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Disparities in access to anti-HER2 therapies in neoadjuvant chemotherapy: A prognostic analysis based on real-world data comparing Brazil's public and private healthcare systems

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ABSTRACT

Background: Trastuzumab has significantly improved the treatment of HER2-positive breast cancer, particularly in the neoadjuvant setting, where its combination with chemotherapy increases the pathologic complete response (pCR) rate. This retrospective cohort study assesses the implications of disparities in access to trastuzumab within the Brazilian public healthcare system, focusing on pCR, overall survival (OS) and disease-free survival (DFS) in non-metastatic, HER2-positive breast cancer patients undergoing neoadjuvant chemotherapy (NAC).

Methods: The study was conducted in the *Hospital Pérola Byington* (PEROLA), a public institution, and in the *Hospital do Servidor Público Estadual* (HSPE), a private institution. pCR was defined as the absence of residual invasive or in situ tumors in the breast and axillary nodes. OS and DFS were calculated by Kaplan-Meier survival analysis for a 5-year period.

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Results: From 2011 to 2020, 381 patients at PEROLA and 78 at HSPE underwent NAC. Trastuzumab availability was higher at HSPE (83.4 % vs. 60.0 %, $p < 0.0001$). Use of trastuzumab correlated with significantly higher pCR rates at both the PEROLA (54.3 % vs. 26.4 %, $p < 0.0001$) and the HSPE (52.7 % vs. 26.4 %, $p < 0.0001$). HER2-positive patients with pCR at HSPE also had better OS (80 % vs. 61 %, $p < 0.0001$) and DFS (89 % vs. 67 %, $p < 0.0001$) compared to those at PEROLA.
Conclusion: There were significant differences in the provision of trastuzumab between the public and private healthcare systems, adversely affecting clinical outcomes and patient survival. The current data highlight the pressing need to address equity in cancer treatment to improve prognosis for every patient.

1. Introduction

Breast cancer (BC), the most common cancer worldwide, demands attention [1]. The incidence of breast cancer is higher in developed countries due to several factors, including advances in screening methods and medical infrastructure [2], lifestyle-related risk factors [3] and an aging population [4]. Conversely, mortality rates are higher in developing countries, mainly due to late-stage diagnoses and restricted access to affordable treatments. Consequently, around 60 % of global BC deaths occur in these regions [5,6]. In the United States, improved treatment and screening after 1975 were associated with a 58 % reduction in BC mortality in 2019. Approximately 29 % of this reduction was associated with treating metastatic BC, 25 % with screening, and 47 % with treating stage I-III BC [7].

In Brazil, BC is the most prevalent cancer among women, with an incidence rate of 61 new cases per 100,000 individuals [8]. Notably, 15–20 % of these cases involve overexpression of the human epidermal growth factor receptor 2 (HER2+), a particularly aggressive subtype linked to high cancer-specific mortality rates [9,10]. For decades, HER2+ BC was associated with poor outcomes and higher mortality rates compared to other subtypes [11]. However, the advent of trastuzumab has significantly changed the treatment paradigm of HER2-positive BC patients in metastatic [12], adjuvant [13] and neoadjuvant settings [14]. New HER2-targeted therapies such as pertuzumab have expanded treatment options for HER2-positive BC [15]. In the AMAZONA III study, the largest BC cohort in Brazil, almost a quarter of participants were diagnosed with HER2+ BC [16].

Combining trastuzumab with chemotherapy decreases BC recurrence and associated mortality by one-third [17]. Typically, women with HER2+ BC are treated with a combination of chemotherapy drugs and trastuzumab, with survival rates improving remarkably.

Neoadjuvant chemotherapy (NAC) is recommended for patients diagnosed with stage II/III HER2+ BC. The disease stage can impact the patient's clinical response to treatment and the likelihood of achieving pathologic complete response (pCR), which is associated with better event-free survival and overall survival (OS) rates [18,19]. Meta-analyses with large patient cohorts have shown a link between pCR and improved survival outcomes [19]. Early detection, prompt treatment and timely postsurgical systemic therapy are crucial for survival rates [20,21].

In Brazil, where approximately 75 % of the population depends on the public healthcare system (Unified Health System/SUS), access to treatment can face significant delays [21]. Trastuzumab was integrated into the SUS on July 25, 2012, for the treatment of locally advanced and early-stage HER2-positive breast cancer, with public hospital distribution beginning in January 2013. Initially, HER2 status confirmation required molecular testing (FISH or CISH) for tumors with immunohistochemical scores of 2+ or 3+ [22]. However, since 2018, positive HER2 status identified through immunohistochemistry alone has enabled access to trastuzumab, streamlining the process and enhancing accessibility. Pertuzumab, approved in 2021 for metastatic HER2+ breast cancer, marked a significant step towards dual HER2 blockade in the SUS [23]. Despite this progress, the combination of trastuzumab, pertuzumab, and chemotherapy in the neoadjuvant setting remains largely unavailable in the SUS, except through clinical trials, underscoring persistent disparities in treatment access.

Real-world data (RWD) are important, particularly in countries where access to treatment is not universal. The impact of trastuzumab on survival outcomes and prognostic factors for early HER2+ BC patients in clinical practice is not yet well established in the Brazilian population. Therefore, this study was designed to evaluate the impact of disparities in the availability of trastuzumab within the SUS on pCR, OS and disease-free survival (DFS).

