

Real-world evidence of neoadjuvant chemotherapy for breast cancer treatment in a Brazilian multicenter cohort: Correlation of pathological complete response with overall survival

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ABSTRACT

Objectives: We aimed to evaluate the pCR rate in patients receiving NAC for the treatment of breast cancer (BC) in a multicenter cohort in Brazil. Additionally, we aimed to use RWD to assess the impact of pCR on OS and DFS. **Methods:** This was a retrospective, multicenter cohort study that included female patients over 18 years of age who were diagnosed with nonmetastatic breast cancer and received NAC. OS and DFS at five years were estimated by the Kaplan–Meier method. Additionally, we conducted a multivariate analysis to identify factors that were significantly associated with pCR and OS.

Results: From 2011 to 2020, 1891 patients were included in the study, and 421 (22.3%) achieved pCR (ypT0 ypN0). Considering the presence of residual DCIS, pCR was achieved in 467 patients (23.5%). The pCR rate varied between the subtypes: HER-2+ ($p = 0.016$) and clinical stage IIIA and IIIB ($p < 0.001$). Among HER-2+ patients, those who received trastuzumab had a significantly higher pCR rate than those who did not receive trastuzumab ($p < 0.0001$). Similarly, patients with TNBC who received treatment with platinum-based regimens also showed higher pCR rates ($p < 0.0001$). OS was grouped according to pCR status, and the OS rate was 88.3% in the pCR group and 58.1% in the non-pCR group ($p < 0.0001$). The five-year DFS was 92.2% in the pCR group and 64.3% in the non-pCR group ($p < 0.0001$).

Conclusion: The pCR rate and its prognostic value varied across BC subtypes. In our study, pCR could be used as a surrogate of favorable clinical outcome, as it was associated with higher OS and DFS rates.

1. Introduction

Breast cancer (BC) is the most common neoplasm in Brazil and worldwide. It is estimated that in 2023, there will be 73,250 new cases of BC in Brazil, with a significant proportion being diagnosed at an

advanced stage [1,2].

The treatment for BC involves neoadjuvant chemotherapy (NAC) aimed at reducing tumor size. Pathological complete response (pCR) serves as a prognostic factor, as various randomized controlled trials (RCTs) and meta-analyses have demonstrated that patients who receive

Abbreviations: pCR, Pathological complete response; NAC, Neoadjuvant chemotherapy; BC, Breast cancer; RWD, Real-world data; OS, Overall survival; DFS, Disease-free survival; DCIS, Ductal carcinoma in situ; TNBC, Triple negative breast cancer; RCTs, Randomized controlled trials.

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NAC and achieve pCR experience improved overall survival (OS) and disease-free survival (DFS), regardless of the breast cancer subtype [3].

RCTs represent the gold standard by which the efficacy of new cancer therapies is evaluated. The effectiveness of these treatments, however, is examined based on rigorous inclusion criteria to minimize errors. Clinical trials typically include, at best, 5% of all cancer patients, and this subset of individuals is not representative of the typical cancer patient population. Patients in clinical trials are generally younger and have fewer or no comorbidities. This lack of representativeness of “real world” patients can limit the generalizability results from RCTs [4].

Despite an increase in the number of randomized clinical trials (RCTs) in Brazil during the past five years, more are needed. In 2022, Brazil accounted for only 2.5% of the studies conducted worldwide [5].

The term real-world data (RWD) is defined as “healthcare information derived from multiple sources outside research settings.” These sources can include electronic health records, billing data, product registries, public databases, and data collected through personal devices and health apps. RWD can provide support for research aimed at understanding and evaluating patterns of treatment utilization and outcomes among heterogeneous patients who may not be eligible for clinical trials [6].

Overall survival (OS) in RWD is an accepted measure among oncologists due to its objectivity and comparability with overall survival data observed in clinical trials [7,8]. Additionally, the American Society of Clinical Oncology (ASCO) has provided guidance on the classification of evidence levels, with RWD typically classified as level III or IV, indicating moderate to low levels of evidence. However, ASCO’s guidance framework recognizes RWD as a valuable tool for clinical oncology research, particularly for addressing unanswered questions or exploring topics that may be considered impractical in clinical trials [9].

