

## RESEARCH ARTICLE

# Profile, treatment patterns, and influencing factors of anthracycline use in breast cancer patients in China: A nation-wide multicenter study

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### Abstract

**Background:** Anthracycline-based chemotherapy (ABC) is one of the standard therapies against breast cancer. However, few guidelines are currently available to optimize the use of ABC. Therefore, the present analysis aimed at determining the profile and treatment patterns of ABC and the association of clinicopathological characteristics with ABC selection.

**Methods:** We retrospectively analyzed the data of a nation-wide multicenter epidemiological study, which collected the medical records of breast cancer patients receiving chemotherapy in different settings from seven geographic regions in China (NCT03047889).

**Results:** In total, 3393 patients were included, with 2917 treated with ABC. Among them, 553 (89.8%), 2165 (81.7%), and 814 (25.7%) were subjected to ABC as neoadjuvant, adjuvant, and advanced chemotherapy, respectively. The most frequently used regimens were anthracycline-taxane-based combinations for neo- and adjuvant chemotherapy, along with taxanes and oral fluorouracils for the palliative stages. In the overall cohort, patients aged < 40 or 40-65 ( $p < 0.001$ ), in premenopause ( $p < 0.001$ ), without comorbidities ( $p = 0.016$ ), with invasive ductal carcinoma ( $p = 0.001$ ), high lymph node involvement ( $p < 0.001$ ), in the pTNM stage II, III, or IV versus stage I ( $p < 0.001$ ), subjected to mastectomy ( $p < 0.001$ ) or subjected to sentinel lymph node biopsy combined with axillary lymph node dissection ( $p = 0.044$ ), or with a decreased disease-free survival ( $p < 0.001$ ) were more likely to be recommended to ABC.

**Conclusion:** Taken together, ABC remained the mainstay of breast cancer treatment, especially in neo and adjuvant therapy. ABC was mainly used as a combination therapy, and the correlation between influencing factors and ABC choice varied during different settings, indicating the preference and different perspectives of medication considered by medical oncologists regarding the use ABC in China.

### KEYWORDS

anthracycline, breast cancer, chemotherapy, epidemiological study, nation-wide

## 1 | INTRODUCTION

Breast cancer has become the most common malignancy worldwide (11.7% of the total new cases) surpassing lung cancer, according to the latest estimates on the global cancer burden in 2020 released by the International Agency for Research on Cancer (IARC).<sup>1</sup> Breast cancer is also the most commonly diagnosed cancer among Chinese women, with new cases accounting for approximately 20% of the total new cases of cancer in 2020, ranking fourth in terms of cancer mortality, accounting for approximately

one in ten cancer deaths.<sup>1</sup> Although the noteworthy progress of intensive endocrine therapy and effective targeted therapy, cytotoxic chemotherapy still plays a dominant role in the clinical treatment of breast cancer. In the context of precision medicine, breast cancer has entered the era of classified treatment, and chemotherapeutic strategies need to be individualized.<sup>2</sup> Therefore, the application of chemotherapy in routine clinical practice is still the object of intense research.

As a class of antineoplastics, anthracyclines (such as doxorubicin and epirubicin) substantially improved the

disease-specific survival and are recognized as a standard therapy to combat breast cancer as demonstrated by the results of several clinical trials.<sup>3-7</sup> Currently, regimens that include doxorubicin are listed in The National Comprehensive Cancer Network guidelines as an alternative option in all risk levels and stages of breast cancer except for the lowest risk and early-stage breast cancer.<sup>3</sup> However, the use of other anticancer agents has led to the study of a greater number of combinations of chemotherapeutic drugs in specific patients, and consequently anthracycline-based chemotherapy (ABC) has been in decline for decades.<sup>8,9</sup> Additionally, anthracyclines exert remarkable adverse effects and among them, cardiotoxicity is the main one. Mounting evidence indicates that anthracyclines induce cardiotoxicity through topoisomerase-2 $\beta$  inhibition together with oxidative stress mediated by reactive oxygen species generation.<sup>10</sup> It also increases the risk of treatment-related acute myeloid leukemia and myelodysplastic syndrome.<sup>11</sup> Thus, it is essential to further clarify the factors involved in side effects and identify the population who may be prone to receive ABC.

Therefore, this retrospective clinical analysis enrolled 3387 patients with advanced breast cancer from seven geographic areas who received chemotherapy as neoadjuvant, adjuvant, or advanced palliative treatment, to explore the current overview and therapeutic patterns of anthracycline use, and determine the clinicopathological factors influencing the selection of ABC in different settings in China. The initial recurrence after adjuvant chemotherapy was also discussed, optimizing the clinical ABC use and patient management.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and data collection

A retrospective observational analysis was performed using the data of a hospital-based multicenter epidemiological survey launched in 2015 (clinical trials.gov identifier: NCT03047889). The program collected medical information of advanced breast cancer patients between January 1, 2012, and December 31, 2014, involving 21 hospitals in seven different geographic regions in China, representing distinctive breast cancer burden levels. The National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College was the leading center for coordinating the overall research. Critical data included demographic information, medical history, disease characteristics, clinical management, and follow-up.

The designed case report form was used to obtain all the aforementioned information from the electronic medical record systems by trained oncologists. The eligibility criteria were the following: advanced breast cancer patients who were first treated in each collaborative hospital from January 1, 2012, to December 31, 2014, including patients with recurrent and metastatic breast cancer diagnosed before 2012. The exclusion criterion was represented by the lack of availability of the medical records.

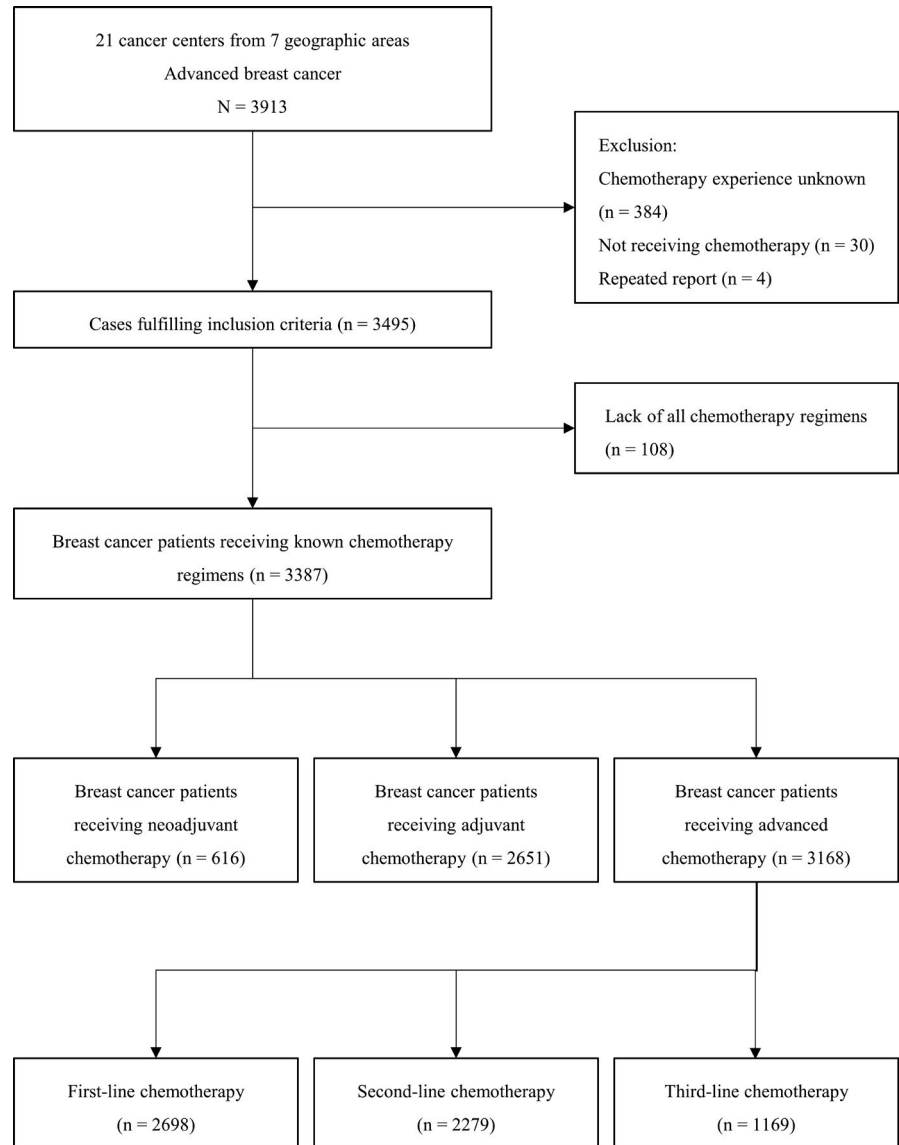
An enrollment scheme in the form of alternating pre-specified months for inpatient admission from year to year was adopted to avoid selection bias. Since aside from the Spring Festival, hospitalizations are similar during other months of the year, each hospital was assigned random numbers of month to make the population more representative and the program more feasible. In each selected month, additional patients from adjacent months were reviewed if fewer inpatients were included than the intended number until the total for the year reached the target quantity.