2. Methods

2.1. Study design and data source

This retrospective, multicenter, longitudinal cohort study involved a review of medical records from patients who received NAC for BC at two major referral centers in São Paulo, Brazil: Hospital Pérola Byington (PEROLA) and Hospital do Servidor Público Estadual (HSPE).

PEROLA is one of the largest public institutions dedicated to women's health and cancer treatment in Brazil, providing care to patients from across the state of São Paulo through the Brazilian public healthcare system (SUS). It serves as a national reference center for breast cancer treatment and is representative of public healthcare services available to the general population.

HSPE, on the other hand, is a tertiary hospital that primarily serves civil servants and their dependents, offering care through the state health insurance system. As a specialized institution, it reflects the experience of patients within the supplementary healthcare sector, representing a significant subset of the Brazilian healthcare landscape.

These two institutions were selected to capture data from both public and semi-private healthcare settings, reflecting differences in access to treatments, protocols, and patient populations. Although they are located in São Paulo, the largest city in Brazil, their patient base includes referrals from various regions, providing insights that are generalizable to broader healthcare practices across the country.

2.2. Inclusion criteria

The inclusion criteria were as follows: female patients aged 18 years or older with a confirmed diagnosis of non-metastatic HER2-positive breast cancer who underwent neoadjuvant chemotherapy (NAC) followed by surgery between January 2011 and December 2020.

2.3. Exclusion criteria

The exclusion criteria were as follows: patients with inflammatory BC; bilateral BC; BC during pregnancy and/or postpartum; participation in clinical trials; incomplete data and/or loss to follow-up.

2.4. Neoadjuvant chemotherapy regimens

Patients received NAC according to institutional protocols and the availability of medications at each institution. At PEROLA, NAC regimens were standardized and typically included four cycles of doxorubicin plus cyclophosphamide, followed by four cycles of docetaxel. Access to anti-HER2 therapy, such as trastuzumab, was limited and

prioritized based on drug availability within the public healthcare system. At HSPE, NAC regimens followed a similar structure; however, access to anti-HER2 therapies was more consistent, allowing a greater proportion of patients to receive trastuzumab both in the neoadjuvant and adjuvant phases. Dose-dense chemotherapy and double blocked was not part of the treatment protocol at either institution during the study period.

2.5. Adjuvant treatment

Following the completion of NAC, all patients who received trastuzumab during the neoadjuvant phase continued it in the adjuvant setting, ensuring treatment uniformity. Patients who did not receive trastuzumab during NAC did not receive it postoperatively. No patients received pertuzumab or T-DM1 during any phase of treatment. Additionally, all hormone receptor-positive (HR+) patients received endocrine therapy, with tamoxifen prescribed for premenopausal women and aromatase inhibitors for postmenopausal women.

2.6. Definition of pCR

pCR was defined as no residual invasive tumor or ductal carcinoma in situ (DCIS) in the primary tumor bed or in the ipsilateral axillary lymph nodes (ypT0 ypN0) [24].

2.7. Statistical analysis

To assess the relationship between clinical data and pCR, patients were divided into pCR and non-pCR groups. To identify associations between clinical data and outcomes, categorical variables were compared using Fisher's exact test or the chi-square test. Student's t-test was used to assess intergroup differences in normally distributed data. OS was defined as the length of time between curative surgery and death and DFS as the length of time between curative surgery and the first local, regional or systemic relapse, or death. The Kaplan-Meier method and the log rank test were used to assess differences in OS and DFS between the pCR and non-pCR subgroups. Both OS and DFS were right-censored at 5 years. For inferential analyses, p-values <0.05 were considered statistically significant. Multivariate logistic regression was performed to evaluate the association between various clinical and pathological variables and the likelihood of achieving pCR. Cox proportional hazards models were used to assess the impact of these variables on OS and DFS, including interaction effects between access to trastuzumab and pCR.

2.8. Ethical aspects

The study was registered in *Plataforma Brazil* and approved by a research ethics committee (CAAE 39097520.4.2001.0069). Informed consent was waived (retrospective analyses), and the confidentiality and integrity of the medical records were preserved.

3. Results

3.1. Selected patients

Between 2011 and 2020, 1601 patients at PEROLA and 290 at HSPE underwent NAC. Of these, 381 patients at PEROLA (23.6 %) and 78 at HSPE (26.8 %) were HER2+ ($p < 0.001$). Fig. 1 shows the flowchart of enrolled patients.

3.2. Clinical and pathological characteristics of patients undergoing NAC

In the PEROLA cohort, 30.9 % of the patients who achieved pCR were premenopausal and 20.2 % were postmenopausal ($p = 0.023$). Additionally, 38.1 % had a family history of BC and 23.9 % did not ($p = 0.029$) (Table 1). Response rates varied with histological grade. Patients with grade 2 tumors had a pCR rate of 40.4 %, while those with grades 1 or 3 had lower rates ($p = 0.029$). Of the patients achieving pCR, 41.5 % had a Ki-67 expression level <14 and 22.9 % had higher levels ($p = 0.006$). The pCR rate was higher in hormone receptor (HR)-negative patients (29.6 %) compared to HR-positive patients (13.9 %) ($p = 0.002$). Lymph node involvement (N0 versus others) correlated strongly with pCR, with 76.5 % of N0 patients achieving pCR compared to 23.1 % of those with any nodal involvement ($p < 0.0001$). Clinical stage I patients showed a significantly higher rate of pCR (63.9 %) compared to more advanced stages ($p = 0.009$).

