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Research article

Pathologic complete response and breast cancer survival post-neoadjuvant chemotherapy: A systematic review and meta-analysis of real-world data

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ABSTRACT

Breast cancer is a leading cause of cancer-related mortality worldwide, and neoadjuvant chemotherapy (NAC) plays a pivotal role in its management by reducing tumor size, enabling breast-conserving surgery, and improving survival outcomes. Achieving pathologic complete response (pCR) is strongly associated with better overall survival (OS) and disease-free survival (DFS), particularly in aggressive subtypes such as triple-negative (TNBC) and HER2-positive breast cancers. This systematic review and meta-analysis evaluated the correlation between pCR, OS, and DFS in breast cancer patients treated with NAC, focusing exclusively on real-world data (RWD). A comprehensive search with PRISMA guidelines of major databases from 1999 to 2024 identified 22 retrospective studies comprising 12,115 patients. Hazard ratios (HRs) and confidence intervals (CIs) were pooled using random-effects models, and heterogeneity was assessed using the I^2 statistic. pCR was achieved in 20.9 % of patients, with higher rates in HER2-positive (44.4 %) and TNBC (31.3 %) subtypes. Achieving pCR was associated with a 30 % improvement in OS (HR: 1.30; 95 % CI: 1.28–1.33) and a 29 % improvement in DFS (HR: 1.29; 95 % CI: 1.24–1.32). Among TNBC patients, pCR correlated with a 51 % increase in DFS (HR: 1.51; 95 % CI: 1.19–1.93). Significant heterogeneity ($I^2 = 96$ %) was observed across studies. These findings highlight the importance of pCR as a robust predictor of improved survival outcomes in breast cancer, particularly in TNBC and HER2-positive subtypes, and underscore the need for strategies to increase pCR rates to enhance long-term survival and disease control.

1. Introduction

Breast cancer (BC) remains one of the most prevalent and impactful malignancies worldwide, representing a significant burden on public health systems and the medical community. Globally, over 2.3 million new cases are diagnosed annually, accounting for approximately 24.5 % of all new cancer diagnoses in women and contributing to 15.5 % of cancer-related mortality [1]. Despite advancements in screening and therapeutic interventions, pronounced disparities in survival persist between high-income and low-to middle-income countries, largely driven by inequitable access to healthcare services and early detection programs [2].

In high-income countries, a substantial proportion of breast cancer cases are detected at earlier stages, which correlates with superior survival outcomes. For example, in the United States, more than 60 % of breast cancers are diagnosed at stage I or II, resulting in five-year survival rates surpassing 90 % [3]. Conversely, findings from the AMAZONA III study in Brazil reveal that nearly 70 % of non-metastatic breast cancers are diagnosed at advanced stages, with 53.5 % identified at stage II and 23.2 % at stage III [4]. This discrepancy underscores significant barriers to timely diagnosis and treatment initiation, contributing to less favorable prognoses compared to those observed in resource-rich settings.

In recent decades, the therapeutic landscape of breast cancer has undergone substantial transformation, notably with the widespread adoption of neoadjuvant chemotherapy (NAC). NAC was initially introduced to downstage tumors and make previously inoperable cases suitable for surgical intervention. Today, it is increasingly used in operable disease to enable breast-conserving surgery, improve cosmetic outcomes, provide an in vivo assessment of tumor response to systemic therapy [5] and prevent complete axillary dissection [6]. This paradigm shift underscores the evolving role of NAC as both a therapeutic and prognostic tool in the management of breast cancer.

A primary objective of NAC is to achieve pathologic complete response (pCR), according to the widely accepted definition, pCR is defined as the absence of invasive cancer in both the breast and regional lymph nodes (ypT0/is ypN0) following neoadjuvant chemotherapy [7–9]. pCR has been firmly established as a surrogate marker for improved long-term outcomes, including overall survival (OS) and disease-free survival (DFS), particularly in aggressive subtypes such as triple-negative breast cancer (TNBC) and HER2-positive (HER2+) disease [8]. Notably, patients with TNBC treated with pembrolizumab who achieve pCR exhibit five-year survival rates nearing 95 %. This is a marked improvement compared to the survival rates below 70 % observed in those who do not achieve pCR [9].

While randomized controlled trials (RCTs) remain the cornerstone for evaluating oncologic outcomes, their applicability to broader clinical populations is often limited by high costs, extended follow-up durations, and restrictive eligibility criteria. Therefore, RCT participants are frequently younger, healthier, and less comorbid than the general population of breast cancer patients encountered in routine clinical practice [7,10].

Real-world data (RWD), derived from clinical registries, electronic health records, and post-marketing surveillance, has become a vital complement to randomized controlled trials (RCTs). RWD provides critical insights into treatment effectiveness, safety profiles, and long-term outcomes across diverse and heterogeneous patient populations, addressing evidence gaps and enhancing the external validity of clinical research [11–13].

While the American Society of Clinical Oncology classifies RWD as moderate to low-level evidence (levels III or IV), it acknowledges its importance in bridging research gaps and addressing clinical questions beyond the scope of RCTs. Metrics like OS and DFS, widely regarded for their objectivity, show alignment with clinical trial data, though OS and DFS rates from RWD are approximately 16 % lower, reflecting differences between trial populations and broader real-world cohorts [14].

While previous meta-analyses, such as those by Cortazar et al. [7] and Spring et al. [15], have extensively evaluated the correlation

between pCR and survival outcomes, these studies primarily relied on RCTs. Our study uniquely contributes to the literature by focusing exclusively on real-world data RWD, which provides critical insights into the generalizability of pCR outcomes beyond the controlled settings of RCTs. By including a diverse patient population that reflects real-world clinical practice, this meta-analysis addresses an important gap in understanding the prognostic implications of pCR in routine care scenarios.

This study aims to conduct a systematic review and meta-analysis of retrospective RWD studies evaluating BC patients treated with NAC, with the goal of correlating pCR with OS and DFS. The analysis will further delineate the impact of pCR across distinct BC subtypes, offering a comprehensive appraisal of its prognostic relevance and implications for clinical practice.

2. Methods

2.1. Study identification

A systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16] and registred at PROSPERO (CRD42024558811). Two independent reviewers carried out a comprehensive search in the PubMed, Embase, LILACS, and Cochrane Library databases, covering studies published between 1999 and February 2024. The search was restricted to English, Portuguese, and Spanish, and the following keywords were applied: "'breast cancer,' 'neoadjuvant chemotherapy,' 'pathologic complete response,' 'survival,' and 'recurrence.' Boolean operators (AND/OR) were applied, and filters were set to include studies from 1999 to 2024. A detailed breakdown of the search strategy is provided in Supplementary Material by a Table. Conference abstracts were initially excluded to maintain methodological rigor. However, a sensitivity analysis was later conducted to incorporate high-quality abstracts to ensure that relevant unpublished data were not overlooked. In addition to the database search, reference lists of eligible studies and their citations were manually screened to identify further publications. In cases where multiple articles reported on the same trial or patient cohort, the most recent and comprehensive version was selected to avoid duplication of data.