A recent analysis of the ASCO Value Framework concluded that estimates of OS and DFS for cancer therapies in the real-world setting were 16% lower than the rates observed in RCTs [10].

The objective of our study was to evaluate the rates of pCR in patients receiving NAC for the treatment of BC in Brazil within a multicenter cohort. Additionally, we aimed to use RWD to assess the impact of pCR on OS and DFS.

2. Materials and methods

2.1. Study design and data source

This was a retrospective, multicenter, longitudinal cohort study. We reviewed medical records of patients who received NAC for the treatment of breast cancer. The study was conducted at two reference services for breast cancer treatment in Brazil, the Perola Byington Hospital and the State Public Servant Hospital, both located in the city of São Paulo.

2.2. Inclusion criteria

The inclusion criteria were as follows: female patients diagnosed with nonmetastatic breast cancer; treated with NAC; above 18 years of age; and underwent surgery after receiving NAC between January 2011 and December 2020.

2.3. Exclusion criteria

The exclusion criteria were as follows: inflammatory breast cancer; bilateral breast cancer; breast cancer during pregnancy and/or postpartum; participation in other randomized controlled trials (RCTs); and incomplete data and/or loss to follow-up.

2.4. Neoadjuvant chemotherapy

The patients received NAC in accordance with institutional protocols

and based on the availability of access to medications. Access to medications for the treatment of HER-2+ patients is not universal in Brazil. The treatment regimens used were 4 cycles of doxorubicin + cyclophosphamide followed by 4 cycles of docetaxel for all patients. HER2-positive patients may have used the same regimen with or without trastuzumab, and TNBC patients may have received regimens containing carboplatin.

2.5. pCR definition

We defined pCR as no residual invasive tumor and ductal carcinoma in situ (DCIS) in the primary tumor bed and ipsilateral axillary lymph nodes (ypT0 ypN0) [11].

2.6. Statistical analysis

The primary outcome of the study was to assess the relationship between clinical data and pCR. Hence, patients were divided into pCR and non-pCR groups. We aimed to determine whether there was an association between clinical data and outcomes by performing Fisher’s or chi-square tests to compare categorical covariates. Student’s *t*-test was used to assess between-group differences in normally distributed data.

OS was defined as the duration between curative surgery and death. DFS was defined as the duration between curative surgery and the first local, regional or systemic relapse or death.

To assess OS and DFS, the Kaplan–Meier method and long rank test were used to assess differences in the pCR and non-pCR subgroups. Both OS and DFS curves considered 5 years as the cutoff for right censoring. For inferential analyses, a *p* value < 0.05 was considered to indicate statistical significance.

Additionally, we conducted a multivariate analysis to identify significant associations between pathologic complete response (pCR) and overall survival (OS). We employed a forest plot to visually represent these associations.

2.7. Ethics

The study was submitted at Platform Brazil and approved by the Research Ethics Committee (Approval number: CAAE 39097520.4.2001.0069). An informed consent form was dismissed (retrospective analyses), and the confidentiality and integrity of the medical records was preserved.

3. Results

3.1. Patient cohort

From January 2011 to December 2020, a total of 2020 patients who received NAC were initially selected for the study. However, 129 patients (6.4%) were excluded based on the exclusion criteria. As a result, 1891 patients were included in the study. Fig. 1 shows detailed information on the excluded patients.

The mean age of the patients included in the study was 50.2 years, with a standard deviation of 10.8 years. The majority of patients were in the premenopausal stage (1073 or 56.7%), had no family history of breast cancer (1442 or 76.2%), had invasive ductal carcinoma (IDC) (1795 or 90.6%), had a histological grade of 2 (928 or 46.8%), and had a Ki67 > 14 (1583 or 83.7%).

Regarding the subtypes, 229 patients (11.5%) had luminal A, 622 (31.4%) had luminal B, 454 (22.9%) were HER-2 positive, and 586 (29.5%) had triple-negative breast cancer (TNBC). The most prevalent tumor size was T3 (739 or 37.3%), with lymph node involvement (N1) in 818 patients (51.3%) and clinical stage IIIA in 754 patients (39.9%).