In this study, the demographic features and clinicopathological characteristics of the patients such as age, menopausal status, body mass index, comorbidity, family history of breast cancer, grade, stage, molecular subtype, and therapeutic approaches were evaluated. The primary endpoint was to investigate the current profile and treatment patterns of anthracycline use in real-world clinical practice in China. The secondary endpoint was to determine factors associated with anthracycline selection.

### 2.2 | Patient selection

Our analysis process is summarized in Figure 1. A total of 3913 patients with advanced breast cancer were originally enrolled in this epidemiological program. Among them, 3495 fulfilled the inclusion criteria while 384 were excluded because it was unknown whether they received chemotherapy, 30 because of not being subjected to chemotherapy, and four because of repeated reports. Among the remaining patients, 3387 receiving available chemotherapy regimens were identified after the exclusion of 108 due to lack of all chemotherapeutic data. Finally, the data of 616 patients treated with neoadjuvant chemotherapy, 2651 patients subjected to adjuvant chemotherapy, and 3168 patients treated with palliative chemotherapy were analyzed, of which 2698, 2279, and 1169 received first-, second-, and third-line chemotherapy, respectively. In our research, when patients received certain agents/regimens, it was specified whether they used specific agents/regimens alone or in combination

**FIGURE 1** Flowchart of the study and the inclusion of patients subjected to chemotherapy at neoadjuvant, adjuvant, and advanced settings



with other therapies. Some patients received chemotherapy at more than one setting.

### 2.3 | Statistical analysis

Categorical variables and continuous variables not normally distributed were presented as frequency plus percentage and median plus interquartile range. Differences in clinicopathological features between two groups were examined by the chi-square test or Fisher exact probability test and Wilcoxon rank-sum test for categorical variables and rank variables, respectively. All statistical tests were two-sided, and a value of  $p < 0.05$  was considered statistically significant. Statistical analysis and graph drawing were performed using SPSS Statistics 23.0 (IBM Corporation) and GraphPad Prism 7.0 (GraphPad Software).

## 3 | RESULTS

### 3.1 | Demographic and clinicopathological characteristics

The entire cohort was composed of 2917 (86.0%) patients who used ABC in different treatment stages as opposed to 476 (14.0%) patients who had never been treated with any anthracyclines. The main clinicopathological characteristics of the enrolled patients are listed in Table 1. In general, patients aged  $<40$  or 40–65 versus  $\geq 65$  years (88.1% for  $<40$  years, 86.2% for 40–65 years, 65.3% for  $\geq 65$  years,  $p < 0.001$ ), in premenopause versus postmenopause (88.4% vs. 83.1%,  $p < 0.001$ ), with lymph node stage 1, 2 or 3 versus stage 0 (80.4% for stage 0, 88.0% for stage 1, 90.2% for stage 2, 90.9% for stage 3,  $p < 0.001$ ), in the pTNM stage II, III, or IV versus stage I (80.9% for stage I, 88.4% for stage II, 91.0% for stage III, 84.3% for stage IV,

TABLE 1 Overall clinicopathological characteristics and treatment regimens of the enrolled patients

| Characteristics                 | All subjects, No. | Anthracycline-based chemotherapy <sup>a</sup> , No. (%) | Anthracycline-free chemotherapy <sup>b</sup> , No. (%) | p-value          |
|---------------------------------|-------------------|---|--|------------------|
| Patients ( <i>n</i> )           | 3393              | 2917 (86.0)   | 476 (14.0)   |                  |
| Age at diagnosis (years)        |                   |   |  | <b>&lt;0.001</b> |
| <40                             | 939               | 827 (88.1)  | 112 (11.9)   |                  |
| 40–65                           | 2336              | 2013 (86.2)   | 323 (13.8)   |                  |
| ≥65                             | 118               | 77 (65.3)   | 41 (34.7)  |                  |
| Menopausal status               |                   |   |  | <b>&lt;0.001</b> |
| Premenopausal                   | 1566              | 1384 (88.4)   | 182 (11.6)   |                  |
| Postmenopausal                  | 1582              | 1315 (83.1)   | 267 (16.9)   |                  |
| Unknown                         | 245               | 218   | 27   |                  |
| BMI                             |                   |   |  | 0.453            |
| Normal (<24)                    | 1643              | 1408 (85.7)   | 235 (14.3)   |                  |
| Overweight (≥24)                | 1385              | 1200 (86.6)   | 185 (13.4)   |                  |
| Unknown                         | 365               | 309   | 56   |                  |
| Comorbidity                     |                   |   |  | <b>0.016</b>     |
| Yes                             | 639               | 533 (83.4)  | 106 (16.6)   |                  |
| No                              | 2574              | 2241 (87.1)   | 333 (12.9)   |                  |
| Unknown                         | 180               | 143   | 37   |                  |
| Family history of breast cancer |                   |   |  | 0.676            |
| Yes                             | 147               | 128 (87.1)  | 19 (12.9)  |                  |
| No                              | 3059              | 2626 (85.8)   | 433 (14.2)   |                  |
| Unknown                         | 187               | 163   | 24   |                  |
| Tumor grade (IDC)               |                   |   |  | 0.286            |
| I+II                            | 981               | 875 (89.2)  | 106 (10.8)   |                  |
| III                             | 571               | 519 (90.9)  | 52 (9.1)   |                  |
| NA or Unknown                   | 1841              | 1523  | 318  |                  |
| Tumor size stage                |                   |   |  | 0.475            |
| 1                               | 613               | 536 (87.4)  | 77 (12.6)  |                  |
| 2                               | 1291              | 1147 (88.8)   | 144 (11.2)   |                  |
| 3                               | 346               | 307 (88.7)  | 39 (11.3)  |                  |
| 4                               | 13                | 10 (76.9)   | 3 (23.1)   |                  |
| Unknown                         | 1130              | 917   | 213  |                  |
| Lymph node stage                |                   |   |  | <b>&lt;0.001</b> |
| 0                               | 1323              | 1064 (80.4)   | 259 (19.6)   |                  |
| 1                               | 823               | 724 (88.0)  | 99 (12.0)  |                  |
| 2                               | 676               | 610 (90.2)  | 66 (9.8)   |                  |
| 3                               | 571               | 519 (90.9)  | 52 (9.1)   |                  |
| pTNM stage                      |                   |   |  | <b>&lt;0.001</b> |
| I                               | 251               | 203 (80.9)  | 48 (19.1)  |                  |
| II                              | 955               | 844 (88.4)  | 111 (11.6)   |                  |
| III                             | 1056              | 961 (91.0)  | 95 (9.0)   |                  |
| IV                              | 261               | 220 (84.3)  | 41 (15.7)  |                  |
| Unknown                         | 870               | 689   | 181  |                  |

(Continues)