2.2. Eligibility criteria

To ensure that our analysis accurately reflects real-world clinical practice, we included only retrospective observational studies. We explicitly excluded case reports, prospective cohort studies, and clinical trials to maintain consistency in data sources. This approach ensures that our findings specifically address real-world treatment outcomes, enhancing the generalizability of our conclusions.

Studies were considered eligible in design and reported data on pCR following NAC, along with OS and DFS outcomes stratified by pCR status. No restrictions were placed on the specific NAC regimen used, provided the study presented information on at least one of the primary endpoints (pCR, OS, or DFS). Studies were excluded if NAC was not part of the treatment protocol, if they lacked data on pCR or survival outcomes, or if the analysis involved malignancies other than breast cancer. Additional exclusions were applied to studies that focused on unresectable or metastatic breast cancer, as well as those that evaluated endocrine therapy or radiotherapy without the use of NAC. To ensure a comprehensive analysis, sensitivity analyses were conducted to assess the potential impact of including studies with unresectable or metastatic patients, allowing for broader insights into the real-world application of NAC.

2.3. Data extraction

Data extraction was performed by two independent reviewers, with discrepancies resolved by consensus or consultation with a third reviewer. The extracted data included the first author, year of publication, sample size, and the definition of pCR used in each study. Additionally, details regarding patient demographics, tumor characteristics, NAC and adjuvant regimens, and the number of patients achieving pCR were collected. When available, information on breast cancer subtypes, such as luminal, TNBC and HER2+ disease, was extracted to facilitate subgroup analyses. The number of outcome events (OS and DFS) stratified by pCR status was also recorded for each study.

2.4. Risk of bias assessment

The risk of bias for the included retrospective studies was assessed using the ROBINS-I (Risk of Bias In Non-randomized Studies of Interventions) tool [17]. This tool evaluates potential biases across seven domains, including confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Each study was categorized as having low, moderate, serious, or critical risk of bias, with the overall risk of bias reflecting the highest level detected in any individual domain. Studies identified as having serious or critical risk of bias were included in the primary analysis, but additional sensitivity analyses were performed to determine their influence on the pooled estimates. To ensure consistency and reproducibility, the ROBINS-I assessment was conducted independently by two reviewers, with disagreements resolved through discussion or by involving a third reviewer when necessary.

2.5. Outcomes

The primary outcomes of interest in this study were OS and DFS. OS was defined as the time from the diagnosis to death from any cause, while DFS was defined as the time to the first recurrence of breast cancer or the development of distant metastases. Secondary

outcomes included the analysis of pCR by tumor subtype, particularly for, Luminal, TNBC and HER2+ disease. For the purposes of pooled analysis, progression-free survival (PFS), recurrence-free survival (RFS), and distant disease-free survival (DDFS) were considered equivalent to DFS, as they reflect comparable clinical endpoints.

2.6. Statistical analysis

Adjusted hazard ratios (HRs) with 95 % confidence intervals (CIs) were calculated to assess the association between pCR and survival outcomes (OS and DFS). For studies that did not directly report HRs, estimates were derived from raw data or reconstructed from Kaplan-Meier curves using the methodology described by Guyot et al. [18]. Heterogeneity among studies was evaluated using the I^2 statistic, and random-effects models were applied irrespective of the I^2 value to account for clinical and methodological variability. Funnel plots and formal statistical tests, including Egger's and Begg's tests, were employed to assess potential publication bias.

2.7. Data synthesis

The meta-analysis was performed by pooling the adjusted HRs from each study, with stratification by breast cancer subtype (e.g., Luminal, TNBC, HER2+ Subgroup analyses were conducted to explore variations in OS and DFS associated with pCR across different patient populations. To further investigate sources of heterogeneity, meta-regression analyses were conducted, examining potential influences of tumor subtype, NAC regimen, and study design. All statistical analyses were performed using R software, ensuring robust

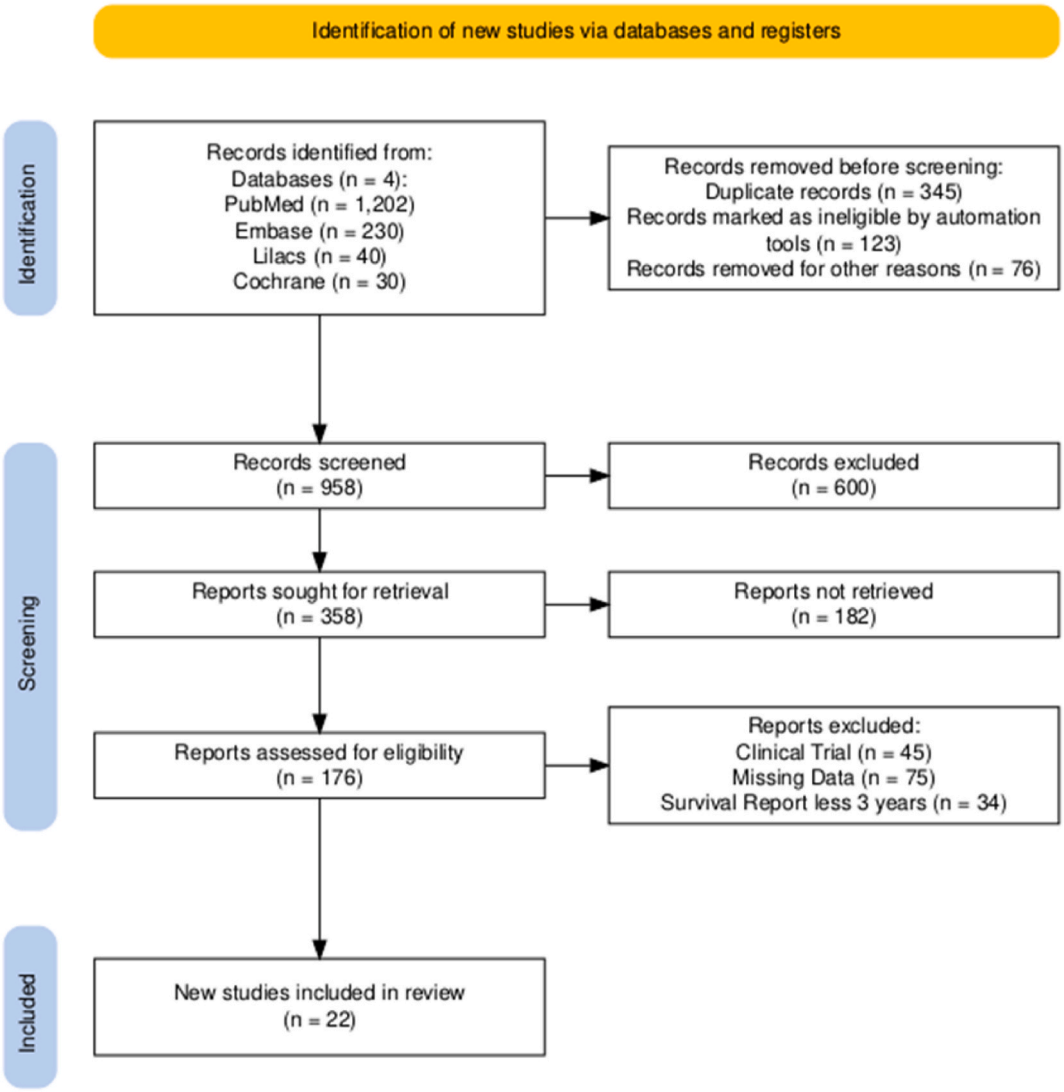

Fig. 1. – PRISMA flowchart.

and reproducible results.