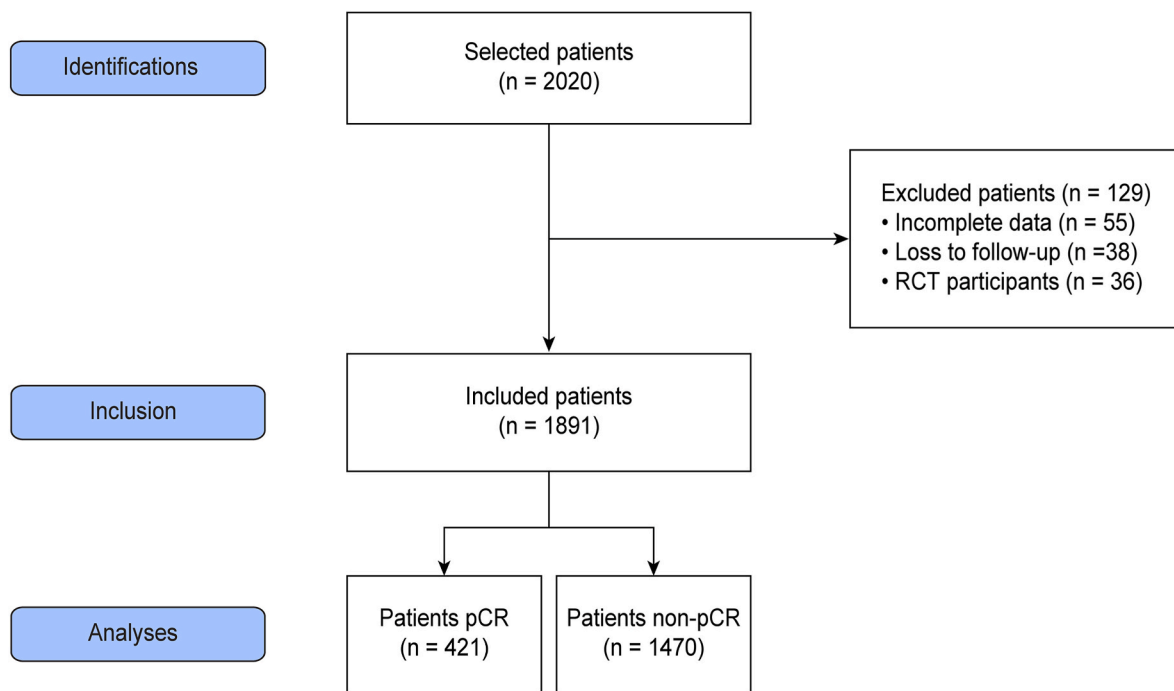


Fig. 1. Flowchart of the multicenter cohort.

3.2. Response to neoadjuvant chemotherapy

In terms of NAC response, we evaluated pathologic response at the time of curative surgery. Of 1891 patients, 421 (22.3%) had pCR (ypT0 ypN0), and considering the presence of residual in situ carcinoma (DCIS), the pCR rate was 467 (23.5%), which was not significant ($p = 0.567$). The pCR rate varied among the subtypes and was more frequent in HER-2+ (28.6%; $p = 0.016$) than in luminal A (17%; $p = 0.420$). pCR was achieved more frequently in clinical stage IIIA and IIIB ($p < 0.001$), but the total number of the other stages was small. These data are shown in Table 1 and Fig. 2.

The tumor size reduction rate (T) was 79.6%, and the lymph node reduction rate (N) was 59.2% in patients who did not achieve pathological complete response (pCR). Among tumors, T4 showed a reduction of 79.6%, T3 showed a reduction of 94.5%, and T2 showed a reduction of 81.4%. All T1 tumors decreased in size. Regarding lymph node involvement, N3 showed an increase of 90%, N2 showed a reduction of 66.9%, N1 showed a reduction of 81.7%, and N0 remained stable.

The effects of key characteristics on pCR are shown in Fig. 4B. Clinical stage IIB, IIIA or IIIB, axillar involvement N2 or the N1, tumor size T3 or T4, and premenopausal patients demonstrated effects on pCR.

The type of NAC regimen was correlated with pCR. Among HER2-positive patients, those who received trastuzumab had a significantly higher rate of pCR than those who did not receive trastuzumab ($p < 0.0001$). Similarly, in patients with triple-negative breast cancer (TNBC), those who underwent treatment with platinum-based regimens also showed higher rates of pCR ($p < 0.0001$). These data are shown in Table 2.