At HSPE cohort, pCR was not significantly associated with menopausal status or tumor size. Family history remained a strong predictor of pCR, with 62.5 % of patients with a family history achieving pCR compared to 24.2 % without ($p = 0.008$). Patients with grade 1 tumors were more likely to achieve pCR (60 %) ($p = 0.045$). Low levels of Ki-67 expression were associated with higher rates (62.5 %) of pCR ($p = 0.009$). No significant associations were found between pCR and other factors such as age, HR status and clinical staging.

Fig. 2A/B show the factors significantly associated with pCR in the PEROLA and HSPE cohorts, respectively.

3.3. Association between pCR and access to anti-HER2 treatments

Access to trastuzumab during NAC differed between the two institutions. At HSPE, 84.4 % of the patients (n = 65) were treated with the AC-TH regimen (Doxorubicin/Cyclophosphamide/Paclitaxel/Trastuzumab), whereas at PEROLA, only 60 % (n = 228) were ($p < 0.0001$). pCR rates were 25.4 % (n = 97) at PEROLA and 32 % (n = 25) at HSPE ($p < 0.0001$).

Patients who received trastuzumab had higher pCR rates at both institutions. PEROLA (54.3 % vs. 26.4 %, $p < 0.0001$) and HSPE (56.7 %

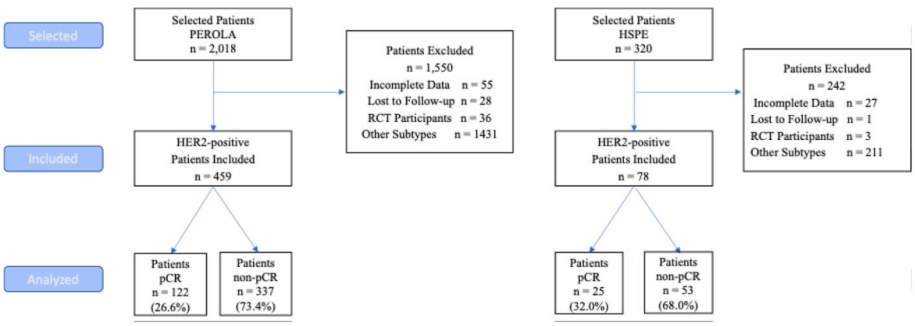

Fig. 1. Flowchart of the patients enrolled in the study.
pCR: pathologic complete response; NAC: neoadjuvant chemotherapy; RCT: randomized controlled trial. PEROLA: *Hospital Pérola Byington;* HSPE: *Hospital do Servidor Público Estadual.*

Table 1
Comparative analysis of clinical and pathological characteristics following neoadjuvant chemotherapy in both study institutions.

Characteristics	PEROLA (n = 381)					HSPE (n = 78)				
	pCR (n = 97)		non-pCR (n = 284)		p-value*	pCR (n = 25)		non-pCR (n = 53)		p-value
	n	%	n	%		n	%	n	%	
Age, years; mean (SD)	48.9 (10.6)		48.8 (10.9)		0.934	50.1 (10.4)		49.9 (10.8)		0.938
Menopausal status										
Premenopausal	58	30.9	130	69.1	0.023	15	38.5	24	61.5	0.331
Menopausal	39	20.2	154	79.8		10	25.6	29	74.4	
Family history										
Yes	24	38.1	38	61.9	0.029	10	62.5	6	37.5	0.008
No	74	23.9	243	76.1		15	24.2	47	75.8	
Histological type										
IDC	82	24.5	253	75.5	0.320	18	27.7	47	72.3	0.170
IDC with ILC	12	36.4	21	63.6		4	50.0	4	50.0	
Others	3	23.1	10	76.9		3	60.0	2	40.0	
Histological grade										
G1	3	23.1	10	76.9	0.029	3	60.0	2	40.0	0.045
G2	21	40.4	31	59.6		7	53.8	6	46.2	
G3	73	23.1	243	76.9		15	25.0	45	75.0	
Ki-67 expression										
<14	22	41.5	31	58.5	0.006	10	62.5	6	37.5	0.009
>14	75	22.9	253	77.1		16	24.6	46	75.4	
Hormone receptor status										
HR +	14	13.9	87	86.1	0.002	5	23.8	16	76.2	0.500
HR -	83	29.6	197	70.4		20	35.1	37	64.9	
Tumor size (T)										
T1	7	46.7	8	53.3	0.233	2	66.7	1	33.3	0.291
T2	28	26.2	80	73.8		10	41.7	14	58.3	
T3	35	22.6	120	77.4		7	24.1	22	75.9	
T4	27	26.0	77	74.0		6	27.3	16	72.7	
Lymph node involvement (N)										
N0	13	76.5	4	23.5	<0.0001	4	80.0	1	20.0	0.064
N1	41	19.8	166	80.2		9	22.5	31	77.5	
N2	40	27.4	105	72.6		11	36.7	19	63.3	
N3	3	27.3	8	72.7		1	33.3	2	66.7	
Clinical staging (TNM) AJCC 7th version										
I	7	63.6	4	36.4	0.009	1	50.0	1	50.0	0.374
IIA	9	47.4	10	52.6		3	60.0	2	40.0	
IIB	16	20.0	63	80.0		5	29.4	12	70.6	
IIIA	35	22.6	120	77.4		7	25.0	21	75.0	
IIIB	27	25.7	78	74.3		8	34.8	15	65.2	
IIIC	3	27.3	8	72.7		1	33.3	2	66.7	

PEROLA: *Hospital Perola Byington*; HSPE: *Hospital do Servidor Publico Estadual.*
pCR: pathologic complete response; SD: standard deviation; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; family history: first degree. *p-value: chi-square test.

vs. 26.4 %, $p < 0.001$) (Fig. 3).