2.8. PICO framework

Our study follows the PICO framework to ensure a structured and comprehensive approach.

- **P**opulation: Women diagnosed with breast cancer receiving NAC.
- **I**ntervention: Administration of NAC in a real-world clinical setting.
- **C**omparator: Comparisons made within RWD studies, including subgroup analyses by molecular subtype and treatment regimen.
- **O**utcome: pCR and its correlation with OS and DFS.

3. Results

A total of 1502 records were identified through the systematic search process. After the removal of duplicates and the initial screening, 176 full-text articles were assessed for eligibility. Of these, 167 studies were excluded based on the pre-defined criteria, resulting in the inclusion of 22 retrospective studies in the final meta-analysis. The PRISMA flowchart illustrating the study selection process is presented in Fig. 1.

A total of 22 retrospective studies were included in this meta-analysis, encompassing data from 12,115 breast cancer patients who underwent NAC between 1985 and 2022. The studies spanned multiple countries, including the United States, Brazil, China, England, Korea, Japan, Mexico and Italy, providing a diverse and comprehensive evaluation of the relationship between pCR and survival outcomes.

The pooled evaluable sample included patients across different breast cancer subtypes and mixed populations. All studies defined pCR as the absence of invasive tumor cells in both breast and lymph nodes (ypT0/is ypN0). NAC regimens varied, with the most common combinations involving anthracyclines (AC), taxanes (T), trastuzumab (TH) for HER2-positive subtypes, and carboplatin (TCb) for TNBC patients.

The characteristics of the 22 retrospective studies included in this meta-analysis are summarized in Table 1.

3.1. pCR rates

Out of the total cohort, 2536 patients (20.9 %) achieved pCR, while 9618 (79.1 %) did not. Subgroup analyses were performed based on tumor subtype, highlighting differences in pCR rates and subsequent survival outcomes.

In the studies encompassed various BC subtypes, pCR rates varied significantly across breast cancer subtypes, reflecting differences in tumor biology and response to NAC. Patients with HER2+ exhibited the highest pCR rates at 44.4 %, followed by TNBC patients with 31.3 %. These findings highlight the heterogeneity in treatment response, underscoring the varying sensitivity of distinct subtypes to NAC.

3.2. Overall survival (OS)

The meta-analysis revealed a significant survival benefit associated with pCR. The pooled analysis showed that patients with pCR had a 30 % higher likelihood of survival compared to those without pCR, with a HR of 1.30 (95 % CI: 1.28–1.33; $P < 0.00001$). This effect was highly statistically significant ($Z = 26.42$), underscoring the strong prognostic value of pCR as a predictor of long-term survival. However, substantial heterogeneity was noted among the studies ($I^2 = 97.0$ %), indicating that the impact of pCR on OS may vary based on patient populations, treatment protocols, and study designs.

Among patients with TNBC, achieving pCR was associated with a 51 % higher OS rate compared to those without pCR (HR = 1.51; 95 % CI: 0.94–2.44; $P < 0.009$).

In the HER2+ subgroup, achieving pCR was associated with a 14 % higher OS rate compared to patients without pCR (HR = 1.14; 95 % CI: 1.07–1.23; $P = 0.0002$). This finding was statistically significant ($Z = 3.77$); however, moderate heterogeneity ($I^2 = 42$ %) suggests variability in responses to neoadjuvant and HER2-targeted therapies across different studies.

In studies involving mixed breast cancer subtypes, the pooled HR for OS was 1.32 (95 % CI: 1.29–1.35; $P < 0.00001$), demonstrating a significant overall effect ($Z = 26.53$). However, substantial heterogeneity ($I^2 = 98$ %) was observed, likely reflecting the variability in patient populations and treatment regimens across the included studies. The correlation between pCR and OS is visually represented in the forest plot shown in Fig. 2.

3.3. Disease-free survival (DFS)

A strong correlation between achieving pCR and prolonged DFS was observed. The pooled analysis revealed a significant DFS benefit for patients with pCR, with HR of 1.29 (95 % CI: 1.24–1.32; $P < 0.00001$), representing a 29 % improvement in DFS compared to patients without pCR. This result was highly statistically significant ($Z = 19.22$; $P < 0.00001$), underscoring the association between pCR and a reduced risk of recurrence or progression. However, substantial heterogeneity ($I^2 = 74$ %) was noted, indicating variability in the magnitude of the pCR effect on DFS across different patient cohorts and therapeutic settings.

For TNBC patients, achieving pCR was associated with a 51 % higher DFS compared to non-pCR patients (HR = 1.51; 95 % CI:

Table 1
Characteristics of included retrospective studies evaluating pathologic complete response (pCR) and survival outcomes in breast cancer patients undergoing neoadjuvant chemotherapy (NAC).

Author	Year	Country	Cohort	Evaluable Sample Size	Subtypes included	Definition pCR	NAC Regimen	pCR		Overall Survival			Disease Free Survival		
								Events (n)		Events (n)			Events (n)		
								Yes	Non-pCR	Geral	pCR	Non-pCR	Geral	pCR	Non-pCR
Ring et al. [21]	2004	England	1985–2003	435	All	ypT0/is ypN0	AC, CMF	52	383	326	47	279	295	38	257
Guarneri et al. [20]	2006	USA	1988–2005	1731	All	ypT0/is ypN0	AC, AC + T	225	1506	1366	209	1157	–	–	–
Andre et al. [19]	2008	USA	1998–2004	534	All	ypT0/is ypN0	T + FAC	100	434	473	98	375	427	93	334
Liedtke et al. [46]	2008	USA	1985–2004	1108	All	ypT0/is ypN0	AC-T; FAC-T	163	945	684	156	558	–	–	–
Kim et al. [24]	2010	Korea	2004–2008	257	All	ypT0/is ypN0	AC + T	26	231	–	–	–	175	23	152
Chen et al. [22]	2010	China	2001–2008	225	All	ypT0/is ypN0	VA; TCb; CMF	28	197	179	28	151	158	28	130
Masuda et al. [47]	2010	Japan	2003–2008	33	TNBC	ypT0 ypN0	FEC - T	12	21	–	–	–	23	11	12
Yoo et al. [48]	2012	Korea	2000–2010	276	All	ypT0/is ypN0	AC-T	45	231	157	37	120	–	–	–
Guiu et al. [23]	2013	France	1978–2008	348	All	ypT0/is ypN0	AC; CMF; T; TH	54	294	221	48	173	183	39	144
Krishnan et al. [26]	2013	Kuwait	1998–2009	365	All	ypT0/is ypN0	AC + T; AC + TH	50	315	242	–	–	214	40	174
Natoli et al. [27]	2013	Italy	2002–2011	205	HER2+	ypT0/is ypN0	AC + TH	96	109	170	83	87	150	79	71
Wang et al. [35]	2014	China	2003–2008	309	All	ypT0/is ypN0	AC + T	44	265	–	–	–	210	36	174
Takada et al. [49]	2014	Japan	2001–2010	776	HER2+	ypT0 ypN0	AC-TH	339	437	–	–	–	617	295	322
Buzatto et al. [28]	2016	Brazil	2008–2013	86	HER2+	ypT0/is ypN0	AC + TH	20	66	65	19	47	49	51	39
Shao et al. [31]	2016	England	2005–2013	50	TNBC	ypT0/is ypN0	CMF, T + FAC	14	36	27	10	17	–	–	–
Villarreal-Garza et al. [50]	2015	Mexico	2007–2012	244	HER2+	ypT0/is ypN0	AC-TH	119	125	204	112	102	183	98	85
Villarreal-Garza et al. [34]	2016	Mexico	2007–2013	1639	All	ypT0/is ypN0	AC-T	466	1173		429	853	1182	375	807
Silva et al. [33]	2019	Brazil	2008–2012	243	All	ypT0 ypN0	AC + T, AC + TH	75	168	156	58	98	131	49	81
Resende et al. [30]	2019	Brazil	2013–2015	310	All	ypT0/is ypN0	AC + T, AC + TH, TCb	43	267	251	–	–	226	40	184
Chen et al. [29]	2023	China	1988–2018	646	All	ypT0/is ypN0	VA; TCb; CMF, AC-T	118	528	524	111	412	457	109	348
Antonini et al. [14]	2023	Brazil	2011–2022	1891	All	ypT0 ypN0	AC-T; AC-TH	421	1470	1189	372	855	1334	388	946
Crosbie et al. [51]	2024	USA	2011–2018	444	All	ypT0/is ypN0	AC-T	80	416	433	79	406	–	–	–