3.3. Survival analysis

We ceased data acquisition in December 2020, and the median follow-up duration was 48 months. During follow-up, 375 events occurred, including 327 cases of distant metastasis and 48 cases of local recurrence.

There were 694 deaths, and the 5-year OS rate was 62.9%. OS was also grouped according to pCR status: the OS rate was 88.3% in the pCR group and 58.1% in the non-pCR group. This difference was significant

($p < 0.0001$). The five-year DFS of pCR was 92.2%, and that of non-pCR was 64.3% ($p < 0.0001$). Fig. 3A shown OS and 3 B DFS.

The effects of key characteristics on OS are shown in Fig. 4B. Clinical stage IIB, IIIA or IIIB (HR, 8.83; 95% CI, 2.58 to 30.15; $p = 0.001$), axillar involvement N2 or the N1, T3 or T4, HER-2+ and premenopausal patients demonstrated effects on OS.

4. Discussion

To our knowledge, this study is the first analysis of the prognostic significance of different pCR definitions on RWD outcomes in a large multicenter cohort of breast cancer patients treated with anthracycline and taxane-based NAC regimens as well as neoadjuvant trastuzumab plus chemotherapy and platinum-based regimens.

The clinical significance of pCR has long been debated. Many researchers have reported improved long-term outcomes in patients who achieved pCR compared to patients with residual tumor at the time of surgery [12–15]. Therefore, achieving pCR has been considered the ultimate goal for a favorable prognosis. Although most NAC trials have shown that pCR is associated with favorable outcomes, we need to know how it works in real-world data.

The concept of surrogacy in clinical research refers to the use of surrogate endpoints as proxies for clinically meaningful outcomes. The idea is that a surrogate endpoint is easier or quicker to measure than the outcome of primary interest and is predictive of that primary outcome. The surrogate endpoint ideally should be an accurate predictor of the 'true' endpoint, which is often long-term patient survival or some other measure of clinical benefit. The pCR serves as a surrogate endpoint at both patient and trial levels. At the patient level, achieving pCR often indicates better long-term outcomes like disease-free survival. At the trial level, higher pCR rates can signify the efficacy of a new treatment across a patient population. However, pCR is not a perfect predictor, and its reliability can vary based on factors like cancer subtype [15].

Our study reported a pCR rate of 22.3%, which is similar to findings from other institutions when not considering subtypes. The reports pCR rates ranging from 13.0% to 26.1% when evaluating all subtypes in RCT data using anthracycline- and taxane-based chemotherapy regimens [11,16,17]. A retrospective study in the public healthcare system in

Table 1
Clinicopathological characteristics of patients.

Characteristics	pCR, n (%) n = 421	non-pCR, n (%) n = 1470	p value
Mean Age years (standard deviation)	49.93 (10.8)	50.5 (10.76)	0.722
Status menopausal			
Premenopausal	230 (54.6)	843 (57.3)	0.321
Menopausal	192 (45.6)	626 (42.6)	0.270
Family history			
Yes	95 (22.5)	354 (24.1)	0.884
No	326 (77.5)	1116 (75.9)	0.519
Histological type			
IDC	402 (95.5)	1393 (94.8)	0.550
IDC with ILC	14 (3.3)	52 (3.5)	0.834
Others	5 (1.2)	25 (1.7)	0.458
Histological grade			
G1	106 (25.2)	359 (24.4)	0.751
G2	199 (47.3)	729 (49.6)	0.400
G3	116 (27.6)	382 (26)	0.520
KI-67			
<14	59 (14)	249 (16.9)	0.152
>14	362 (86)	1221 (83.1)	0.152
Subtypes			
Luminal A	39 (9.3)	190 (12.9)	0.420
Luminal B	133 (31.6)	489 (33.3)	0.519
Luminal HER-2	53 (12.6)	177 (12)	0.762
TNBC	132 (31.4)	454 (30.9)	0.854
HER-2+	64 (15.2)	160 (10.9)	0.016
Tumor size (T)			
T1	13 (3.1)	42 (2.9)	0.804
T2	133 (31.6)	404 (27.5)	0.099
T3	162 (38.5)	577 (39.3)	0.775
T4	113 (26.8)	447 (30.4)	0.158
Lymph node involvement (N)			
N0	112 (26.6)	319 (21.7)	0.034
N1	166 (39.4)	652 (44.3)	0.072
N2	139 (33)	465 (31.6)	0.994
N3	4 (1)	34 (2.4)	0.001
Clinical staging (TNM) AJCC			
I	11 (2.6)	33 (2.2)	0.659
IIA	29 (6.9)	120 (8.2)	0.392
IIB	100 (23.8)	327 (22.2)	0.514
IIIA	164 (38.9)	509 (34.7)	<0.001
IIIB	113 (26.8)	447 (30.4)	<0.001
IIIC	4 (1)	34 (2.3)	0.079