The likelihood of achieving pCR was significantly higher in patients treated with the AC-TH regimen compared to the AC-T regimen (Fig. 4). At PEROLA, the likelihood of achieving pCR was higher in patients undergoing AC-TH treatment (OR >1). At HSPE, AC-TH treatment resulted in even more increased odds of pCR compared to AC-T.

3.4. Survival analysis

The probability of 5-year survival at PEROLA was 58.0 % compared to 79.0 % at HSPE ($p < 0.0001$). The 5-year DFS rates were 64.0 % and 72 %, respectively ($p < 0.0001$).

For the patients achieving pCR, the OS was 80 % at HSPE and 61 % at PEROLA ($p < 0.0001$). Likewise, DFS was 89 % and 67 %, respectively ($p < 0.0001$) (Fig. 5 A/B).

3.5. Multivariate analysis of the interaction between pCR and access to trastuzumab

The two institutions differed significantly regarding the association between access to trastuzumab and pCR, OS and DFS.

At PEROLA, the restricted access to trastuzumab was significantly associated with achieving pCR, with an odds ratio (OR) of 1.2 (95 % confidence interval [CI]: 0.85–1.70, $p = 0.01$). The hazard ratio (HR) for OS was 1.5 (95%CI: 1.10–2.05; $p = 0.005$), indicating a higher risk of mortality for patients without trastuzumab. Similarly, the HR for DFS was 1.6 (95%CI: 1.20–2.10, $p = 0.003$), suggesting a higher risk of disease recurrence or death. Lymph node involvement (N2 vs. N0: HR for OS = 1.70, $p = 0.004$; HR for DFS = 1.80, $p = 0.001$) and advanced tumor stage (III vs. I: HR for OS = 1.55, $p = 0.001$; HR for DFS = 1.65, $p = 0.002$) were also significantly associated with both OS and DFS.

At HSPE, a significant association was found between better trastuzumab access and achieving pCR, with an OR of 2.8 (95%CI: 1.90–4.10, $p = 0.0003$). The HR for OS in this cohort was 0.55 (95%CI: 0.4–0.75, $p = 0.002$), indicating a lower risk of mortality. The HR for DFS was 0.60 (95%CI: 0.45–0.80, $p = 0.004$), showing a lower risk of disease recurrence or death. None of the other clinical factors evaluated was significantly associated with outcome (see Table 2).

4. Discussion

This study highlights that access to trastuzumab, particularly when

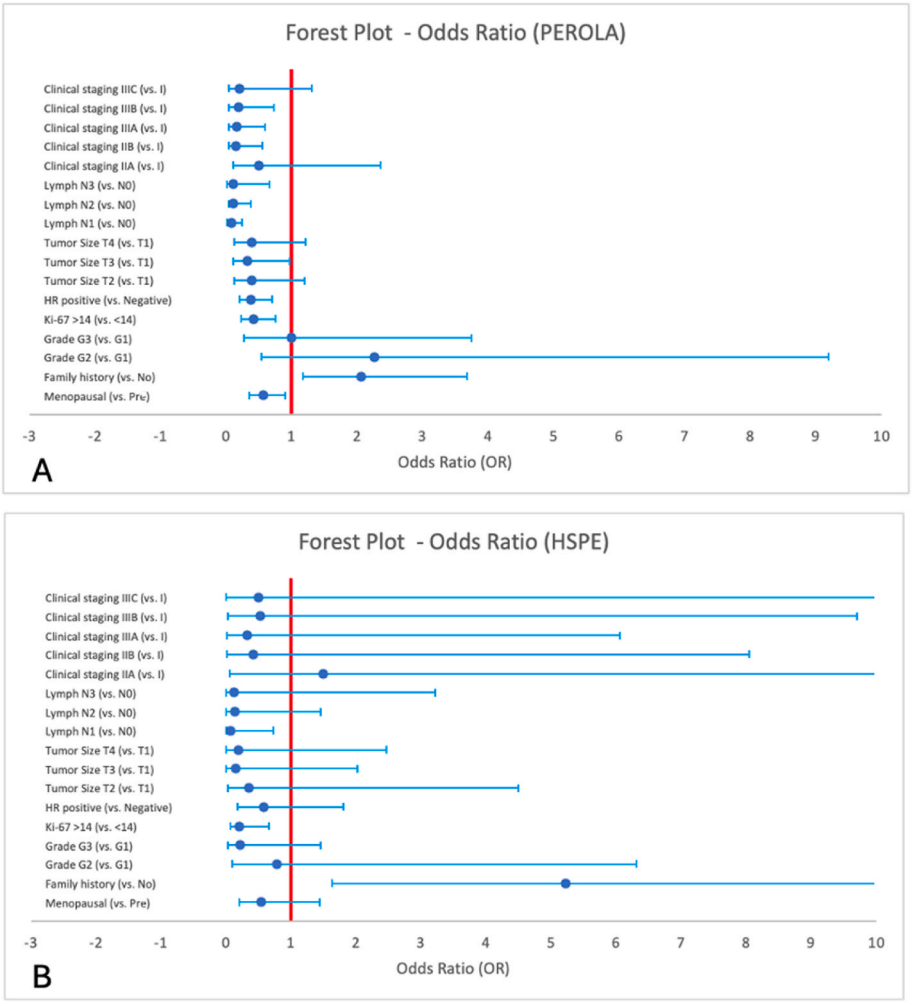

Fig. 2. Forest plot of characteristics associated with pathologic complete response (pCR): **(A)** PEROLA: cohort in the public sector; **(B)** HSPE: cohort in the private sector.
PEROLA: *Hospital Pérola Byington;* HSPE: *Hospital do Servidor Público Estadual.*