TABLE 1 (Continued)

| Characteristics        | All subjects, No. | Anthracycline-based chemotherapy <sup>a</sup> , No. (%) | Anthracycline-free chemotherapy <sup>b</sup> , No. (%) | <i>p</i> -value  |
|------------------------|-------------------|---|--|------------------|
| Histological subtype   |                   |   |  | <b>0.001</b>     |
| IDC                    | 2539              | 2246 (88.5)   | 293 (11.5)   |                  |
| non-IDC                | 574               | 479 (83.4)  | 95 (16.6)  |                  |
| Unknown                | 280               | 192   | 88   |                  |
| Breast surgery         |                   |   |  | <b>&lt;0.001</b> |
| Mastectomy             | 2745              | 2394 (87.2)   | 351 (12.8)   |                  |
| Lumpectomy             | 268               | 229 (85.4)  | 39 (14.6)  |                  |
| No surgery             | 285               | 217 (76.1)  | 68 (23.9)  |                  |
| Other                  | 62                | 55 (88.7)   | 7 (11.3)   |                  |
| Unknown                | 33                | 22  | 11   |                  |
| Lymph node examination |                   |   |  | <b>0.044</b>     |
| SLNB                   | 41                | 34 (82.9)   | 7 (17.1)   |                  |
| ALND                   | 2282              | 2034 (89.1)   | 248 (10.9)   |                  |
| SLNB+ALND              | 71                | 64 (90.1)   | 7 (9.9)  |                  |
| No surgery             | 128               | 106 (82.8)  | 22 (17.2)  |                  |
| Other                  | 10                | 7 (70.0)  | 3 (30.0)   |                  |
| Unknown                | 861               | 672   | 189  |                  |
| ER status              |                   |   |  | 0.728            |
| Positive               | 1648              | 1442 (87.5)   | 206 (12.5)   |                  |
| Negative               | 1177              | 1035 (87.9)   | 142 (12.1)   |                  |
| Unknown                | 568               | 440   | 128  |                  |
| PR status              |                   |   |  | 0.924            |
| Positive               | 1471              | 1289 (87.6)   | 182 (12.4)   |                  |
| Negative               | 1361              | 1191 (87.5)   | 170 (12.5)   |                  |
| Unknown                | 561               | 437   | 124  |                  |
| HER2 status            |                   |   |  | 0.625            |
| Positive               | 1016              | 892 (87.8)  | 124 (12.2)   |                  |
| Negative               | 1633              | 1444 (88.4)   | 189 (11.6)   |                  |
| Unknown                | 744               | 581   | 163  |                  |
| Ki-67 (%)              |                   |   |  | 0.714            |
| <40                    | 835               | 752 (90.1)  | 83 (9.9)   |                  |
| ≥40                    | 492               | 440 (89.4)  | 52 (10.6)  |                  |
| Unknown                | 2066              | 1725  | 341  |                  |
| DFS (months)           |                   |   |  | <b>&lt;0.001</b> |
| Median (IQR)           |                   | 28.0 (15.0–51.0)  | 38.0 (18.0–76.75)                                      |                  |

Significant *p*-values are indicated in bold.

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; IQR, interquartile range; NA, not applicable; PR, progesterone receptor; pTNM, pathology TNM; SLNB, sentinel lymph node biopsy.

<sup>a</sup>Patients who received anthracyclines in neoadjuvant, adjuvant, or advanced chemotherapy.

<sup>b</sup>Patients who did not receive anthracyclines in neoadjuvant, adjuvant, or advanced chemotherapy.

$p < 0.001$ ), with invasive ductal carcinoma (IDC) versus non-IDC (88.5% for IDC, 83.4% for non-IDC,  $p = 0.001$ ), subjected to mastectomy versus lumpectomy (87.2% vs. 85.4%,  $p < 0.001$ ), or with a decreased disease-free survival

(DFS, 28.0 m, IQR 15.0–51.0,  $p < 0.001$ ) were greatly prone to anthracycline-contained regimens. Furthermore, our results revealed that ABC was more recommended in patients without systemic comorbidities than in those with



comorbidities (87.1% vs. 83.4%,  $p = 0.016$ ), and in those subjected to sentinel lymph node biopsy (SLNB) combined with axillary lymph node dissection (ALND) than in those with other lymph node examination (90.1% for SLNB +ALND,  $p = 0.044$ , Table 1).

### 3.2 | Profile and treatment patterns of anthracycline usage at different chemotherapeutic settings

Among the patients subjected to neoadjuvant chemotherapy, 553 (89.8%) received ABC. Among these (Figure 2A), doxorubicin plus docetaxel (AT)/epirubicin plus docetaxel (ET) was the most used protocol (33.3%), followed by fluorouracil plus doxorubicin and cyclophosphamide (FAC)/fluorouracil plus epirubicin and cyclophosphamide (FEC) (33.1%) and doxorubicin plus cyclophosphamide followed by docetaxel (AC-T)/epirubicin plus cyclophosphamide followed by docetaxel (EC-T)/fluorouracil, epirubicin plus cyclophosphamide followed by docetaxel (FEC-T) (17.9%).

Among the patients subjected to adjuvant treatment, approximately 81.7% received ABC. The protocol consisting of AT/ET/docetaxel plus doxorubicin and cyclophosphamide (TAC)/docetaxel plus epirubicin and cyclophosphamide (TEC) represented the 39.0% of ABC. Furthermore, AC-T/EC-T/FEC-T represented the 16.6% and was ranked as the third most frequently used regimens following doxorubicin plus cyclophosphamide (AC)/epirubicin plus cyclophosphamide (EC)/FAC/FEC, which represented the 36.1% (Figure 2B).

A large proportion of patients (76.9%) in the palliative treatment group received anthracycline-free chemotherapy (AFC) at the first-line setting. As regard the chemotherapeutic agent used (Figure 2C), more than half of the patients (57.7%) were treated with paclitaxel (P)/docetaxel (T), approximately 30.1% were treated with capecitabine (CAP)/S-1, and 27.7% were treated with cisplatin (DDP)/carboplatin (CBP)/nedaplatin (NDP). Anthracyclines, including doxorubicin (A)/epirubicin (E)/pirarubicin (THP), represented the 26.5% among all chemotherapeutic agents, of which over 98% were anthracycline-containing combination, and A/E/THP plus P/T was the most used protocol. A total of 440 (16.3%) received monotherapy, with P/T still the most common option, accounting for nearly half of all monotherapies (45.2%), and anthracyclines constituting only the 3.2% (Figure 2D). During the second-line setting, CAP/S-1 (34.1%), P/T (27.1%), and DDP/CBP/NDP (23.5%) were the top three most frequently used selections, and anthracyclines made up for the 6.0% (Figure 2E). Among these patients,