Abbreviations: pCR: pathologic complete response; AJCC: American joint committee on cancer; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; TNBC: triple negative breast cancer.

Chile involving 439 patients reported a pCR rate of 24.1% [18]. In another study with 240 patients in China, the pCR rate was 12.5% [19]. Rezende et al. [20] included 310 women from the public healthcare system in Brazil who received NAC and observed a pCR rate of 13.9%. Additionally, a retrospective study with 1639 patients in Mexico reported a pCR rate of 28.4% [21]. The use of anthracyclines and taxanes as the backbone of NAC shows consistency between RCTs and RWD data.

Cortazar et al. [22] reported that pCR had the weakest correlations with hormone-receptor-positive, low-grade tumors, HER2-positive tumors and hormone-receptor-positive tumors. Similarly, in studies by von Minckwitz et al. [17], pCR showed the strongest correlations with aggressive breast cancer subtypes, while pCR did not have a strong prognostic value among patients with luminal A or luminal B. Our results were consistent with these findings.

Theoretically, ypT0 ypN0 represents the strictest definition of pCR, meaning complete eradication of all tumor cells in both the breast and LNs. Thus, based on the results from this study, we considered ypT0 ypN0 the preferable definition of pCR. These results were consistent with previous studies by JBCS, CTNeoBC, and MD Anderson [22–24] but not with previous studies by GBG and AGO-B, which suggested ypT0 ypN0 as the best definition of pCR [14]. This discrepancy might be caused by the smaller number of patients and events in ypTis ypN0 (n = 46), resulting in a much lower statistical significance to show prognostic