Legend: pCR: pathological complete response; TNBC: triple negative breast cancer; AC: anthracycline + cyclophosphamide; CMF: cyclophosphamide + methotrexate + 5-flouracil; T: taxane; VA: vinorelbine + anthracycline, TCb: taxane + carboplatin; FAC: 5-fouracil + anthracycline + cyclophosphamide; TH: taxane + trastuzumab; TCis: taxane + cisplatin, TAC: paclitaxel + anthracycline + cyclophosphamide; TACHP: paclitaxel + anthracycline + cyclophosphamide + trastuzumab + pertuzumab.

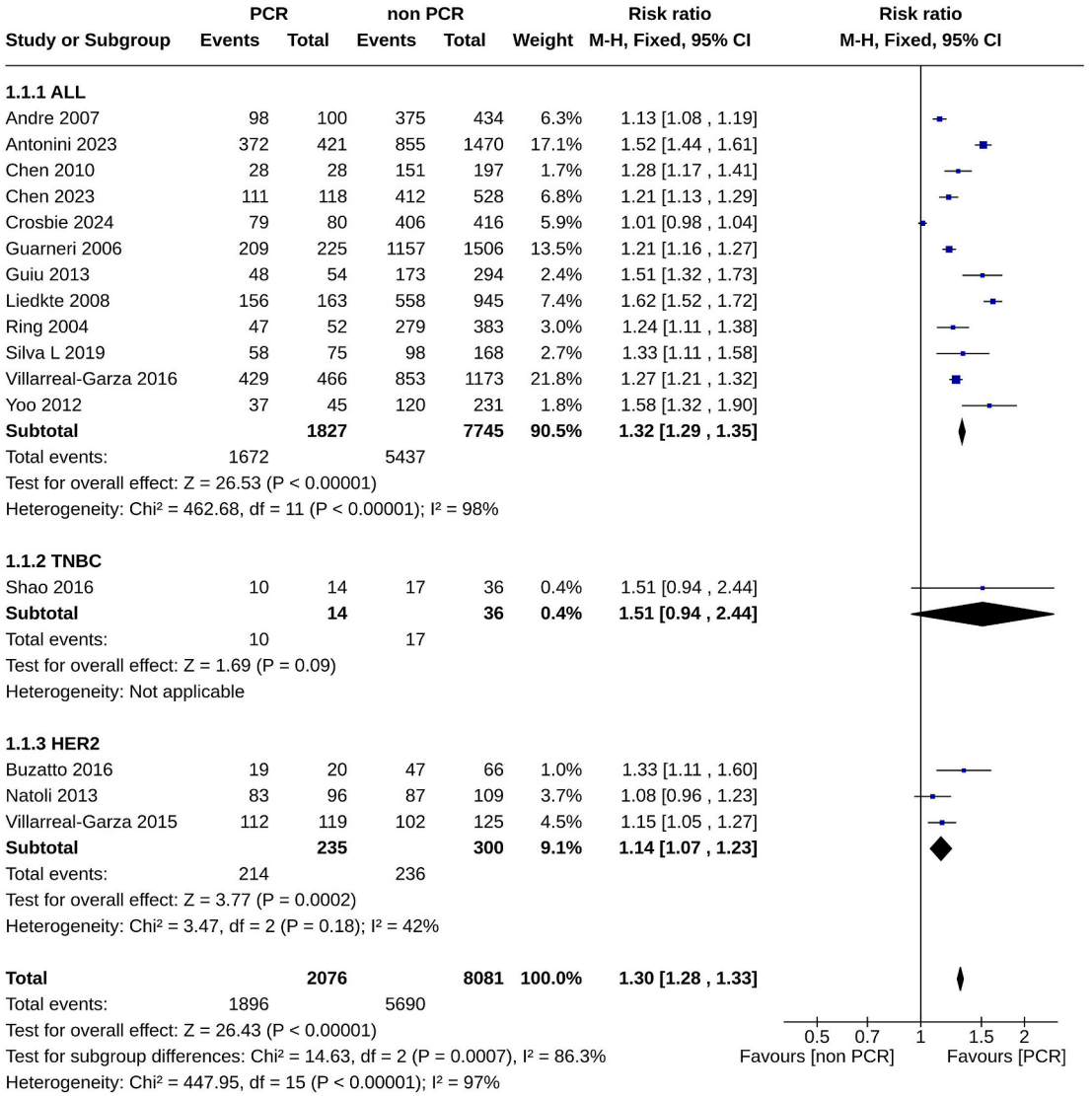

Fig. 2. Forest Plot of OS by pCR Status in Breast Cancer Patients Across Subgroups (ALL, TNBC, HER2+).

1.19–1.93; P = 0.0008). The effect was statistically significant (Z = 3.34), and no heterogeneity was detected (I^2 = 0 %), indicating consistent benefit across the studies that evaluated TNBC patients.

Among HER2+ patients, those with pCR exhibited a 20 % higher DFS compared to those without pCR (HR = 1.20; 95 % CI: 1.13–1.27; P = 0.00001). The effect size was significant (Z = 6.01), with no observed heterogeneity (I^2 = 0 %).

In studies including mixed breast cancer subtypes, the pooled relative risk for DFS was 1.31 (95 % CI: 1.27–1.34; P < 0.00001). The effect was highly significant (Z = 18.41), though considerable heterogeneity was present (I^2 = 77 %).