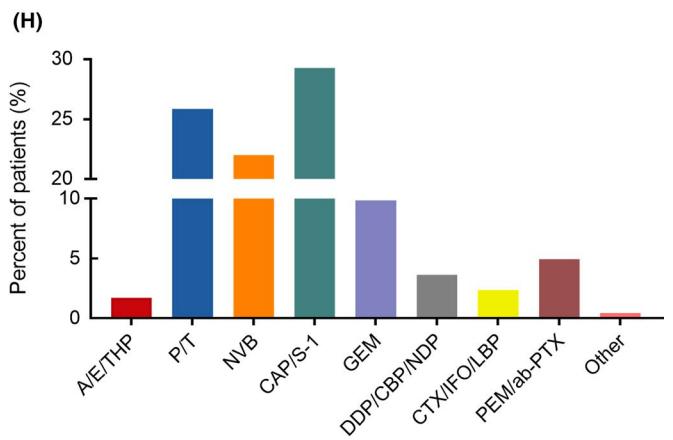
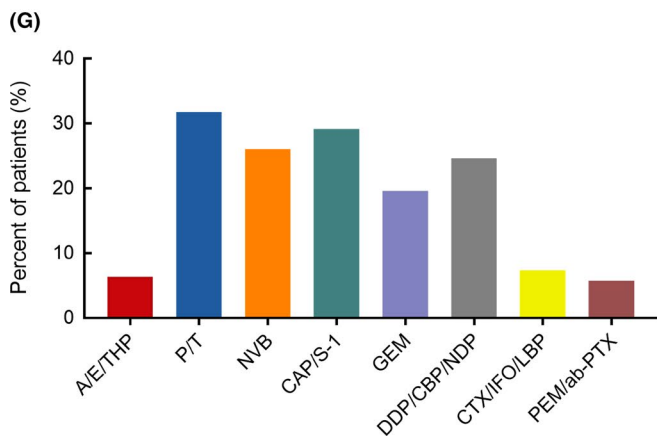
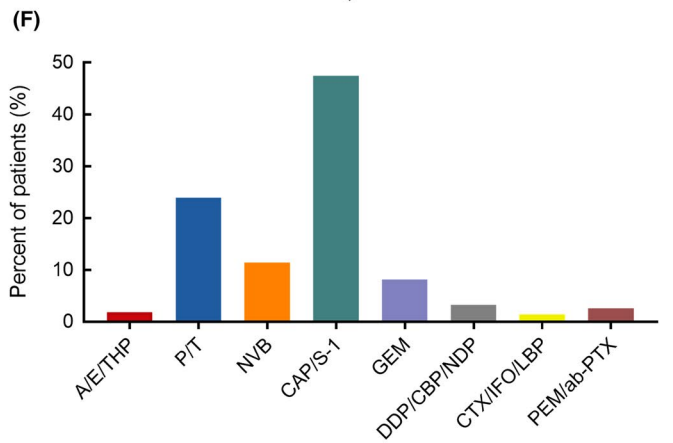
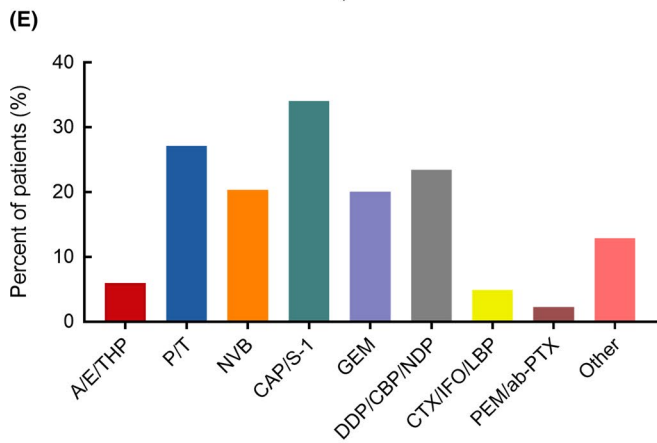
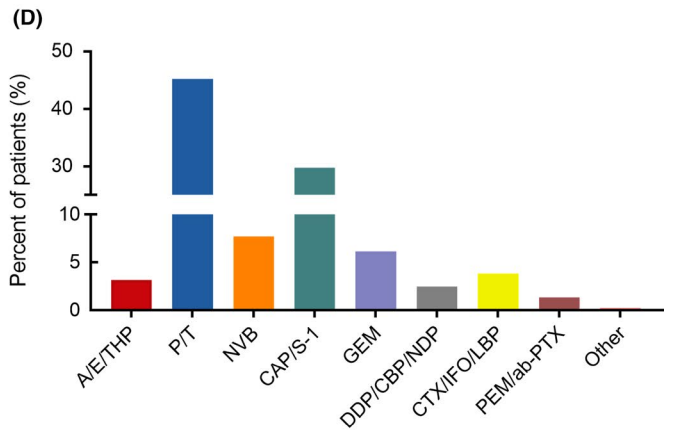
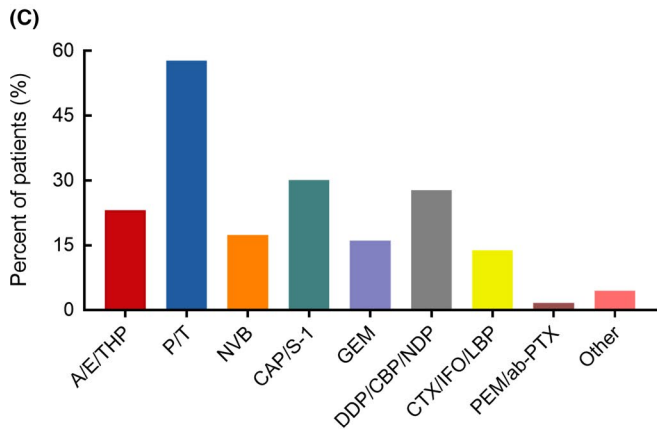
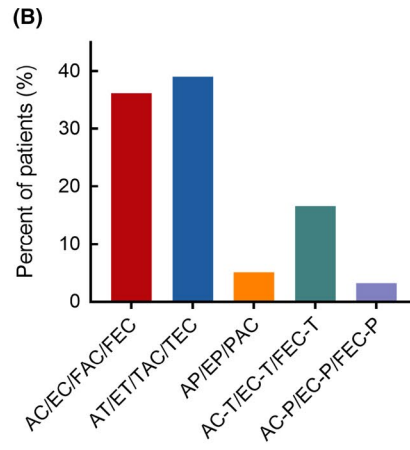
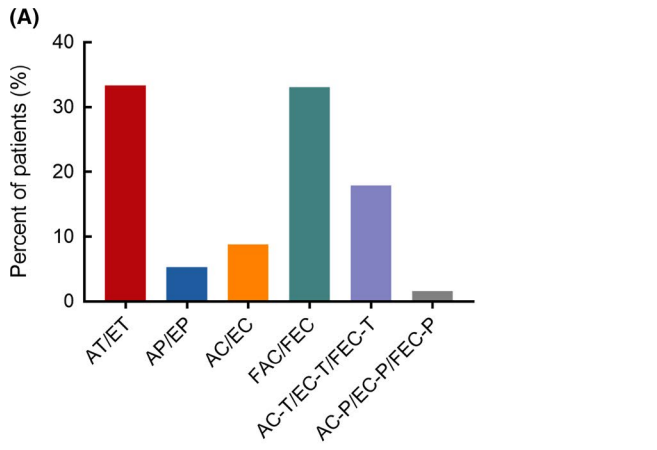
combination therapy was the main form of ABC (91.2%), and A/E/THP plus P/T regimen was the predominant one. A total of 648 (41.2%) were treated with single-agent chemotherapy, with CAP/S-1 being the most common used drug, and anthracyclines representing the 1.9% of the total (Figure 2F). As regard the third-line treatment, anthracyclines accounted for the 6.3% of all chemotherapies, with P/T, CAP/S-1 and vinorelbine as the top three used agents (Figure 2G). A total of 88.9% of patients underwent ABC as the selected combined treatment, mostly A/E/THP plus P/T regimen. Among 468 patients who received monotherapy, CAP/S-1 still ranked first, and anthracyclines constituted the 1.7% (Figure 2H).

### 3.3 | Baseline factors associated with the selection of ABC as neoadjuvant chemotherapy

The data of 616 patients who received neoadjuvant chemotherapy were analyzed and among them, 553 (89.8%) were treated with ABC and 63 (10.2%) were treated with AFC (Table 2). ABC was administered more substantially to patients with a large tumor size (stage 3, 95.7%,  $p = 0.021$ ) or cTNM stage III disease (94.4%,  $p = 0.009$ ). Furthermore, patients with tumor grade III or with IDC nearly received significantly more ABC compared with patients with tumor grade I or II (95.3% vs. 83.5%,  $p = 0.056$ ) and those with non-IDC (91.2% vs. 85.5%,  $p = 0.056$ ), respectively. No association between other baseline characteristics and chemotherapeutic protocols was observed during the neoadjuvant stage.

### 3.4 | Clinicopathological factors associated with the selection of ABC as adjuvant chemotherapy

A total of 2651 patients were subjected to adjuvant chemotherapy. Among these patients, 2165 (81.7%) were treated with ABC, and 486 (18.3%) with AFC (Table 3). ABC was more often used in patients of young age (82.6% for <40 years,  $p < 0.001$ ), those without comorbidity (82.7%,  $p = 0.047$ ), those with low tumor size stage (84.6% for stage 1 + 2,  $p = 0.001$ ), high lymph node involvement (84.9% for stage 2 + 3,  $p = 0.001$ ), IDC (83.2%,  $p < 0.001$ ), or subjected to mastectomy (82.4%,  $p = 0.012$ ) compared with counterparts (Table 3). The remaining factors, such as menopausal status, pTNM stage, and molecular subtypes, had no significant effect on the selection of adjuvant treatment regimen.





**FIGURE 2** Anthracycline usage at different chemotherapeutic settings. (A) Regimens used as neoadjuvant chemotherapy. (B) Regimens used as adjuvant chemotherapy. (C-H) Cytotoxic agents used as advanced first-line chemotherapy (C) and monotherapy (D), second-line chemotherapy (E) and monotherapy (F), and third-line chemotherapy (G) and monotherapy (H). Abbreviations: A, doxorubicin; T, docetaxel; E, epirubicin; P, paclitaxel; C/CTX, cyclophosphamide; F, fluorouracil; THP, pirarubicin; NVB, vinorelbine; CAP, capecitabine; GEM, gemcitabine; DDP, cisplatin; CBP, carboplatin; NDP, nedaplatin; IFO, ifosfamide; LBP, lobaplatin; PEM, pemetrexed; ab-PTX, albumin-bound paclitaxel

### 3.5 | Clinicopathological factors associated with the selection of ABC as advanced first-line chemotherapy

As regard the first-line palliative chemotherapy, 713 (23.1%) patients were treated with ABC, while 2380 (76.9%) with AFC (Table 4). Among patients receiving ABC, anthracycline-containing protocols were more frequently chosen for patients with pTNM stage IV (61.7%,  $p < 0.001$ ), no breast surgery (52.4%,  $p < 0.001$ ), non-IDC (29.6%,  $p < 0.001$ ), estrogen receptor (ER) positive status (24.6%,  $p < 0.001$ ), DFS  $\leq 2$  years (27.4%,  $p < 0.001$ ), or no previous use of anthracyclines (36.9%,  $p < 0.001$ ). Additionally, the statistical results revealed a substantial link between early lymph node involvement (stage 0, 27.0%,  $p = 0.001$ ), no lymph node examination (27.6%,  $p = 0.013$ ), progesterone receptor (PR) positive status (23.5%,  $p = 0.004$ ), no visceral involvement at first recurrence (25.5%,  $p = 0.004$ ), or local treatment (25.0%,  $p = 0.030$ ) and more choice of ABC. No other significant differences were observed on the basis of pre-defined clinicopathological factors.