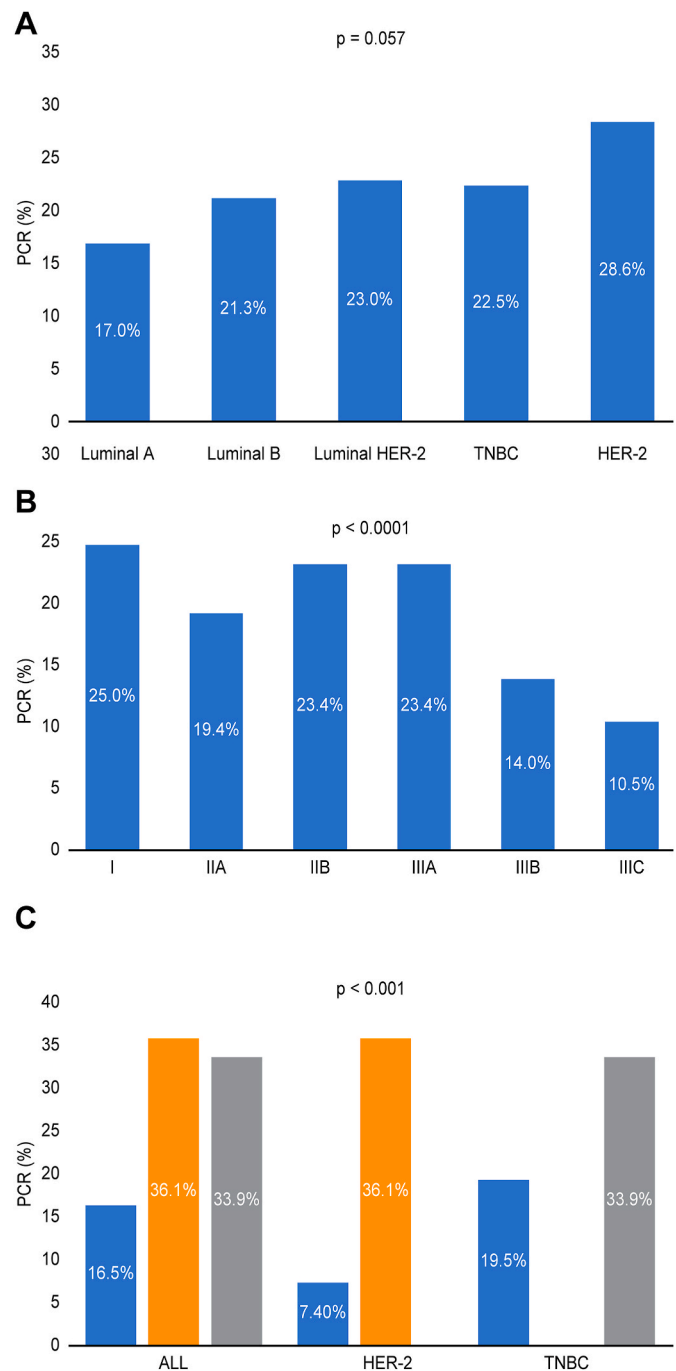


Fig. 2. Pathologic complete response (pCR) according to subtype status (A), clinical stage (B), NAC scheme (AC-T, doxorubicin + cyclophosphamide – taxane; AC-TPlatinum, doxorubicin + cyclophosphamide – taxane + carboplatin; AC-TH, doxorubicin + cyclophosphamide – taxane + Herceptin).

differences in this study.

In the present study, patients with pCR had significantly better DFS and OS than patients without pCR. Our study showed an OS of 89.3% vs. 58.1% with a log-rank p value < 0.0001 at 60 months and a DFS of 92.2% vs. 64.3% with a log-rank p value < 0.001. The NSABP B-18 study, which used an AC regimen, reported a difference in SLD of 75% vs. 58% and OS of 85% vs. 73%. In contrast, the NSABP B-27 study, which used an AC-T regimen, demonstrated an OS of 89% vs. 73% (15, 16). Some retrospective studies on NAC that did not subdivide pCR rates by subtype found that the OS rate varied between 75% and 92% and that the SLD rate varied between 79% and 90.6% (18–21). When comparing

Table 2
NAC schemas and correlation with pCR.

Variables	pCR, n (%)	non-pCR, n (%)	p value
All subtypes	n = 421	n = 1470	
AC-T	215 (51)	1087 (73.9)	<0.001
AC-TPlatinum	101 (24.4)	197 (13.4)	<0.001
AC-TH	105 (24.6)	186 (12.7)	<0.001
HER-2	n = 117	n = 337	
AC-T	12 (10.3)	151 (44.8)	<0.0001
AC-TH	105 (89.7)	186 (55.2)	
TNBC	n = 132	n = 454	
AC-T	31 (23.5)	260 (57.3)	<0.0001
AC-TPlatinum	101 (76.5)	197 (42.7)	

Abbreviations: AC-T: doxorubicin + cyclophosphamide – taxane; AC-TH: doxorubicin + cyclophosphamide – taxane + herceptin; AC-TPlatinum: doxorubicin + cyclophosphamide – taxane + carboplatin.

the OS and SLD rates in the pCR group observed in our study to those reported in previous studies, we found very similar results, once again demonstrating the similarity between RCTs and RWD studies. As previously mentioned, ASCO and FDA consider RWD studies to be important for confirming RCT data [9,10,25].

A meta-analysis by Spring et al. [26] including 52 studies and 27,895 patients (51.1% RCTs, 6.1% nonrandomized clinical trials, and 42.8% retrospective cohort studies) showed that pCR is associated with improved SLD and OS rates. They observed an SLD rate of 88% in patients with pCR and 67% in non-pCR patients and an OS rate of 94% in patients with pCR and 75% in non-pCR patients. These findings are very similar to those in our study [26].

In a comprehensive analysis by Mackelenbergh et al. [27], which aggregated individual patient data from 3710 participants across 11 randomized neoadjuvant trials focused on HER2-positive BC, both clinical tumor size (cT) and clinical nodal status (cN) emerged as significant independent prognostic factors for DFS. However, only cT proved to be a significant independent predictor for OS. Notably, in patients who achieved a pCR, cT, cN, and hormone receptor status were all identified as significant independent predictors for both DFS and OS [27].