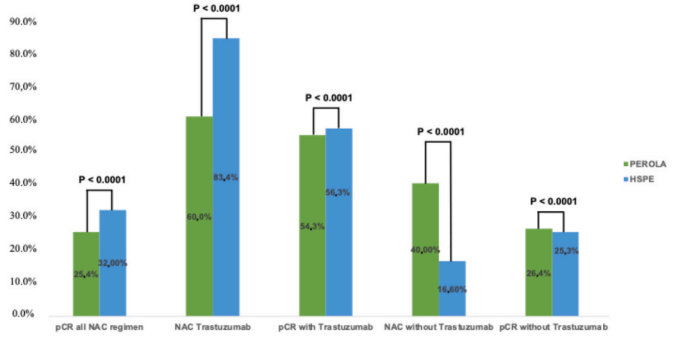

Fig. 3. Association of trastuzumab-based neoadjuvant chemotherapy (NAC) and correlation with pathologic complete response (pCR).

pathological complete response (pCR) is achieved, is a key determinant of overall survival (OS) and disease-free survival (DFS) in breast cancer patients. Multivariate analysis revealed that patients with access to trastuzumab were significantly more likely to achieve pCR, which was strongly correlated with improved survival outcomes. Furthermore, the interaction between access to trastuzumab and pCR underscored this relationship, indicating that the survival benefits of trastuzumab are most pronounced when pCR is achieved. These findings align with previous evidence demonstrating that effective HER2-targeted therapy, particularly when leading to pCR, can substantially lower the risk of recurrence and mortality. This underscores the critical importance of ensuring optimal access to trastuzumab for all eligible patients.

The study also highlights disparities in trastuzumab access between public and private institutions, significantly impacting survival outcomes. These findings are consistent with data from Brazilian registries, such as the AMAZONA III study. We further discuss the influence of socioeconomic factors, differences in surgical timing, radiotherapy access, and the absence of dual HER2 blockade (trastuzumab and pertuzumab) in public hospitals [16].

Although other prognostic factors, such as tumor stage and lymph node involvement, influenced survival, their impact was less significant compared to trastuzumab access and pCR. Factors such as age, menopausal status, tumor histology, and hormone receptor status did not show significant associations with OS or DFS. This emphasizes the pivotal role of trastuzumab and the necessity of prioritizing equitable access and optimizing pCR rates in clinical practice to improve patient outcomes.

In Brazil, disparities in access to trastuzumab reflect broader inequities in the healthcare system. Since ANVISA's approval of trastuzumab in 2002, public sector delays contrast with immediate private sector availability. Currently, disparity regarding access to the drug remains. While private insurance provides access to all approved anti-HER2 agents, including trastuzumab, pertuzumab, trastuzumab

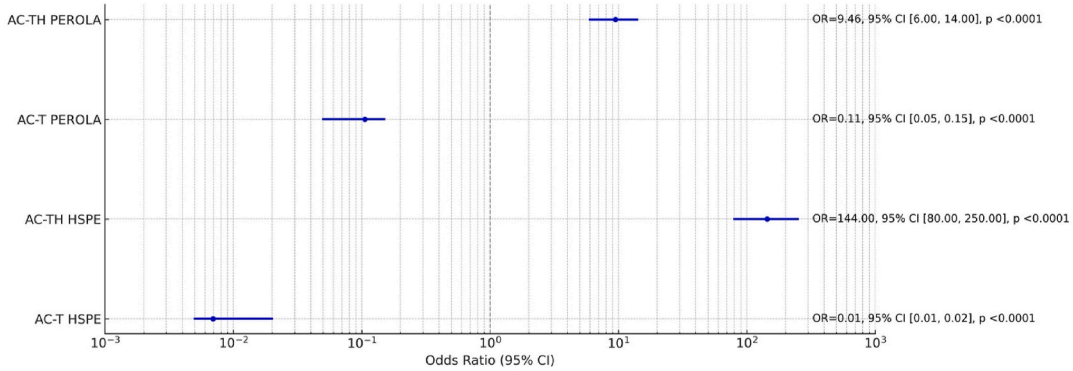

Fig. 4. Forest plot of neoadjuvant chemotherapy treatment and use of trastuzumab and pathologic complete response.
AC: Adriblastine + Cyclophosphamide; T: Docetaxel or Paclitaxel, H: Trastuzumab.