### 3.6 | Initial recurrence after adjuvant chemotherapy

The initial recurrence of patients receiving adjuvant chemotherapy is summarized in Figure S1. A total of 2651 patients showed tumor recurrence after follow-up, including 468 local recurrences, 1760 distant metastases, and 357 local plus distant recurrence. Among them, a significant correlation was found between patients who experienced distant metastasis and ABC treatment (69.7%,  $p = 0.001$ ). With regard to the visceral involvement, the proportion of patients with or without visceral involvement was similar when they were treated with ABC (49.9% vs. 50.1%). Among the patients who received ABC, the most common site of the first recurrence was the bone (38.5%), followed by the lungs (31.1%) and liver (22.4%).

## 4 | DISCUSSION

In the present study, our findings demonstrated that ABC was at the forefront of breast cancer chemotherapy. In the overall cohort, the vast majority of breast cancer patients received anthracyclines as a chemotherapeutic agent,

especially in neo- and adjuvant therapy, where nearly 90% and 80% of patients were treated with anthracyclines, respectively. The most commonly used treatment options for (neo)adjuvant settings were anthracycline-taxane based regimens, as well as taxanes, oral fluorouracils, and taxanes for palliative first to third-line regimens, respectively.

ABC is usually selected in patients with a high risk of recurrence due to the cumulative dose-dependent cardiotoxicity.<sup>12,13</sup> Epidemiological data involving 1116 patients from the University of California indicated that the addition of anthracyclines to chemotherapeutic protocols declined from 95% in 2000–2005 to 65% during the following five years.<sup>14</sup> A population study in China also revealed that the use of ABC without taxanes was included in 55% of the chemotherapeutic regimens in 2003 compared with 25% in 2008.<sup>15</sup> Although a growing body of research showed a declining use of ABC, it is still widely prescribed. The results of a previous pooled analysis of four observational studies demonstrated that 61.9% of the early-stage breast cancer were treated with ABC together with docetaxel, and our results are consistent with these ones.<sup>16</sup>

According to our results and previous studies, more patients with breast cancer in China received ABC than patients in western countries.<sup>13,17</sup> Moreover, with the increase of the treatment line, the proportion of patients receiving monotherapy increased, along with the use of oral chemotherapeutic agents such as CAP/S-1. Anthracyclines showed the same trend, but the combination regimen was still dominant. A potential explanation might be that anthracyclines were covered by medical insurance in China, and a limited supply of novel therapeutic regimens was available at that time. In addition, Chinese patients pay more attention to the efficacy of the therapy and have a higher tolerance for the adverse reactions caused by the treatment compared with breast cancer patients in western countries, promoting the application of cytotoxic drugs and combination therapy in China. This feature in Chinese breast cancer patients was also highlighted in other studies concerning treatment approaches.<sup>18</sup>

As suggested by our study, the selection of ABC was markedly associated with several clinicopathological factors. The overall body of evidence showed that patients who were young, in a premenopausal stage, without comorbidity, and with a severe disease (IDC, lymph node involvement, high pTNM stage, subjected to mastectomy or SLNB+ALND, and shorter DFS) represented

TABLE 2 Analysis of the baseline factors associated with the selection of the neoadjuvant chemotherapy regimen

| Factors                         | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | P-value      |
|---------------------------------|-------------------|---|--|--------------|
| Patients ( <i>n</i> )           | 616               | 553 (89.8)                                | 63 (10.2)                                |              |
| Age at diagnosis (years)        |                   |   |  | 0.891        |
| <40                             | 163               | 146 (89.6)                                | 17 (10.4)                                |              |
| 40–65                           | 430               | 387 (90.0)                                | 43 (10.0)                                |              |
| ≥65                             | 23                | 20 (87.0)                                 | 3 (13.0)                                 |              |
| Menopausal status               |                   |   |  | 0.215        |
| Premenopausal                   | 307               | 280 (91.2)                                | 27 (8.8)                                 |              |
| Postmenopausal                  | 268               | 236 (88.1)                                | 32 (11.9)                                |              |
| Unknown                         | 41                | 37  | 4  |              |
| BMI                             |                   |   |  | 0.677        |
| Normal (<24)                    | 288               | 256 (88.9)                                | 32 (11.1)                                |              |
| Overweight (≥24)                | 279               | 251 (90.0)                                | 28 (10.0)                                |              |
| Unknown                         | 49                | 46  | 3  |              |
| Comorbidity                     |                   |   |  | 0.695        |
| Yes                             | 102               | 91 (89.2)                                 | 11 (10.8)                                |              |
| No                              | 473               | 428 (90.5)                                | 45 (9.5)                                 |              |
| Unknown                         | 41                | 34  | 7  |              |
| Family history of breast cancer |                   |   |  | >0.900       |
| Yes                             | 23                | 21 (91.3)                                 | 2 (8.7)                                  |              |
| No                              | 567               | 509 (89.8)                                | 58 (10.2)                                |              |
| Unknown                         | 26                | 23  | 3  |              |
| Tumor grade at diagnosis (IDC)  |                   |   |  | 0.056        |
| I+II                            | 85                | 71(83.5)                                  | 14(16.5)                                 |              |
| III                             | 43                | 41(95.3)                                  | 2(4.7)                                   |              |
| NA or Unknown                   | 488               | 441                                       | 47                                       |              |
| Tumor size stage at diagnosis   |                   |   |  | <b>0.021</b> |
| 1                               | 57                | 46 (80.7)                                 | 11 (19.3)                                |              |
| 2                               | 191               | 169 (88.5)                                | 22 (11.5)                                |              |
| 3                               | 93                | 89 (95.7)                                 | 4 (4.3)                                  |              |
| 4                               | 81                | 75 (92.6)                                 | 6 (7.4)                                  |              |
| Unknown                         | 194               | 174                                       | 20                                       |              |
| Lymph node stage at diagnosis   |                   |   |  | 0.690        |
| 0                               | 44                | 37 (84.1)                                 | 7 (15.9)                                 |              |
| 1                               | 72                | 64 (88.9)                                 | 8 (11.1)                                 |              |
| 2                               | 38                | 35 (92.1)                                 | 3 (7.9)                                  |              |
| 3                               | 22                | 20 (90.9)                                 | 2 (9.1)                                  |              |
| Unknown                         | 440               | 397                                       | 43                                       |              |

(Continues)

TABLE 2 (Continued)

| Factors                  | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | P-value      |
|--------------------------|-------------------|---|--|--------------|
| Tumor stage at diagnosis |                   |   |  | <b>0.009</b> |
| I                        | 14                | 11 (78.6)                                 | 3 (21.4)                                 |              |
| II                       | 118               | 110 (93.2)                                | 8 (6.8)                                  |              |
| III                      | 178               | 168 (94.4)                                | 10 (5.6)                                 |              |
| IV                       | 35                | 28 (80.0)                                 | 7 (20.0)                                 |              |
| Unknown                  | 271               | 236                                       | 35                                       |              |
| Histological subtype     |                   |   |  | 0.056        |
| IDC                      | 455               | 415 (91.2)                                | 40 (8.8)                                 |              |
| Non-IDC                  | 131               | 112 (85.5)                                | 19 (14.5)                                |              |
| NA or unknown            | 30                | 26  | 4  |              |
| ER status                |                   |   |  | 0.680        |
| Positive                 | 298               | 267 (89.6)                                | 31 (10.4)                                |              |
| Negative                 | 267               | 242 (90.6)                                | 25 (9.4)                                 |              |
| Unknown                  | 51                | 44  | 7  |              |
| PR status                |                   |   |  | 0.754        |
| Positive                 | 248               | 222 (89.5)                                | 26 (10.5)                                |              |
| Negative                 | 320               | 289 (90.3)                                | 31 (9.7)                                 |              |
| Unknown                  | 48                | 42  | 6  |              |
| HER2 status              |                   |   |  | 0.838        |
| Positive                 | 240               | 218 (90.8)                                | 22 (9.2)                                 |              |
| Negative                 | 289               | 261 (90.3)                                | 28 (9.7)                                 |              |
| Unknown                  | 87                | 74  | 13                                       |              |
| Ki-67 at diagnosis (%)   |                   |   |  | 0.200        |
| <40                      | 122               | 112 (91.8)                                | 10 (8.2)                                 |              |
| ≥40                      | 104               | 90 (86.5)                                 | 14 (13.5)                                |              |
| Unknown                  | 390               | 351                                       | 39                                       |              |

Significant *p*-values are indicated in bold.