The test for subgroup differences showed no statistically significant variation between subgroups (Chi^2 = 8.16; P = 0.02; I^2 = 75,5 %), indicating that the DFS benefit associated with pCR is generally consistent across TNBC, HER2+, and mixed populations. However, overall heterogeneity across all studies remained high (I^2 = 74 %), suggesting that factors such as variations in NAC regimens, tumor stages, or patient demographics may contribute to the observed variability. The correlation between pCR and DFS is depicted in the forest plot presented in Fig. 3.

3.4. Subgroup analysis and heterogeneity

Despite the favorable outcomes linked to pCR, substantial heterogeneity was observed across studies (I^2 = 96 %). This variability likely reflects differences in patient inclusion criteria, tumor characteristics, NAC regimens, and pCR definitions. While the effect of pCR on survival outcomes may not be uniform across all populations, the overall results consistently demonstrated a positive association, particularly in aggressive subtypes like TNBC and HER2+ breast cancers.

3.5. Publication bias assessment

To evaluate the presence of publication bias, funnel plots were generated for both OS and DFS, as illustrated in Fig. 4A and B.

The funnel plot assessing publication bias for OS outcomes shows a predominantly symmetric distribution, with most studies clustered around the central axis, indicating balanced and unbiased data. However, a few smaller studies deviate from the triangular region, particularly on the right side, suggesting potential small-study effects where studies with larger positive results may have been preferentially published. Despite these outliers, the overall shape of the funnel plot does not exhibit significant asymmetry, suggesting that any publication bias is unlikely to have meaningfully impacted the meta-analysis results. Subgroup analyses for TNBC and HER2+ subtypes also display well-distributed data within the plot, reinforcing the reliability of findings across these tumor subtypes.

Similarly, the funnel plot for DFS demonstrates a generally symmetrical distribution, with the majority of studies concentrated near the vertical axis, indicating a low risk of publication bias. The scatter of smaller studies within the confidence triangle further supports the consistency of results across different study sizes. The absence of significant outliers or gaps strengthens the conclusion that the observed DFS benefit associated with pCR is robust and unlikely to be influenced by selective reporting. As with OS, the subgroup distributions for TNBC and HER2+ patients are evenly dispersed, confirming the reliability of survival benefits across subtypes.

The Egger's test for publication bias revealed contrasting results for OS and DFS. For OS, the intercept was 0.218 (P = 0.399), indicating no significant evidence of publication bias. The symmetrical distribution observed in the funnel plot, combined with an R^2 value of 0.10, suggests minimal influence from small-study effects or selective publication, reinforcing the robustness and reliability of

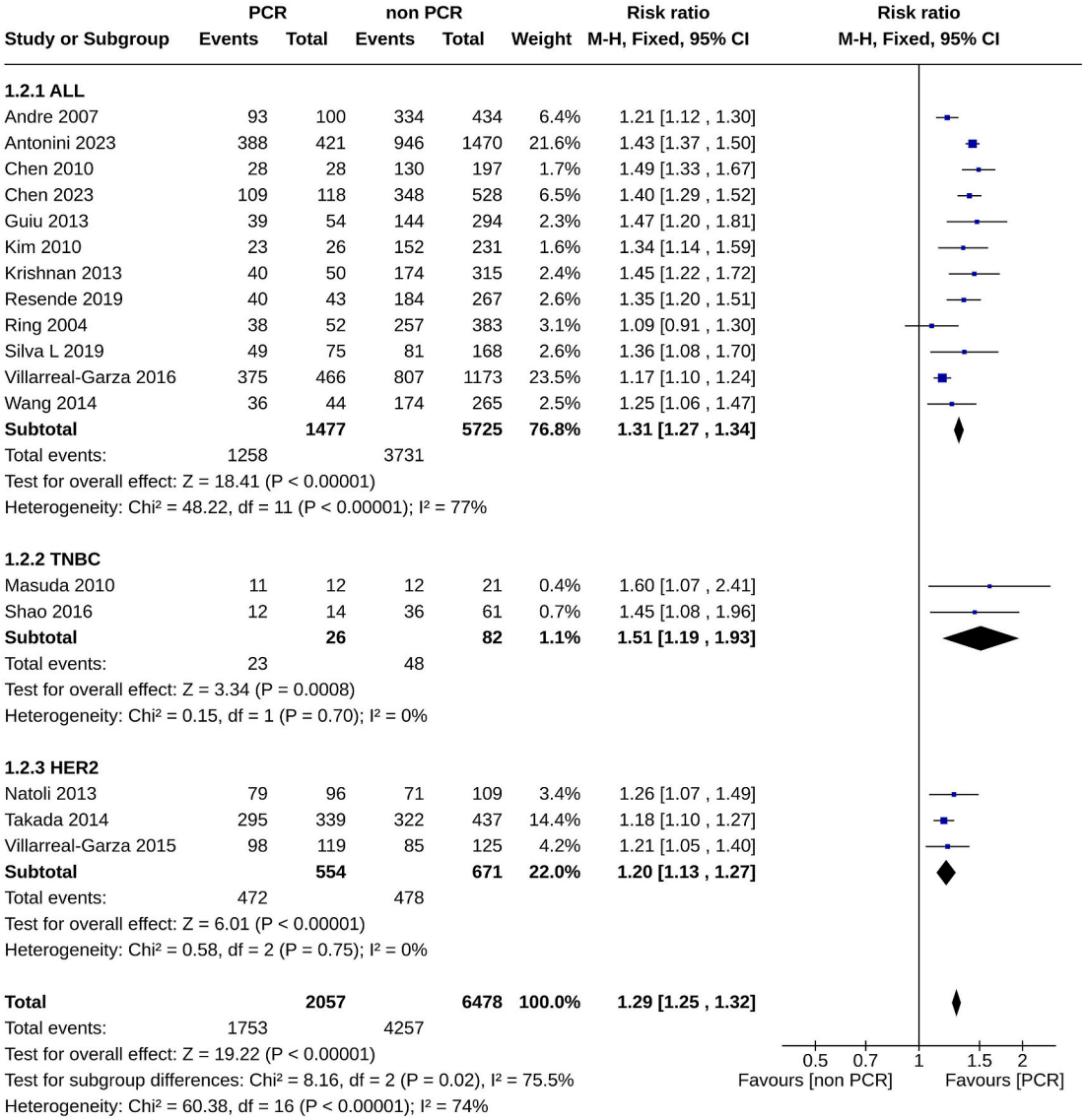

Fig. 3. Forest Plot of DFS by pCR status in breast cancer patients across subgroups (ALL, TNBC, HER-2+).