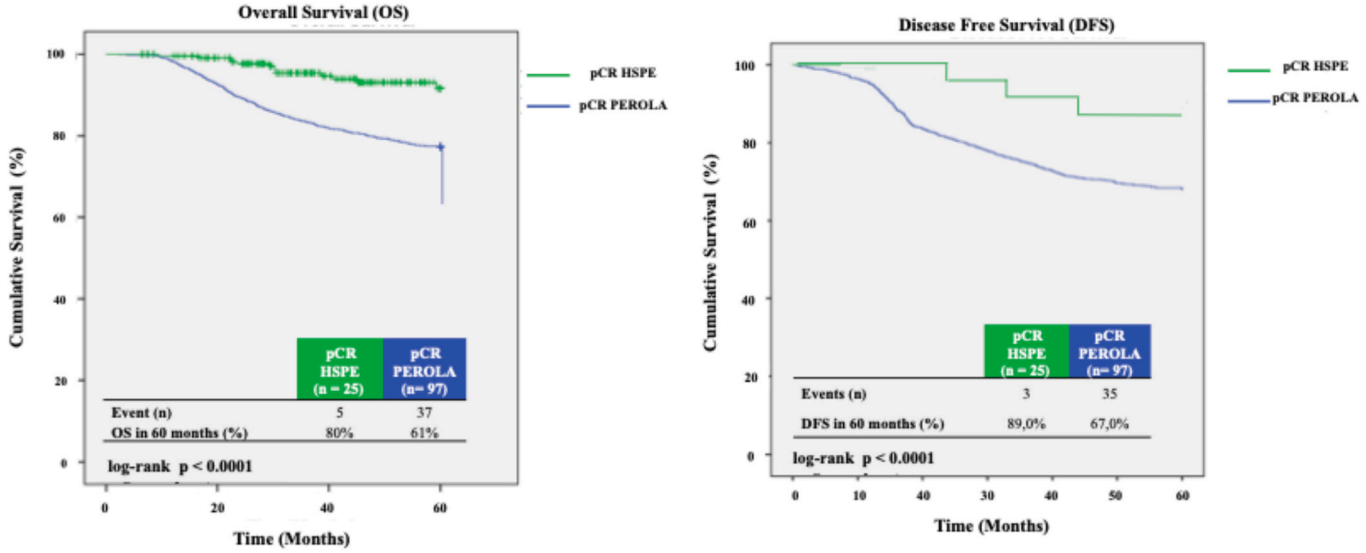

Fig. 5. Survival according to pathologic complete response (pCR) in both participating institutions: **(A)** overall survival; **(B)** disease-free survival.

emtansine and lapatinib, access to HER2-targeted therapy is still restricted within the SUS. This affects outcomes, particularly survival rates, for many patients, as the SUS serves approximately three-quarters of the country's population.

The survival and safety outcomes of highly selected patients under optimal conditions in clinical studies may not be representative of routine clinical practice [25] as social determinants such as access to healthcare and quality of BC care vary across countries, ultimately affecting BC survival [26]. Inadequate access to neoadjuvant treatment for HER2-positive BC impacts patient prognosis. In cases of metastasis, as many as 600 lives could be lost over a 2-year period if trastuzumab is delayed [27].

The observed disparities align with global trends in low- and middle-income countries (LMICs), where financial constraints and under-resourced healthcare systems limit access to advanced therapies. For example, in Latin America, access to trastuzumab varies significantly across countries, with some nations achieving higher pCR rates and improved outcomes through national cancer programs [28,29]. For example, in Latin America, access to trastuzumab varies significantly across countries, with some nations achieving higher pCR rates and improved outcomes through national cancer programs. In contrast, countries with fragmented healthcare delivery face outcomes similar to those observed at PEROLA, where access to trastuzumab was lower [30].

Allocation of resources for anti-HER2 therapies remains a challenge for policymakers in LMICs. Barriers to access, such as drug cost and infrastructure limitations, contribute to poorer cancer outcomes. Studies from other Latin American countries, including Mexico and Argentina, report similar discrepancies between public and private sectors, reinforcing the need for region-wide policy reforms to address cancer treatment inequities [27,30–34].

This is the first Brazilian and Latin American study to evaluate long-term survival outcomes in HER2-positive breast cancer patients undergoing neoadjuvant chemotherapy (NAC), comparing public and private healthcare systems. The pCR rates for all HER2+ patients were significantly different between the two institutions (25.6 % at PEROLA/public and 32 % at HSPE/private) and were lower than rates reported in other studies involving regimens both with and without trastuzumab, which range from 25.4 % to 66.7 % [21]. Access to trastuzumab was 60 % at PEROLA and 83.4 % at HSPE, significantly impacting pCR rates. For patients able to access trastuzumab, pCR rates were 54.3 % at PEROLA compared to 56.3 % at HSPE, a statistically significant difference. For those unable to access trastuzumab, rates were 26.4 % and 25.3 %, respectively. These findings corroborate reports in the literature where pCR rates with trastuzumab range from 29 % to 66 % compared to 25–36 % without trastuzumab [35].

Menopausal status has been shown to affect pCR rates, suggesting a potential biological variance affecting treatment efficacy. Furthermore, a significant correlation exists between a family history of cancer and pCR outcome, implying a genetic or inherited component influencing response to therapy.

Table 2
Multivariate analysis of factors associated with pathologic complete response, overall survival, disease-free survival, and access to trastuzumab in both study institutions.