Randomized clinical trials and real-world studies can yield discrepant results, often due to differences in design, patient populations, and analysis methods. A recent analysis of the ASCO Value Framework concluded that real-world estimates of OS and SLD for cancer therapies were 16% lower than the efficacy reported in RCTs [10]. Comparing our study to the Cortazar et al. [22] meta-analysis,

which included 12 clinical trials and 11,995 patients and reported a pCR rate of 13% with an OS rate of 91.5% and an SLD rate of 83.1% at 60 months, we observed that our OS rate was 3.2% lower and that our DFS rate was 9.1% higher.

When comparing our study to the Spring et al. [26] meta-analysis including 52 studies and 27,984 patients, which examined the correlation of pCR with SLD and OS, we found an SLD rate of 88% in patients with pCR and 67% in non-pCR patients and an OS rate of 94% in patients with pCR and 75% in non-pCR patients. These findings are very similar to those in our study.

In summary, our study, based on RWD from Brazilian patients receiving NAC for breast cancer treatment, demonstrates that this type of study can consider pCR as a prognostic factor, similar to clinical trials. The strengths of our work lie in the data derived from an unselected cohort in the real world, addressing the lack of real-world data from the public healthcare system in Brazil compared to private patients. This study illustrates the pCR rates as well as the association of pCR with improved OS and SLD rates.

5. Conclusions

In conclusion, the pCR rate and its prognostic value varied across BC subtypes. In our study, pCR could be used as a surrogate of favorable clinical outcome, as it was associated with better OS and DFS rates.

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Data availability

Data for the study were extracted from private databases of participating institutions.

Author contributions

MA designed the study, analyzed the data, wrote the manuscript, AM

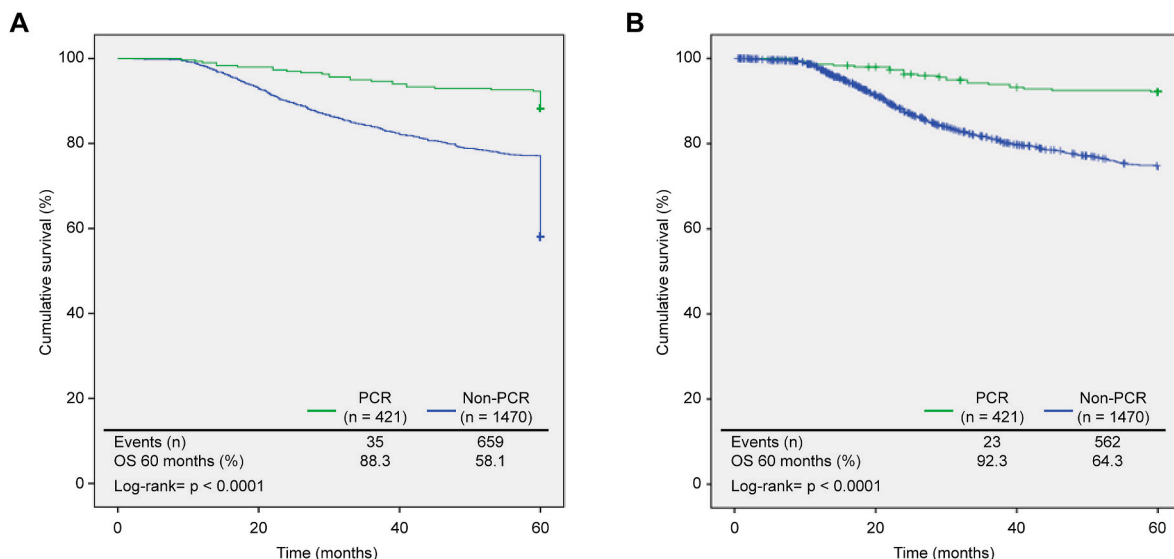


Fig. 3. Overall survival (A) and disease-free survival (B) according to pathologic complete response (pCR) or non-pCR.