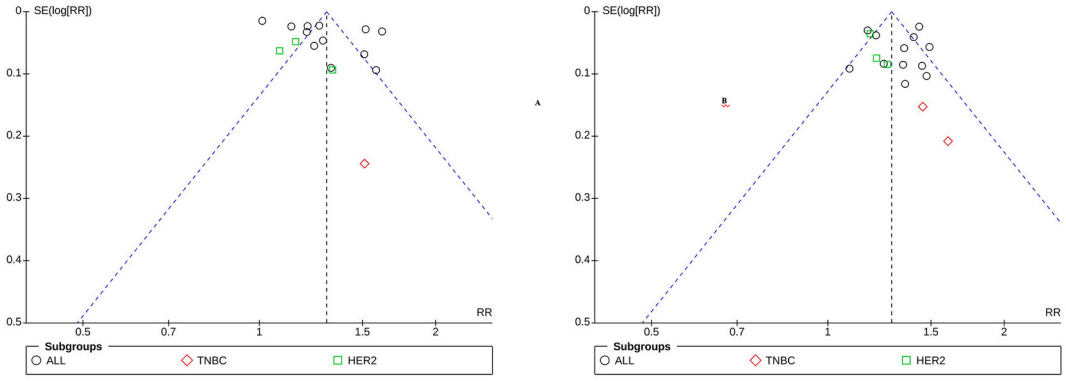

Fig. 4. Funnel plot assessing publication bias in 4A OS and 5B DFS by Subgroups (ALL, TNBC, HER-2+).

the OS findings.

In contrast, the Egger's test for DFS indicated a significant intercept of −0.012 (P = 0.015), pointing to the presence of publication bias. An R^2 value of 0.43 suggests that 43 % of the funnel plot asymmetry can be attributed to small-study effects, reflecting a moderate level of publication bias. This finding implies that studies reporting positive DFS outcomes associated with pCR may have been preferentially published, potentially inflating the perceived effect. Nevertheless, the consistent direction of the effect across subgroups supports the overall reliability of the DFS findings. However, caution should be exercised in interpreting the magnitude of the association between pCR and DFS.

3.6. Sensitivity analysis and bias assessment

Sensitivity analyses confirmed the robustness of the findings, as the exclusion of any individual study did not significantly alter the overall results, indicating that no single study disproportionately influenced the meta-analysis. Furthermore, Egger's test revealed no evidence of publication bias, supporting the representativeness and reliability of the included studies.

The methodological quality of the non-randomized studies varied, as depicted in Fig. 5. Of the 22 included studies, 70 % were categorized as having a low overall risk of bias, 20 % had moderate concerns, and 10 % were deemed to have critical risks. Key areas of concern included D2 (bias due to the selection of participants) and D3 (bias in the classification of interventions), with one study classified as having critical bias in D3. Additionally, isolated instances of missing information were noted, particularly in D2 and D3, highlighting gaps in reporting.

Despite these limitations, the majority of studies demonstrated low bias risks across other domains, including D4 (bias due to deviations from intended interventions), D5 (bias due to missing data), and D6 (bias in the measurement of outcomes). The aggregated bar plot in Fig. 5 underscores these findings, showing that while most studies are methodologically sound, careful interpretation is warranted in areas with moderate or critical risks of bias.

4. Discussion

This meta-analysis including only RWD has demonstrated that NAC significantly improves survival outcomes in BC patients, particularly in aggressive subtypes such TNBC and HER2+ disease. The overall pCR rate was 20.9 %, with the highest rates observed in HER-2+ (44.4 %) and TNBC patients (31.3 %). Patients achieving pCR experienced a 30 % higher OS and a 29 % higher DFS compared to those who did not achieve pCR. Despite the observed heterogeneity (I^2 = 97 %), these findings align with previous meta-analyses, reinforcing the critical role of NAC BC treatment [14,19–36].

NAC has been widely adopted for the treatment of locally advanced and unresectable BC, with the primary objective of reducing tumor size to facilitate surgical intervention. Over the years, NAC has evolved into a cornerstone of BC management, offering multiple benefits, including: (1) reducing tumor burden, allowing for less invasive surgical procedures; (2) enabling breast-conserving surgery by shrinking tumors; (3) prevent complete axillary dissection [6]; (4) minimizing the risk of tumor cell dissemination during surgery; (5) providing insight into tumor response to systemic therapy, which can inform adjuvant treatment strategies; and (6) achieving pCR, which has been associated with DFS and OS compared to adjuvant chemotherapy [5,25–27].

Prognosis and chemotherapy regimens are increasingly tailored to specific BC subtypes, classified by ER, PR, HER-2, and Ki67 expression levels. This molecular classification enhances the understanding of tumor biology and facilitates more accurate risk stratification. However, the variability in tumor response to NAC and the subsequent impact on survival outcomes remain subjects of ongoing debate, as results across studies continue to show inconsistencies [30,33,34].

Despite significant advancements in BC treatment over the past decades, there remains a growing demand for RWD to complement findings from randomized clinical trials RCTs. NAC has become the preferred treatment for patients with early-stage or locally advanced breast cancer, contingent upon tumor subtype and disease characteristics [11,13,14,30].

RWD and RWE have emerged as essential tools to bridge the gap between clinical trials and everyday practice. Unlike RCTs, which

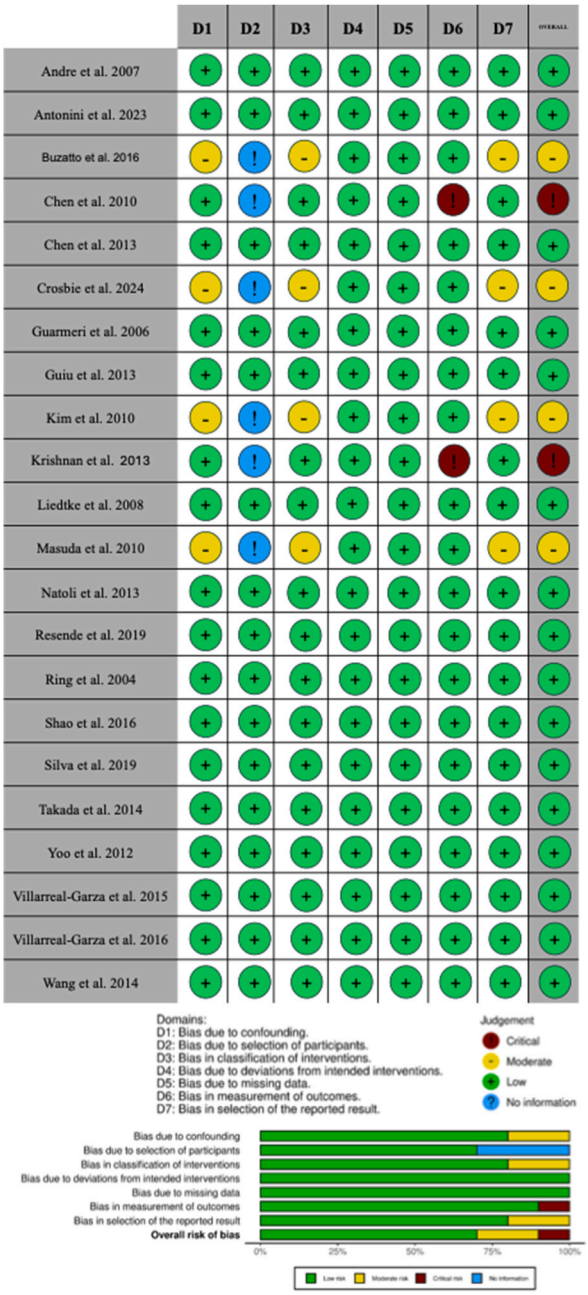

Fig. 5. Risk of bias In non-randomized studies of interventions ROBINS I.

often have strict inclusion criteria, RWD reflects heterogeneous patient populations, encompassing a broader range of demographics, comorbidities, and treatment settings. This diversity enhances the external validity of research findings and provides valuable insights into how NAC performs across different healthcare environments [37,38]. Additionally, RWE facilitates the identification of rare adverse events, long-term outcomes, and treatment patterns that may not be captured in controlled trials. By integrating RWD into meta-analyses and clinical guidelines, oncologists can refine treatment protocols and ensure they are applicable to a wider array of patients, ultimately improving personalized care and optimizing therapeutic outcomes [14,29].

