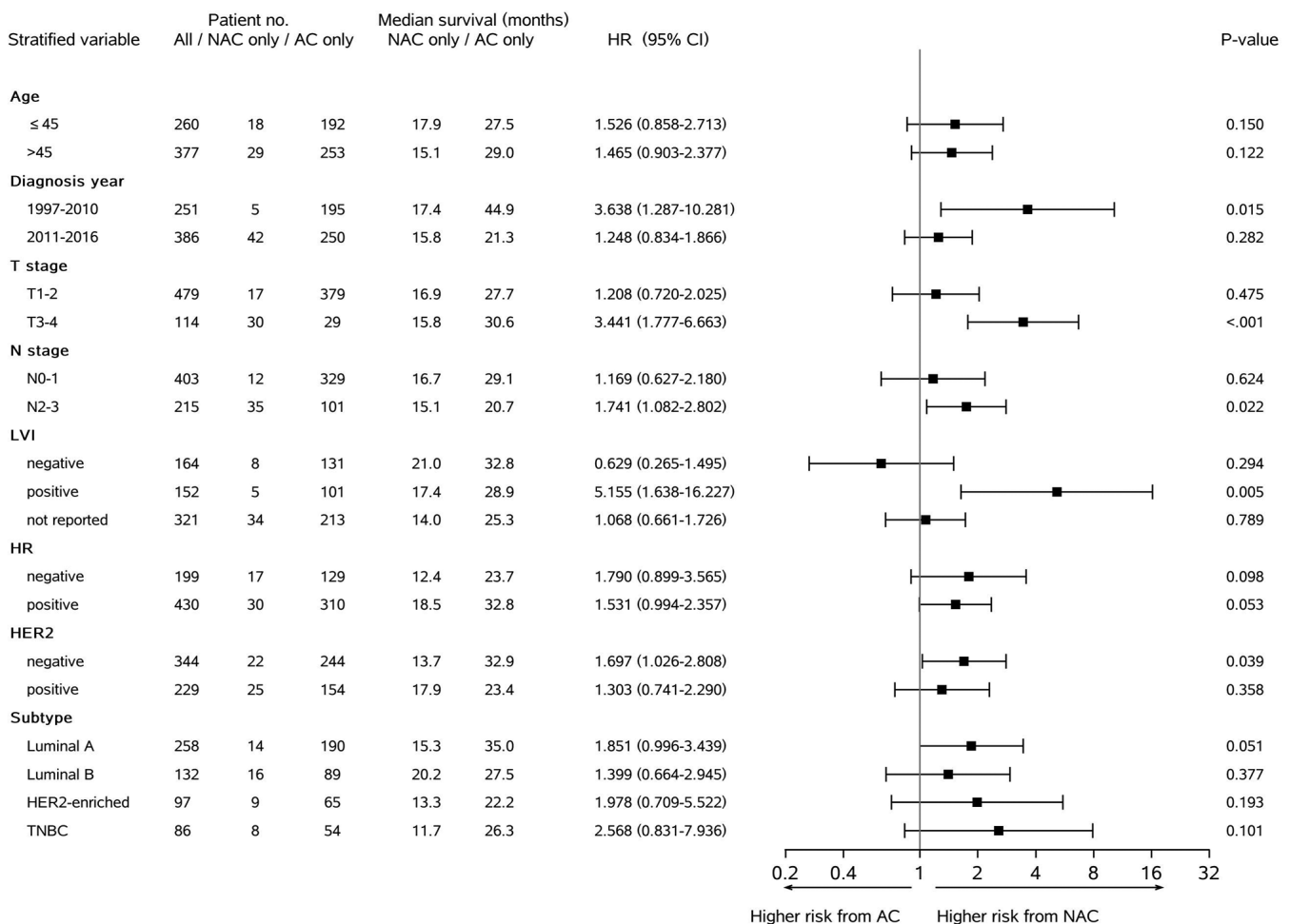


Figure 2. Stratified multivariate Cox model analysis of disease-free survival of chemotherapy modes with the 'AC only' mode set as the reference. NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