Characteristics	Hospital	pCR			OS			DFS		
		OR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value
Access to Trastuzumab (Yes vs No)	**PEROLA**	1.2	0.85–1.70	0.01	1.5	1.10–2.05	0.005	1.6	1.20–2.10	0.003
	HSPE	2.8	1.90–4.10	0.0003	0.55	0.40–0.75	0.002	0.6	0.45–0.80	0.004
Age (continuous)	**PEROLA**	0.98	0.94–1.03	0.15	1.01	0.98–1.05	0.12	1.02	0.99–1.05	0.1
	HSPE	0.97	0.92–1.02	0.13	1.02	0.99–1.06	0.11	1.03	1.00–1.06	0.105
Menopausal Status (Pre vs. Menopausal)	**PEROLA**	1.05	0.80–1.40	0.5	1.1	0.85–1.50	0.25	1.12	0.88–1.42	0.22
	HSPE	1.1	0.85–1.45	0.2	1.15	0.90–1.50	0.15	1.18	0.92–1.50	0.18
Tumor Histology (IDC vs others)	**PEROLA**	1.1	0.70–1.45	0.6	0.95	0.70–1.25	0.7	0.98	0.75–1.28	0.7
	HSPE	1.05	0.75–1.50	0.7	0.9	0.65–1.25	0.6	0.92	0.70–1.20	0.58
Histological Grade (G3 vs G1)	**PEROLA**	1.15	0.85–1.60	0.3	1.05	0.80–1.40	0.4	1.08	0.82–1.42	0.35
	HSPE	1.2	0.95–1.60	0.25	1.1	0.85–1.45	0.25	1.12	0.87–1.44	0.24
KI-67 (<14 % vs >14 %)	**PEROLA**	0.9	0.65–1.25	0.45	0.85	0.65–1.15	0.5	0.87	0.68–1.11	0.48
	HSPE	0.95	0.70–1.30	0.4	0.8	0.55–1.15	0.3	0.82	0.60–1.12	0.35
Hormone Receptor (HR + vs HR-)	**PEROLA**	1.2	0.85–1.70	0.2	1.25	0.90–1.75	0.22	1.3	1.00–1.80	0.18
	HSPE	1.3	0.95–1.80	0.15	1.2	0.85–1.70	0.17	1.22	0.90–1.65	0.16
Tumor Stage (II vs I)	**PEROLA**	1.3	1.00–1.80	0.05	1.3	1.00–1.75	0.045	1.4	1.10–1.90	0.03
	HSPE	1.35	1.05–1.85	0.04	1.4	1.10–1.85	0.02	1.38	1.15–1.90	0.028
Tumor Stage (III vs I)	**PEROLA**	1.5	1.10–2.05	0.005	1.55	1.25–2.05	0.001	1.65	1.30–2.15	0.002
	HSPE	1.6	1.20–2.15	0.002	1.55	1.30–2.05	0.004	1.5	1.20–2.05	0.003
Lymph Node Involvement (N1 vs N0)	**PEROLA**	1.4	1.05–1.90	0.02	1.45	1.10–1.90	0.01	1.55	1.25–1.95	0.006
	HSPE	1.5	1.15–2.00	0.008	1.45	1.20–1.85	0.01	1.42	1.15–1.85	0.009
Lymph Node Involvement (N2 vs N0)	**PEROLA**	1.6	1.20–2.15	0.003	1.7	1.35–2.25	0.004	1.8	1.40–2.35	0.001
	HSPE	1.75	1.40–2.35	0.002	1.65	1.35–2.20	0.006	1.68	1.30–2.15	0.005

PEROLA: *Hospital Perola Byington*; HSPE: *Hospital do Servidor Publico Estadual.*
pCR: pathologic complete response; OS: overall survival; DFS: disease-free survival; HR: hazard ratio; 95%CI: 95 % confidence interval. **Note:** ORs and 95%CIs for achieving pCR were calculated using multivariate logistic regression models, while HRs and 95%CIs for OS and DFS were estimated using Cox proportional hazards regression models. P-values were derived from the Wald test.

In addition, the PEROLA findings underscored the predictive value of histological grade and Ki-67 proliferation index. Lower levels of Ki-67 and higher histological grades are closely associated with differing probabilities of achieving pCR, highlighting their usefulness in predicting prognosis and planning treatment. Similarly, at HSPE, family history and Ki-67 levels significantly influenced the likelihood of achieving pCR, reinforcing the importance of these factors across different patient cohorts.

Patients in both institutions who achieved pCR had significantly better DFS and OS than patients who did not. The OS of patients who achieved pCR at HSPE and PEROLA was 80.0 % vs. 61.0 %, respectively, at 60 months. Other treatments proven to improve outcomes in HER2-positive disease, such as adjuvant pertuzumab [36] for patients with positive lymph nodes and adjuvant T-DM1 [37] for those who did not achieve pCR, were unfortunately unavailable at the time of the study and remain unavailable to this day.

pCR constitutes a significant prognostic factor for survival [35,38]. A cohort study showed that in patients with HER2-positive BC treated with trastuzumab, those failing to achieve pCR had a 5-year DFS rate of 78 % compared to 95 % for patients who achieved pCR [39]. Furthermore, Cortazar et al. [18]identified a substantial correlation between pCR and long-term survival in HER2-negative patients treated with trastuzumab. A possible explanation for the difference in outcomes in favor of the patients at HSPE who achieved pCR is that a large proportion of PEROLA patients who achieved pCR did not receive trastuzumab. The effect of adjuvant trastuzumab may have played a role in these results. Patients who do not receive trastuzumab in the neoadjuvant setting could potentially receive it in the adjuvant setting; however, that did not occur due to lack of access, impacting OS.