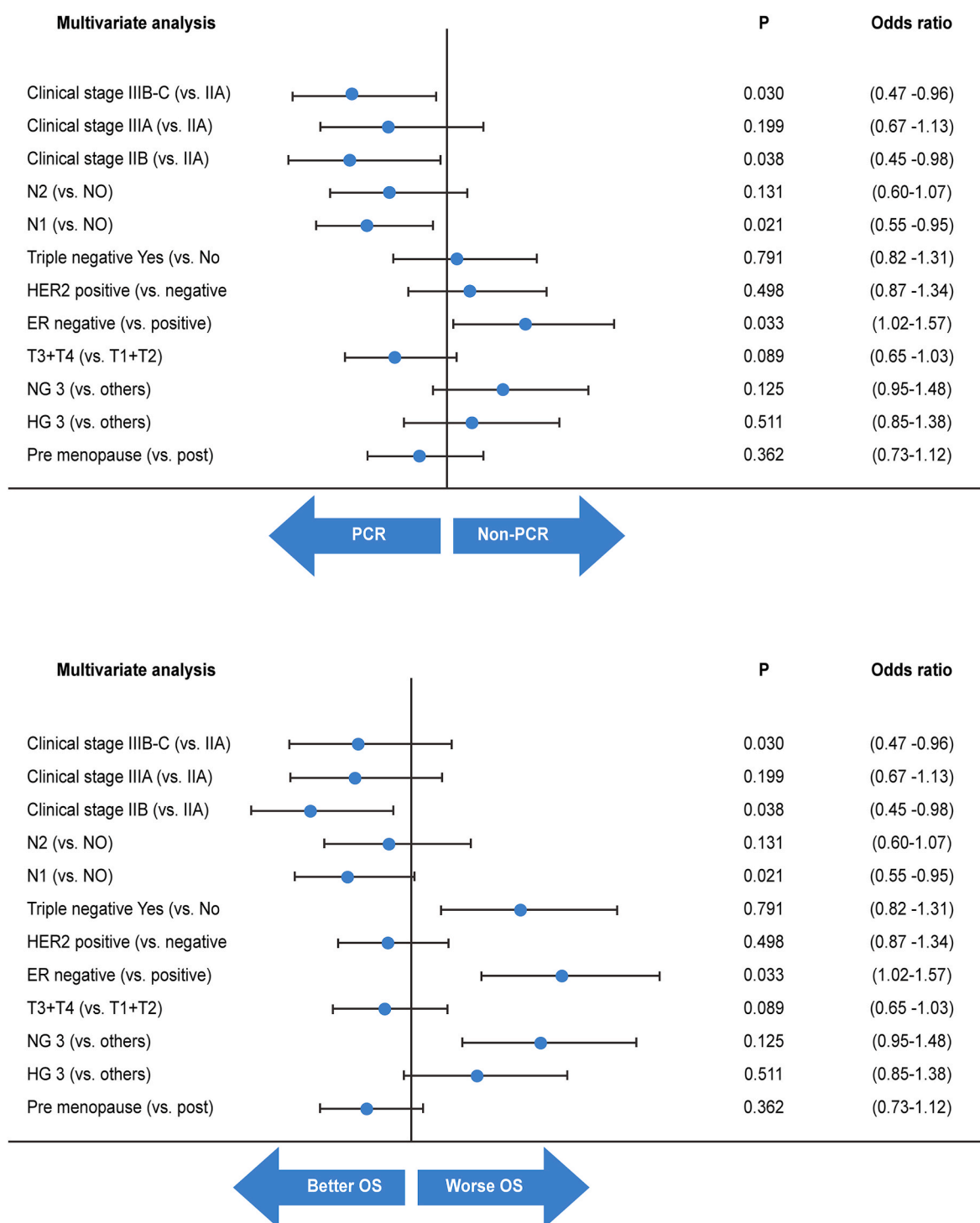


Fig. 4. Multivariate analysis of factors affecting pathologic complete response (pCR) (A) and overall survival (OS) (B); HG, histologic grade; NG, nuclear grade.

designed the study, wrote the manuscript, FGBR manuscript revision, GDP analyzed the data, MDT manuscript revision, AGA manuscript revision, OF manuscript revision, RGCL manuscript revision, LHG manuscript revision, JML manuscript revision.

Declaration of generative AI and AI-assisted technologies in the writing process

None.

Declaration of competing interest

None.

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