BC-related mortality (14). An Early Breast Cancer Trialists Collaborative Group meta-analysis which compared NAC and AC (10 RCTs, N=4,756, 9-year median follow-up) reported that NAC was significantly associated with a higher BCS rate (65 vs. 49%) and significantly higher LR rate (LRR; +5.5%; RR 1.37, 95% CI 1.17-1.61,  $P=0.0001$ ) (6). To interpret these results with caution, certain researchers believed that it was the NAC-related more conservative surgery which contributed to a higher LRR (6,11). Recently, a retrospective analysis of 19,151 stage II-III TNBC patients from the National Cancer Database reported that the NAC patients had a lower OS compared with the AC patients (73.6 vs. 76.8%,  $P<0.0001$ ) (31). Furthermore, the subgroup of patients with pCR after the NAC were associated with a significantly improved 5-year OS compared with the non-PCR patients (86.2 vs. 62.3%,  $P<0.0001$ ) (31). The authors concluded that NAC may be inferior to AC in TNBC for tumor control; however, the role of patient selection bias could not be completely ruled out (31). In the present retrospective study, a poorer PFS was associated with the 'NAC only' vs. 'AC only' groups in TNBC patients as well.

The potential role of many factors in causation meant it was challenging to explain the study findings. Numerous patient, disease and physician factors can influence the choice and continuation of NAC or AC in patients with BC. Through multivariate

analyses that adjust these factors, the present study assessed the independent risk profiles of chemotherapy modes on DFS. This analysis strategy along with stratifying the population in the present study, demonstrated that compared with the traditional 'AC only' approach, the 'NAC only' approach was associated with a higher risk of tumor recurrence. Based on the results of the present study it was hypothesized that an independent link of 'NAC only' with a higher risk of recurrence in the real-world practice exists. It was hypothesized that this could be due to the possible unintentional use of 'inadequate' chemotherapy cycles in NAC patients and unrecognized difference of drug mechanism of NAC vs. AC regimen in medical and surgical practice. Furthermore, the present study indicated that the aforementioned differences could be more evident in subgroup patients with BC characterized as T2-3, N2-3, LVI+ or HER2-negative.

The strengths of the present study included the large sample size of real-world data about patients with BC with first tumor recurrence, a large number of covariates for model adjustment and the use of stratified analyses. The limitations of the present study included being unable to infer a cause-effect relationship from this retrospective observational study, the possible existence of unadjusted confounders, the lack of pCR and drug side effect data, and the lack of recorded reasons to add or discontinue the NAC or AC for additional analysis. Furthermore, the



different BC populations and treatment administrations (e.g., BCS procedure, inclusion of platinum in TNBC NAC, trastuzumab availability, and pCR as guidance) mean it would be challenging to simply compare and apply the findings of the present study to patients with BC outside of China.

While the results of the present study require further evaluation, oncologists should be aware that patients with BC with a high risk of recurrence could benefit from the use of full cycles of NAC or adding AC after 'inadequate' NAC for improved tumor control.

NAC alone is potentially associated with a higher risk of tumor recurrence in high-risk BC subgroup patients based on real-world data from clinical practice. Patient selection of chemotherapy mode was involved in practice but could not fully explain this finding.

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### Availability of data and material

The anonymised datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

ZSL designed and supervised this study. ZSL, YL and YJL were responsible for the data analysis and manuscript writing. YGS, YRZ, XHJ, HH and KYD participated in the data collection, data quality control, data interpretation, and analysis discussion. YJL and JZ contributed to the interpretation of data and study results as well as providing critical discussion and revision of the manuscript. ZSL and YL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of The Fourth Hospital of Hebei Medical University (approval no. 2017-288). All patients provided written informed consent before study enrollment.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declared that they have no competing interests.

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