Abbreviations: BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; NA, not applicable; PR, progesterone receptor.

the categories of patients more likely treated with ABC. When the neoadjuvant regimen was used, a significant association was found between patients treated with anthracyclines and high malignancy (such as large tumor size, cTNM stage III disease, IDC, or grade III tumor), which was similar to the association observed in the entire cohorts. However, in the adjuvant setting, the patients treated with ABC were more often young, with no comorbidity, with a small tumor size together with high lymph node stages, and subjected to mastectomy. Anthracyclines are cytotoxic antineoplastic drugs with a potent activity against breast carcinoma and are one of the preferred agents selected for breast cancer therapy at all stages. In the (neo-) adjuvant settings, ABC is more

likely to be selected for patients with higher TNM stages or pathological grades of early breast cancer. Moreover, anthracyclines require patients to tolerate the adverse reactions of medications, and young patients with better organ function may have more chance to receive ABC. When considering ABC as the advanced frontline therapy, more potential factors seem to be involved. Among patients using ABC, some might be newly diagnosed with advanced breast cancer; some might have favorable pathological stages or subtypes after radical surgery, and anthracyclines were chosen to combat the recurrence or metastasis rather than as adjuvant therapy. In addition, the previous absence of ABC increased the chance in choosing ABC during the palliative setting.

TABLE 3 Analysis of the clinicopathological factors associated with the selection of the adjuvant chemotherapy regimen

| Factors                         | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | p-value          |
|---------------------------------|-------------------|---|--|------------------|
| Patients (n)                    | 2651              | 2165 (81.7)                               | 486 (18.3)                               |                  |
| Age at diagnosis (years)        |                   |   |  | <b>&lt;0.001</b> |
| <40                             | 777               | 642 (82.6)                                | 135 (17.4)                               |                  |
| 40–65                           | 1804              | 1482 (82.2)                               | 322 (17.8)                               |                  |
| ≥65                             | 70                | 41 (58.6)                                 | 29 (41.4)                                |                  |
| Menopausal status               |                   |   |  | 0.094            |
| Premenopausal                   | 1240              | 1028 (82.9)                               | 212 (17.1)                               |                  |
| Postmenopausal                  | 1207              | 969 (80.3)                                | 238 (19.7)                               |                  |
| Unknown                         | 204               | 168                                       | 36                                       |                  |
| BMI                             |                   |   |  | 0.254            |
| Normal (<24)                    | 1262              | 1043 (82.6)                               | 219 (17.4)                               |                  |
| Overweight (≥24)                | 1090              | 881 (80.8)                                | 209 (19.2)                               |                  |
| Unknown                         | 299               | 241                                       | 58                                       |                  |
| Comorbidity                     |                   |   |  | <b>0.047</b>     |
| Yes                             | 481               | 379 (78.8)                                | 102 (21.2)                               |                  |
| No                              | 2032              | 1680 (82.7)                               | 352 (17.3)                               |                  |
| Unknown                         | 138               | 106                                       | 32                                       |                  |
| Family history of breast cancer |                   |   |  | 0.162            |
| Yes                             | 120               | 104 (86.7)                                | 16 (13.3)                                |                  |
| No                              | 2384              | 1946 (81.6)                               | 438 (18.4)                               |                  |
| Unknown                         | 147               | 115                                       | 32                                       |                  |
| Tumor grade (IDC)               |                   |   |  | 0.581            |
| I+II                            | 862               | 732 (84.9)                                | 130 (15.1)                               |                  |
| III                             | 481               | 403 (83.8)                                | 78 (16.2)                                |                  |
| NA or Unknown                   | 1308              | 1030                                      | 278                                      |                  |
| Tumor size stage                |                   |   |  | <b>0.001</b>     |
| 1+2                             | 1622              | 1373 (84.6)                               | 249 (15.4)                               |                  |
| 3+4                             | 267               | 204 (76.4)                                | 63 (23.6)                                |                  |
| Unknown                         | 762               | 588                                       | 174                                      |                  |
| Lymph node stage                |                   |   |  | <b>0.001</b>     |
| 0+1                             | 1623              | 1292 (79.6)                               | 331 (20.4)                               |                  |
| 2+3                             | 1028              | 873 (84.9)                                | 155 (15.1)                               |                  |
| pTNM stage                      |                   |   |  | 0.265            |
| I                               | 210               | 165 (78.6)                                | 45 (21.4)                                |                  |
| II                              | 833               | 697 (83.7)                                | 136 (16.3)                               |                  |
| III                             | 921               | 775 (84.1)                                | 146 (15.9)                               |                  |
| IV                              | 81                | 68 (84.0)                                 | 13 (16.0)                                |                  |
| Unknown                         | 606               | 460                                       | 146                                      |                  |
| Breast surgery                  |                   |   |  | <b>0.012</b>     |
| Lumpectomy                      | 211               | 159 (75.4)                                | 52 (24.6)                                |                  |

(Continues)

TABLE 3 (Continued)

| Factors                | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | <i>p</i> -value  |
|------------------------|-------------------|---|--|------------------|
| Mastectomy             | 2295              | 1890 (82.4)                               | 405 (17.6)                               |                  |
| Other/<br>Unknown      | 145               | 116                                       | 29                                       |                  |
| Lymph node examination |                   |   |  | <b>0.677</b>     |
| SLNB                   | 31                | 24 (77.4)                                 | 7 (22.6)                                 |                  |
| ALND                   | 1928              | 1614 (83.7)                               | 314 (16.3)                               |                  |
| SLNB+ALND              | 60                | 53 (88.3)                                 | 7 (11.7)                                 |                  |
| No surgery             | 90                | 76 (84.4)                                 | 14 (15.6)                                |                  |
| Other                  | 8                 | 6 (75.0)                                  | 2 (25.0)                                 |                  |
| Unknown                | 534               | 392                                       | 142                                      |                  |
| Histological subtype   |                   |   |  | <b>&lt;0.001</b> |
| IDC                    | 2149              | 1789 (83.2)                               | 360 (16.8)                               |                  |
| non-IDC                | 397               | 300 (75.6)                                | 97 (24.4)                                |                  |
| Unknown                | 105               | 76  | 29                                       |                  |
| ER status              |                   |   |  | <b>0.720</b>     |
| Positive               | 1267              | 1057 (83.4)                               | 210 (16.6)                               |                  |
| Negative               | 974               | 807 (82.9)                                | 167 (17.1)                               |                  |
| Unknown                | 410               | 301                                       | 109                                      |                  |
| PR status              |                   |   |  | <b>0.326</b>     |
| Positive               | 1153              | 968 (84.0)                                | 185 (16.0)                               |                  |
| Negative               | 1097              | 904 (82.4)                                | 193 (17.6)                               |                  |
| Unknown                | 401               | 293                                       | 108                                      |                  |
| HER2 status            |                   |   |  | <b>0.580</b>     |
| Positive               | 810               | 677 (83.6)                                | 133 (16.4)                               |                  |
| Negative               | 1321              | 1116 (84.5)                               | 205 (15.5)                               |                  |
| Unknown                | 520               | 372                                       | 148                                      |                  |
| Ki-67 (%)              |                   |   |  | <b>0.149</b>     |
| <40                    | 707               | 603 (85.3)                                | 104 (14.7)                               |                  |
| ≥40                    | 435               | 357 (82.1)                                | 78 (17.9)                                |                  |
| Unknown                | 1509              | 1205                                      | 304                                      |                  |

Significant *p*-values are indicated in bold.

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; NA, not applicable; PR, progesterone receptor; pTNM, pathology TNM; SLNB, sentinel lymph node biopsy.