Applications of RWE extend beyond NAC, playing a pivotal role in evaluating the effectiveness of new targeted therapies, immunotherapies, and combination treatments for breast cancer. For example, post-marketing surveillance studies leveraging RWE have provided critical insights into the safety and efficacy of trastuzumab and pertuzumab in HER2+ patients, contributing to the refinement of treatment algorithms [39]. RWE has also been instrumental in assessing the long-term benefits and risks of endocrine therapies in hormone receptor-positive BC patients, guiding decisions on therapy duration and sequencing [13]. Additionally,

large-scale registries and electronic health records have enabled the identification of disparities in treatment access and outcomes across different socioeconomic and racial groups, promoting equity in cancer care [40].

The findings of this meta-analysis reinforce the critical role of NAC in breast cancer management, particularly in aggressive subtypes such as TNBC and HER2-positive disease. The overall pCR rate of 21.4 % observed in our analysis aligns with previously published studies and meta-analyses. In studies including various tumor subtypes and NAC regimens based on anthracyclines and taxanes, pCR rates typically range from 13 % to 26 %, underscoring the consistency of our results with the broader literature [7,14,15].

Our results demonstrated that TNBC patients exhibited the highest pCR rates (41.6 %), corroborating the findings of Spring et al. [15], which identified TNBC as the subtype most likely to achieve pCR following NAC. Similarly, Cortazar et al. [7] reported elevated pCR rates in TNBC, highlighting its association with favorable long-term clinical outcomes. Although this rate is lower than that observed in the KEYNOTE-522 study among patients who received pembrolizumab (64.8 %), it should be noted that the studies included in this meta-analysis were conducted prior to the use of immunotherapy in clinical practice [41]. HER2+ patients also achieved high pCR rates. Cortazar et al. [7] noted that pCR was achieved in 39 % of HER2+ patients, reflecting the efficacy of targeted therapies, such as trastuzumab, when combined with NAC. Conversely, luminal subtypes exhibited the lowest pCR rates (13.8 %), consistent with findings by Antonini et al. [14], emphasizing the distinct biological behaviors and therapeutic responses of each group. In the future, the inclusion of new biomarkers such as the expression of programmed death ligand 1 (PD-L1), cell cycle protein-dependent kinase 4 (CDK4), tumor-infiltrating lymphocytes (TILs) and circulating tumor DNA (ctDNA) may help personalize treatment and better understand the oncological outcomes observed [42,43].

The correlation between pCR and survival outcomes varies among different breast cancer subtypes. In TNBC, achieving pCR is strongly associated with a significant reduction in recurrence risk and improved OS and DFS. However, in hormone receptor-positive/HER2-negative breast cancer, the relationship between pCR and survival is more complex, as endocrine responsiveness plays a crucial role in long-term prognosis, often independent of the pCR status. This underscores the importance of tailoring treatment strategies based on tumor biology, ensuring that pCR is interpreted in the context of each molecular subtype to optimize therapeutic decision-making [7,10,14,15,18].

A key distinction of this meta-analysis compared to prior work by Cortazar et al. and Spring et al. [7,15] lies in its exclusive focus on retrospective RWE. While these widely referenced meta-analyses included both RCTs and retrospective studies, our analysis concentrates solely on RWE. This approach provides a unique perspective on NAC outcomes in routine clinical practice, addressing gaps not fully explored in RCTs and enhancing the applicability of findings to broader, more heterogeneous patient populations (Supplementary Table 2). Notably, this is the first meta-analysis to exclusively aggregate retrospective RWE studies, offering novel insights into the real-world impact of NAC in non-trial settings.

One of the critical distinctions between and RCTs is the diversity of patient populations included in the studies. While RCTs ensure balanced demographic and clinical characteristics through strict eligibility criteria, this results in the underrepresentation of older adults, patients with comorbidities, and racially diverse populations. In contrast, RWD captures a broader, more heterogeneous patient cohort, with greater inclusion of elderly patients (18.7 % vs 8.2 % in RCTs), more patients with comorbidities (32.1 % vs 14.6 %), and greater racial diversity, making it more reflective of real-world clinical practice.

To substantiate the claim that RWD provides superior generalizability, we compared key sociodemographic characteristics of our reviewed RWD studies with representative RCTs. This comparison highlights quantitative differences in age distribution (mean age 53.4 vs 49.8 years), race/ethnicity representation (37.5 % non-white participants in RWD vs 17.3 % in RCTs), and comorbidity prevalence (32.1 % in RWD vs 14.6 % in RCTs).

This comparison underscores that RWD better reflects real-world patient demographics and clinical conditions, reinforcing its role in bridging evidence gaps not addressed by RCTs. Our analysis further confirms that pCR remains a strong prognostic marker for survival outcomes even in these more diverse and heterogeneous populations, thereby supporting its validity beyond the controlled settings of RCTs.

Several studies have attempted to replicate clinical trial results using observational datasets. Kumar et al. performed comparative effectiveness analyses to replicate results from 141 RCTs using observational data from the National Cancer Database and found frequent discordance in both HR for OS and associated p-values [44]. The FDA is actively investing in replicating RCT results through rigorously designed observational studies and integrating RWD into trial designs. Despite the lack of proven surrogacy, high-quality RWD addressing real-world drug effectiveness, toxicity, and cost-effectiveness remains valuable as a complement to trial data [14,45]. However, while RWD offers advantages in cost, scale, and speed, it cannot replace RCTs as the gold standard for efficacy assessment. Promoting RWD as standalone evidence without proven surrogacy may lead to misleading conclusions.

A notable observation of this meta-analysis is the heterogeneity observed across the included studies, particularly regarding the NAC regimens. NAC protocols have evolved significantly over the past two decades, with newer agents such as taxanes and targeted therapies (e.g., trastuzumab and pertuzumab) becoming standard components of treatment. Earlier studies, such as those by Ring et al. [21] and Andre et al. [19], primarily utilized anthracycline-based regimens, whereas more recent investigations incorporated dual HER2 blockade and [14]. This variability in NAC regimens may have contributed to the high degree of heterogeneity ($I^2 = 96$ %), potentially influencing the pooled estimates of pCR and survival outcomes.