In the meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group, with a median follow-up of 10.7 years, 26.6 % of patients experienced recurrence of HER2-positive BC and 19.7 % died of the disease [17]. The effectiveness of trastuzumab has been corroborated in the real world, particularly when administered with a neoadjuvant aim, achieving pCR rates of 53.3–56.3 %, comparable to or better than those recorded in trials combining chemotherapy with trastuzumab [40,41].

In agreement with the literature, this study showed that not achieving pCR was an indicator of poorer DFS [18,35]. These findings collectively underscore the significance of prompt diagnosis and proper disease management.

Disparities often exist between randomized controlled trials (RCTs) and RWD studies due to variations in design, patient demographics and analytical approaches. The American Society of Clinical Oncology Value Framework concluded that real-world approximations of OS and the duration of DFS for cancer treatments were approximately 16 % lower than outcomes reported in RCTs [41,42].

Today trastuzumab-based NAC is no longer the gold standard in HER2-positive disease. Associating pertuzumab (dual blockade) has resulted in an impressive improvement in pCR rates [43–45]; however, pertuzumab is unavailable in public institutions in the neoadjuvant setting.

The broader implications of these findings extend beyond the clinical setting, underscoring the necessity of integrating real-world data (RWD) into national cancer policies. Policymakers must address disparities in drug access by expanding SUS coverage of anti-HER2 therapies and streamlining approval processes to reduce delays. Efforts to implement national breast cancer programs, similar to initiatives in Chile and Colombia, could improve access and align public-sector outcomes more closely with private-sector standards.

Understanding the factors contributing to disparities between public and private healthcare systems is essential for interpreting the differences observed in treatment outcomes. In the context of our study, several biases may have influenced the results, reflecting broader

systemic inequities in cancer care delivery. Disparities in treatment and outcomes between public and private institutions may be influenced by several factors beyond access to medications. Socioeconomic differences can impact patient adherence to treatment, while delays in diagnostics, surgery, and initiation of therapy are more prevalent in the public healthcare system. Although access to antihormonal therapy for hormone receptor-positive patients was similar in both cohorts, variations in hospital infrastructure, patient follow-up, and multidisciplinary care contribute to differing clinical outcomes. Additionally, while access to clinical trials could introduce bias, patients participating in such trials were excluded from this analysis to ensure homogeneity. These systemic differences highlight the need to address inequalities to improve cancer care outcomes across diverse healthcare setting.

Limitations of this study include its retrospective design and the focus on two specific institutions. However, its strength lies in leveraging RWD to evaluate the impact of access to trastuzumab on outcomes for HER2-positive breast cancer patients. This study addresses the gap in evidence comparing outcomes in the SUS with those in private healthcare settings, offering valuable insights into the realities of routine clinical practice. It captures variations in patient demographics, healthcare delivery, and treatment access, reflecting the challenges faced in everyday care. These findings underscore the importance of equitable access to treatments like trastuzumab in achieving improved outcomes and highlight the critical role of RWD in informing healthcare policies and optimizing patient care delivery.

5. Conclusion

Our RWD findings highlight the urgent need to address disparities in access to targeted therapies, particularly in the neoadjuvant setting, which significantly impacts long-term outcomes. Bridging systemic inequities between public and private institutions is crucial to improving survival rates and reducing treatment gaps across socioeconomic groups. The absence of pertuzumab and T-DM1 in the public sector underscores the limited therapeutic options available. This study reinforces the need for enhanced resource allocation and policy reforms to promote cancer care equity. These findings reflect broader patterns of healthcare inequality in Brazil and similar challenges in other countries. We advocate for expanding access to essential therapies and fostering multidisciplinary care in public healthcare to improve breast cancer outcomes.

CRediT authorship contribution statement

Marcelo Antonini: Writing – original draft, Methodology, Conceptualization. **André Mattar:** Writing – original draft, Methodology, Conceptualization. **Denise Joffily Pereira da Costa Pinheiro:** Writing – review & editing. **Isabela Bastos Maia:** Writing – review & editing. **Marina Diógenes Teixeira:** Writing – review & editing. **Andressa Gonçalves Amorim:** Writing – review & editing. **Odair Ferraro:** Writing – review & editing. **Larissa Chrispim de Oliveira:** Writing – review & editing. **Marcellus do Nascimento Moreira Ramos:** Writing – review & editing. **Francisco Pimentel Cavalcante:** Writing – review & editing. **Felipe Zerwes:** Conceptualization. **Marcelo Madeira:** Writing – review & editing. **Romualdo Barroso-Sousa:** Writing – review & editing. **Eduardo de Camargo Millen:** Writing – review & editing. **Antonio Luiz Frasson:** Writing – review & editing. **Fabricio Palermo Brenelli:** Writing – review & editing. **Gil Facina:** Writing – review & editing. **Rogério Fenile:** Writing – review & editing. **Luiz Henrique Gebrim:** Writing – review & editing. **Juliana Monte Real:** Writing – review & editing.

Data availability

The data are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations:

95%CI	95 % confidence interval
BC	Breast cancer
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
HER2+	Human epidermal growth factor receptor 2
HR	Hazard ratio
HSPE	*Hospital do Servidor Publico Estadual*
LMICs	Low- and middle-income countries
NAC	Neoadjuvant chemotherapy
OR	Odds ratio
OS	Overall survival
pCR	pathologic complete response
PEROLA	*Hospital Perola Byington*
RCTs	Randomized controlled trials
RWD	Real-world data
SUS	The Brazilian Public Healthcare System/Unified Health System

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