Emerging studies emphasized the adverse effects of anthracyclines, and further efforts have been made to prevent and treat them, especially against cardiotoxicity.<sup>19–21</sup> Several drugs and/or therapies are proposed as cardioprotective agents/approaches during the treatment with ABC, such as dexrazoxane,  $\beta$ -blockers, ACE inhibitors, telomerase therapy, and matrix metalloproteinase inhibitors.<sup>22–26</sup> However, it is also critical to determine the factors influencing the selection of ABC. Unfortunately, few studies addressed this question, and more investigations are needed. In a study on hormone receptor-positive

early-stage breast cancer, ABC was administered more often to young patients (40% of the patients <65 years), to the ones with stage III disease (69%) or higher 21-gene recurrence scores, and positive lymph nodes encouraged the selection of ABC in the absence of high recurrence scores.<sup>9</sup> As regard the clinicopathological characteristics, the results of this study were highly compatible with that of our analysis. Additionally, our analysis revealed that ABC administration was correlated with distant metastasis, which might be due to its use in patients with severe diseases, together with the resistance to anthracyclines.<sup>27</sup>

TABLE 4 Analysis of the clinicopathological factors associated with the selection of the advanced first-line chemotherapy regimen

| Factors                         | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | p-value          |
|---------------------------------|-------------------|---|--|------------------|
| Patients ( <i>n</i> )           | 3093              | 713 (23.1)                                | 2380 (76.9)                              |                  |
| Age at diagnosis (years)        |                   |   |  | 0.131            |
| <40                             | 874               | 183 (20.9)                                | 691 (79.1)                               |                  |
| 40–65                           | 2119              | 502 (23.7)                                | 1617 (76.3)                              |                  |
| ≥65                             | 100               | 28 (28.0)                                 | 72 (72.0)                                |                  |
| Menopausal status               |                   |   |  | 0.774            |
| Premenopausal                   | 1451              | 333 (22.9)                                | 1118 (77.1)                              |                  |
| Postmenopausal                  | 1423              | 333 (23.4)                                | 1090 (76.6)                              |                  |
| Unknown                         | 219               | 47  | 172                                      |                  |
| BMI                             |                   |   |  | 0.611            |
| Normal (<24)                    | 1493              | 355 (23.8)                                | 1138 (76.2)                              |                  |
| Overweight (≥24)                | 1272              | 292 (23.0)                                | 980 (77.0)                               |                  |
| Unknown                         | 328               | 66  | 262                                      |                  |
| Comorbidity                     |                   |   |  | 0.672            |
| Yes                             | 587               | 140 (23.9)                                | 447 (76.1)                               |                  |
| No                              | 2354              | 542 (23.0)                                | 1812 (77.0)                              |                  |
| Unknown                         | 152               | 31  | 121                                      |                  |
| Family history of breast cancer |                   |   |  | 0.704            |
| Yes                             | 140               | 30 (21.4)                                 | 110 (78.6)                               |                  |
| No                              | 2784              | 635 (22.8)                                | 2149 (77.2)                              |                  |
| Unknown                         | 169               | 48  | 121                                      |                  |
| Tumor grade (IDC)               |                   |   |  | 0.284            |
| I+II                            | 893               | 139 (15.6)                                | 754 (84.4)                               |                  |
| III                             | 524               | 93 (17.7)                                 | 431 (82.3)                               |                  |
| NA or Unknown                   | 1676              | 481                                       | 1195                                     |                  |
| Tumor size stage                |                   |   |  | 0.101            |
| 1+2                             | 1729              | 310 (17.9)                                | 1419 (82.1)                              |                  |
| 3+4                             | 326               | 71 (21.8)                                 | 255 (78.2)                               |                  |
| Unknown                         | 1038              | 332                                       | 706                                      |                  |
| Lymph node stage                |                   |   |  | <b>0.001</b>     |
| 0                               | 1209              | 326 (27.0)                                | 883 (73.0)                               |                  |
| 1                               | 752               | 150 (19.9)                                | 602 (80.1)                               |                  |
| 2                               | 624               | 133 (21.3)                                | 491 (78.7)                               |                  |
| 3                               | 508               | 104 (20.5)                                | 404 (79.5)                               |                  |
| pTNM stage                      |                   |   |  | <b>&lt;0.001</b> |
| I                               | 231               | 34 (14.7)                                 | 197 (85.3)                               |                  |
| II                              | 865               | 146 (16.9)                                | 719 (83.1)                               |                  |
| III                             | 962               | 150 (15.6)                                | 812 (84.4)                               |                  |
| IV                              | 235               | 145 (61.7)                                | 90 (38.3)                                |                  |

(Continues)



TABLE 4 (Continued)

| Factors                | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | p-value          |
|------------------------|-------------------|---|--|------------------|
| Unknown                | 800               | 238                                       | 562                                      |                  |
| Breast surgery         |                   |   |  | <b>&lt;0.001</b> |
| Mastectomy             | 2492              | 490 (19.7)                                | 2002 (80.3)                              |                  |
| Lumpectomy             | 247               | 59 (23.9)                                 | 188 (76.1)                               |                  |
| No surgery             | 267               | 140 (52.4)                                | 127 (47.6)                               |                  |
| Other                  | 58                | 16 (27.6)                                 | 42 (72.4)                                |                  |
| Unknown                | 29                | 8   | 21                                       |                  |
| Lymph node examination |                   |   |  | <b>0.013</b>     |
| SLNB                   | 38                | 8 (21.1)                                  | 30 (78.9)                                |                  |
| ALND                   | 2085              | 433 (20.8)                                | 1652 (79.2)                              |                  |
| SLNB+ALND              | 60                | 3 (5.0)                                   | 57 (95.0)                                |                  |
| No surgery             | 116               | 32 (27.6)                                 | 84 (72.4)                                |                  |
| Other                  | 8                 | 1 (12.5)                                  | 7 (87.5)                                 |                  |
| Unknown                | 786               | 236                                       | 550                                      |                  |
| Histological subtype   |                   |   |  | <b>&lt;0.001</b> |
| IDC                    | 2320              | 444 (19.1)                                | 1876 (80.9)                              |                  |
| Non-IDC                | 517               | 153 (29.6)                                | 364 (70.4)                               |                  |
| Unknown                | 256               | 116                                       | 140                                      |                  |
| ER status              |                   |   |  | <b>&lt;0.001</b> |
| Positive               | 1494              | 367 (24.6)                                | 1127 (75.4)                              |                  |
| Negative               | 1095              | 191 (17.4)                                | 904 (82.6)                               |                  |
| Unknown                | 504               | 155                                       | 349                                      |                  |
| PR status              |                   |   |  | <b>0.004</b>     |
| Positive               | 1341              | 315 (23.5)                                | 1026 (76.5)                              |                  |
| Negative               | 1253              | 236 (18.8)                                | 1017 (81.2)                              |                  |
| Unknown                | 499               | 162                                       | 337                                      |                  |
| HER2 status            |                   |   |  | 0.755            |
| Positive               | 919               | 187 (20.3)                                | 732 (79.7)                               |                  |
| Negative               | 1504              | 314 (20.9)                                | 1190 (79.1)                              |                  |
| Unknown                | 670               | 212                                       | 458                                      |                  |
| Ki-67 (%)              |                   |   |  |                  |
| <40                    | 746               | 129 (17.3)                                | 617 (82.7)                               |                  |
| ≥40                    | 461               | 72 (15.6)                                 | 389 (84.4)                               |                  |
| Unknown                | 1886              | 512                                       | 1374                                     |                  |
| DFS                    |                   |   |  | <b>&lt;0.001</b> |
| ≤2 years               | 1557              | 427 (27.4)                                | 1130 (72.6)                              |                  |
| >2 years               | 1536              | 286 (18.6)                                | 1250 (81.4)                              |                  |
| Metastatic sites       |                   |   |  | 0.527            |
| Distant                | 2021              | 452 (22.4)                                | 1569 (77.6)                              |                  |
| Local                  | 521               | 125 (24.0)                                | 396 (76.0)                               |                  |
| Both                   | 471               | 115 (24.4)                                | 356 (75.6)                               |                  |

(Continues)

TABLE 4 (Continued)

| Factors                                  | All subjects, No. | Anthracycline-based chemotherapy, No. (%) | Anthracycline-free chemotherapy, No. (%) | p-value          |
|--|-------------------|---|--|------------------|
| Unknown                                  | 80                | 21  | 59                                       |                  |
| Visceral involvement at first recurrence |                   |   |  | <b>0.004</b>     |
| Yes                                      | 1558              | 328 (21.1)                                | 1230 (78.9)                              |                  |
| No                                       | 1497              | 381 (25.5)                                | 1116 (74.5)                              |                  |
| Unknown                                  | 38                | 4   | 34                                       |                  |
| Previous use of anthracyclines           |                   |   |  | <b>&lt;0.001</b> |
| Yes                                      | 2135              | 251 (11.8)                                | 1884 (88.2)                              |                  |
| No                                       | 344               | 127 (36.9)                                | 217 (63.1)                               |                  |
| Unknown                                  | 614               | 335                                       | 279                                      |                  |
| Local treatment                          |                   |   |  | <b>0.030</b>     |
| Yes                                      | 1209              | 302 (25.0)                                | 907 (75.0)                               |                  |
| No                                       | 1780              | 384 (21.6)                                | 1396 (78.4)                              |                  |
| Unknown                                  | 104               | 27  | 77                                       |                  |

Significant *p*-values are indicated in bold.