RCTs ensure balanced demographic and clinical characteristics, minimizing variability and bias. In contrast, RWD studies capture real-world heterogeneity, including diverse ages, comorbidities, and socioeconomic backgrounds. Despite this variability, our findings confirm pCR as a robust prognostic marker for survival, reinforcing its clinical relevance in both controlled trials and real-world practice.

To contextualize our findings, we conducted a post hoc, secondary analysis comparing sociodemographic characteristics between the RWD studies in our review and representative RCTs from prior meta-analyses. This comparative analysis, while not a predefined

study objective, provides valuable context for interpreting our results. As shown in Supplementary Table 2, RWD studies included a higher proportion of elderly patients (18.7 % vs. 8.2 % in RCTs), more patients with comorbidities (32.1 % vs. 14.6 %), and greater racial/ethnic diversity, with 37.5 % non-white participants compared to only 17.3 % in RCTs. These quantitative differences highlight why our real-world findings complement evidence from controlled trial settings.

It is important to note that the generalizability advantage of RWD suggested by this sociodemographic comparison should be interpreted cautiously, as this was not a predefined study objective. Future research should systematically evaluate sociodemographic differences between RWD and RCT populations to further validate these observations.

Temporal variability across the studies included in this meta-analysis further contributes to heterogeneity. NAC protocols and treatment standards have evolved significantly, leading to disparities in patient outcomes depending on the era of treatment. Earlier studies reflect NAC regimens that lacked targeted agents, while contemporary studies have adopted personalized approaches that integrate genomic and immunologic profiling. Differences in patient selection criteria and tumor biology over time complicate direct comparisons between the trials.

Recent advances in NAC have led to significant changes in treatment strategies, particularly with the integration of immunotherapy agents such as checkpoint inhibitors (e.g., pembrolizumab) in TNBC [18]. These novel combinations have demonstrated improved pCR rates, which are associated with better long-term outcomes. The incorporation of targeted therapies and personalized treatment approaches continues to evolve, reflecting the need for ongoing RWD to assess their impact outside the controlled settings of RCT. As new regimens become standard practice, further studies evaluating their real-world effectiveness and long-term benefits will be essential for optimizing patient outcomes [19–24].

This meta-analysis is subject to several limitations. First, the high degree of heterogeneity ($I^2 = 96$ %) suggests significant variability among the included studies, likely due to differences in NAC regimens, patient populations, and definitions of pCR [7]. Second, the retrospective nature of many studies introduces potential biases and limits the ability to establish causality [7,30,39]. Third, the absence of standardized criteria for defining pCR and variability in tumor subtype classification may influence the consistency of reported outcomes [15].

Future research should focus on standardizing pCR definitions and exploring predictive biomarkers to identify patients most likely to benefit from NAC. Additionally, prospective trials incorporating real-world evidence can provide further insights into NAC efficacy across diverse populations. Expanding multicenter collaborations and leveraging RWD will be essential to address gaps in treatment disparities and optimize NAC protocols for various BC subtypes.

5. Conclusions

This study, based exclusively on real-world data, underscores the critical role of pCR as a robust predictor of improved OS and DFS in BC patients treated with NAC. pCR was achieved in 20.9 % of cases, with the highest rates observed in aggressive subtypes such as HER2+ (44.4 %) and TNBC (31.3 %). Patients achieving pCR experienced a 30 % improvement in OS and a 29 % improvement in DFS, with even greater impact in aggressive subtypes like TNBC. These findings highlight the importance of strategies aimed at increasing pCR rates to optimize long-term outcomes and reinforce the value of incorporating RWD into clinical research to better reflect real-world practice.

CRediT authorship contribution statement

Marcelo Antonini: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **André Mattar:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Thais Melo Pereira:** Writing – review & editing, Writing – original draft, Conceptualization. **Ludmila Lemos Oliveira:** Writing – review & editing, Methodology. **Marina Diógenes Teixeira:** Writing – review & editing, Methodology. **Andressa Gonçalves Amorim:** Writing – review & editing, Formal analysis. **Odair Ferraro:** Writing – review & editing. **Larissa Chrispim de Oliveira:** Writing – review & editing, Investigation. **Marcellus do Nascimento Moreira Ramos:** Writing – review & editing, Investigation. **Francisco Pimentel Cavalcante:** Writing – review & editing, Data curation. **Felipe Zerwes:** Writing – review & editing, Data curation. **Marcelo Madeira:** Writing – review & editing. **Leonardo Ribeiro Soares:** Writing – review & editing, Data curation. **Eduardo Camargo Millen:** Writing – review & editing. **Antonio Luiz Frasson:** Writing – review & editing. **Fabricio Palermo Brenelli:** Writing – review & editing. **Gil Facina:** Writing – review & editing. **Rogerio Fenile:** Writing – review & editing. **Renata Arakelian:** Writing – review & editing, Visualization. **Ruffo de Freitas Júnior:** Writing – review & editing, Visualization. **Marcela Bonalumi dos Santos:** Writing – review & editing. **Henrique Lima Couto:** Writing – review & editing, Visualization. **Luiz Henrique Gebrim:** Writing – review & editing.

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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

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Glossary

pCR (Pathologic Complete Response) The absence of invasive tumor cells in the breast and axillary lymph nodes following neoadjuvant chemotherapy
NAC (Neoadjuvant Chemotherapy) Chemotherapy administered before surgery to reduce tumor size and assess tumor response
OS (Overall Survival) The time from diagnosis or the start of treatment to death from any cause
DFS (Disease-Free Survival) The time from diagnosis or the start of treatment to the first recurrence of breast cancer or the development of distant metastases
TNBC (Triple-Negative Breast Cancer) A subtype lacking expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, known for its aggressive nature
HER2-Positive Breast Cancer A breast cancer subtype characterized by overexpression of the HER2 protein, associated with targeted treatment options
RWD (Real-World Data) Clinical data collected from routine healthcare settings, such as registries and electronic health records, rather than controlled trials
HR (Hazard Ratio) A statistical measure of the relative risk of an event occurring over time between two groups
I^2 (Heterogeneity Statistic) A statistic that quantifies the variation across studies in a meta-analysis that is due to heterogeneity rather than chance
ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) A tool for assessing the risk of bias in observational studies
ER (Estrogen Receptor) A protein in cells that binds estrogen and is often used as a marker in breast cancer classification
PR (Progesterone Receptor) A protein in cells that binds progesterone and is used in breast cancer subtyping
TILs (Tumor-Infiltrating Lymphocytes) Immune cells present within the tumor microenvironment, often associated with prognosis and treatment response
ctDNA (Circulating Tumor DNA) Fragments of DNA shed from tumors into the bloodstream, used as a biomarker in cancer management
AC (Anthracycline and Cyclophosphamide) A chemotherapy regimen commonly used in breast cancer treatment
T (Taxane) A class of chemotherapy agents that interfere with cell division
TH (Taxane and Trastuzumab) A chemotherapy combination used for HER2-positive breast cancer
TCb (Taxane and Carboplatin) A chemotherapy regimen often used for triple-negative breast cancer
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines for reporting systematic reviews and meta-analyses
FDA (Food and Drug Administration) A U.S. regulatory agency responsible for approving drugs and therapies

Appendix A. Supplementary data

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