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; NA, not applicable; PR, progesterone receptor; pTNM, pathology TNM; SLNB, sentinel lymph node biopsy.

Several limitations in this work should be mentioned. Above all, its retrospective nature study is associated with limitations, including temporal lag, missing data, a broad spectrum of treatment regimens, and slight differences in the treatment of patients in each hospital, making difficult to control all potential confounders. The retrospective nature also precludes the attribution of a link between clinicopathological features and the selection of anthracyclines, supporting the need of further studies on this topic. Furthermore, our study is underpowered to assess the efficacy of chemotherapy and clinical outcome due to the observational nature and insufficient medical records available. Besides, a slight bias was present in the analysis of neo- and adjuvant chemotherapy, since the participants enrolled in this study were all patients with advanced breast cancer. However, despite the above-mentioned limitations, the present study also possesses strengths, such as a large and representative sample size, reliable data, and rigorous analyses; thus, it would be useful to optimize the clinical use of ABC.

Collectively, ABC was still used as the main component of the chemotherapeutic regimens to combat breast cancer, and it was the most frequently used protocol in the neo- and adjuvant settings. Combination therapy was the predominant mode of ABC administration, although at the palliative stages, with the increase of the number of the treatment lines, the proportion in the use of monotherapy expanded. The correlation between clinicopathological

characteristics and the choice of ABC varied at different settings, suggesting the preference and different perspectives of medication considered by medical oncologists in the use ABC in China. To date, several promising predictors of ABC efficacy or resistance in breast cancer have been proposed and assessed, such as GR, NUP98, FKBP12, and ERCC,<sup>28–31</sup> to guide the selection of the appropriate treatment and maximize the benefit of chemotherapy for patients, avoiding unnecessary adverse events, costs, and risk of progression.

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#### CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

#### ETHICS STATEMENT

This work was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Ref. 15-115/1042). Patient consent for this study was not required as there were no risks anticipated to the enrolled

participants. All data analyzed were in aggregate information and were stripped of any patient identifiers.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in this publication. Further inquiries can be directed to the corresponding authors.

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## REFERENCES

1. Latest global cancer data: Cancer burden rises to 19.3 million new cases and 10.0 million cancer deaths in 2020. <https://www.iarc.who.int/news-events/latest-global-cancer-data-cancer-burden-rises-to-19-3-million-new-cases-and-10-0-million-cancer-deaths-in-2020/>. Accessed April 02, 2021.
2. Mesquita A, Costa JL, Schmitt F. Utility of circulating tumor DNA in different clinical scenarios of breast cancer. *Cancers*. 2020;12:3797.
3. Buzdar AU, Blumenschein GR, Gutterman JU, et al. Postoperative adjuvant chemotherapy with fluorouracil, doxorubicin, cyclophosphamide, and BCG vaccine. A follow-up report. *JAMA*. 1979;242:1509-1513.
4. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet (London, England)*. 2012;379:432-444.
5. Eiermann W, Pienkowski T, Crown J, et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. *J Clin Oncol*. 2011;29:3877-3884.
6. Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: breast international group 02-98 randomized trial. *J Natl Cancer Inst*. 2008;100:121-133.
7. Burnell M, Levine MN, Chapman J-A, et al. Cyclophosphamide, epirubicin, and Fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by Paclitaxel versus Doxorubicin and cyclophosphamide followed by Paclitaxel in node-positive or high-risk node-negative breast cancer. *J Clin Oncol*. 2010;28:77-82.
8. Lobefaro R, Zattarin E, Nichetti F, et al. Antitumor activity and efficacy of shorter versus longer duration of anthracycline-taxane neoadjuvant chemotherapy in stage II-III HER2-negative breast cancer: a 10-year, retrospective analysis. *Ther Adv Med Oncol*. 2020;12:1758835920970081.
9. Henderson J, Adams P, Barber K. Factors determining anthracycline use in hormone receptor positive. Early-stage breast cancer. *Clin Breast Cancer*. 2019;19:e475-e480.
10. Abdel-Qadir H, Bobrowski D, Zhou L, et al. Statin exposure and risk of heart failure after anthracycline- or trastuzumab-based chemotherapy for early breast cancer: a propensity score-matched cohort study. *J Am Heart Assoc*. 2021;10:e018393.
11. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. *J Clin Oncol*. 2014;32:2541-2552.
12. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med*. 2015;13:195.
13. Crozier JA, Swaika A, Moreno-Aspitia A. Adjuvant chemotherapy in breast cancer: to use or not to use, the anthracyclines. *World J Clin Oncol*. 2014;5:529-538.
14. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US oncology research trial 9735. *J Clin Oncol*. 2009;27:1177-1183.
15. Li Q, Yang Z, Fan J, et al. A nation-wide multicenter 10-year (1999-2008) retrospective study of chemotherapy in Chinese breast cancer patients. *Oncotarget*. 2017;8:75864-75873.
16. Xu B, Shao Z, Wang S, et al. Treatment patterns for adjuvant docetaxel-based chemotherapy in early-stage breast cancer in China: a pooled retrospective analysis of four observational studies. *Chinese J Cancer Res = Chung-kuo yen cheng yen chiu*. 2018;30:327-339.
17. Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. *J Clin Oncol*. 2012;30:2232-2239.
18. Wu Y, Han Y, Yu P, et al. Endocrine therapy for hormone receptor-positive advanced breast cancer: a nation-wide multicenter epidemiological study in China. *Front Oncol*. 2020;10:599604.
19. Dent SF, Botros J, Rushton M, et al. Anthracycline-induced cardiotoxicity in patients with early-stage breast cancer: the Canadian Cancer Trials Group (CCTG) MA.21 experience. *Breast cancer Res Treat*. 2020;184:733-741.
20. Chung IY, Lee JW, Moon HG, et al. Effect of standard low-dose anthracycline chemotherapy on late congestive heart failure in breast cancer survivors aged between 50 and 59 at diagnosis: a nationwide study. *Breast (Edinburgh, Scotland)*. 2020;53:125-129.
21. Ruddy KJ, Sangaralingham LR, Van Houten H, et al. Utilization of cardiac surveillance tests in survivors of breast cancer and lymphoma after anthracycline-based chemotherapy. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005984.
22. Cai F, Luis MAF, Lin X, et al. Anthracycline-induced cardiotoxicity in the chemotherapy treatment of breast cancer: preventive strategies and treatment. *Mol Clin Oncol*. 2019;11:15-23.
23. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics. 2019. *CA Cancer J Clin*. 2019;69(5):363-385.
24. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2006;48:2258-2262.

25. Chatterjee S, Hofer T, Costa A, et al. Telomerase therapy attenuates cardiotoxic effects of doxorubicin. *Mol Ther*. 2021;29(4):1395-1410.
26. Chan BYH, Roczkowsky A, Cho WJ, et al. MMP inhibitors attenuate doxorubicin cardiotoxicity by preventing intracellular and extracellular matrix remodelling. *Cardiovasc Res*. 2021;117:188-200.
27. Chen B, Lai J, Dai D, et al. PARPBP is a prognostic marker and confers anthracycline resistance to breast cancer. *Ther Adv Med Oncol*. 2020;12:1758835920974212.
28. Elkashif A, Bingham V, Haddock P, et al. Glucocorticoid receptor expression predicts good outcome in response to taxane-free, anthracycline-based therapy in triple negative breast cancer. *J Oncol*. 2020;2020:3712825.
29. Mullan PB, Bingham V, Haddock P, et al. NUP98 - a novel predictor of response to anthracycline-based chemotherapy in triple negative breast cancer. *BMC Cancer*. 2019;19:236.
30. Xing M, Wang J, Yang Q, et al. FKBP12 is a predictive biomarker for efficacy of anthracycline-based chemotherapy in breast cancer. *Cancer Chemother Pharmacol*. 2019;84:861-872.
31. Abdel-Fatah TMA, Ali R, Sadiq M, et al. ERCC1 is a predictor of anthracycline resistance and taxane sensitivity in early stage or locally advanced breast cancers. *Cancers*. 2019;11.

## SUPPORTING INFORMATION

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

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