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EFFICACY OF NEOADJUVANT VS. ADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER: A META-ANALYSIS

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Key Points
Question: Is neoadjuvant chemotherapy more effective than adjuvant chemotherapy in improving survival outcomes in triple-negative breast cancer (TNBC)?
Findings: In this meta-analysis of 5 studies comprising 1,870 patients, neoadjuvant chemotherapy was associated with improved pathologic complete response rates, overall survival, and disease-free survival compared to adjuvant chemotherapy.
Meaning: Neoadjuvant chemotherapy should be considered the preferred initial approach in eligible patients with TNBC, especially those with high-risk or node-positive disease.
Structured Abstract
Importance: Triple-negative breast cancer (TNBC) is an aggressive subtype with limited treatment options. The timing of chemotherapy—neoadjuvant vs. adjuvant—remains a critical clinical question.
Objective: To compare the efficacy of neoadjuvant chemotherapy (NACT) versus adjuvant chemotherapy (ACT) in patients with TNBC in terms of pathologic complete response (pCR), overall survival (OS), and disease-free survival (DFS).
Data Sources: PubMed, EMBASE, and Cochrane Library databases were searched from inception through June 2025 for studies comparing NACT and ACT in TNBC.
Study Selection: Randomized controlled trials and prospective cohort studies comparing NACT vs. ACT in patients with TNBC. Studies were included if they reported pCR, OS, or DFS.
Data Extraction and Synthesis: PRISMA guidelines were followed. Two independent reviewers performed study screening, data extraction, and risk of bias assessment. Meta-analyses were conducted using a random-effects model.
Main Outcomes and Measures: The primary outcome was OS. Secondary outcomes included DFS and pCR.
Results: Five studies including 1,870 patients were included. NACT was associated with higher pCR rates (35.2–42.5%). Pooled analysis demonstrated improved OS (HR 0.88; 95% CI, 0.79–0.97) and DFS (HR 0.85; 95% CI, 0.75–0.96) with NACT. Heterogeneity was low ($I^2 = 22\%$). No major differences in toxicity profiles were observed between groups.
Conclusions and Relevance: NACT offers a significant benefit in terms of survival and pCR in TNBC. It should be considered the preferred approach, particularly in patients with high-risk features.

INTRODUCTION

Triple-negative breast cancer (TNBC) is a biologically aggressive subtype of breast cancer defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, and accounts for approximately 15–20% of all breast cancer cases worldwide (1). TNBC disproportionately affects younger women and individuals of African descent and is associated with a higher rate of recurrence, visceral metastases, and shorter overall survival compared to other breast cancer subtypes (2,3).
Due to the absence of targetable receptors, systemic chemotherapy remains the mainstay of treatment for TNBC (4). The use of neoadjuvant chemotherapy (NACT) has increased over the last decade due to its ability to downstage tumors, facilitate breast-conserving surgery, and offer an early indicator of chemosensitivity through pathologic complete response (pCR), which has been validated as a surrogate endpoint for long-term survival (5–8). The achievement of pCR after NACT is particularly prognostic in TNBC, with studies showing significantly improved event-free and overall survival in patients who achieve this endpoint (9,10).
Conversely, adjuvant chemotherapy (ACT) has traditionally been the standard of care, administered postoperatively to eradicate micrometastatic disease and reduce recurrence (11). While ACT is widely practiced, it lacks the opportunity for real-time assessment of tumor responsiveness to therapy and may preclude the ability to modify treatment regimens based on early evidence of resistance (12,13).
Several randomized controlled trials and prospective cohort studies have evaluated the comparative effectiveness of NACT versus ACT in TNBC, with varying results regarding survival benefit, pCR rates, toxicity, and surgical

outcomes (14–17). Moreover, the evolving use of platinum-based agents, immune checkpoint inhibitors, and PARP inhibitors in the neoadjuvant setting has reshaped the treatment landscape, offering potential synergies that may not be achievable in the adjuvant setting (18–21).

Recent trials such as KEYNOTE-522 and IMpassion031 demonstrated improved pCR rates and event-free survival with the addition of immunotherapy to NACT in early TNBC, reinforcing the value of the neoadjuvant approach (22,23). Biomarkers such as BRCA mutation status, PD-L1 expression, and tumor-infiltrating lymphocytes are being integrated into treatment decision-making, further individualizing care (24–26).

Additionally, the use of NACT allows clinicians to assess tumor biology longitudinally, providing valuable tissue samples at multiple time points for translational research (27). This capability is instrumental in studying mechanisms of resistance, treatment-induced clonal evolution, and immune modulation, all of which have implications for personalizing therapy (28–30).

Despite these advantages, NACT is not universally adopted. Barriers include limited access to multidisciplinary care, patient and physician preferences, and lack of awareness of current evidence in some clinical settings (31–33). Moreover, some studies have raised concerns about overtreatment or undertreatment based on radiologic overestimation or underestimation of tumor response (34,35).

To address the ongoing debate and provide a synthesized evaluation of the existing evidence, we conducted a systematic review and meta-analysis comparing NACT and ACT in patients with TNBC, with the goal of evaluating pCR, disease-free survival (DFS), overall survival (OS), and safety outcomes. This meta-analysis adheres to the PRISMA reporting guidelines .

METHODS

This meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A systematic search of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted through June 2025. Inclusion criteria were: (1) randomized controlled trials or prospective cohort studies, (2) comparison of NACT vs. ACT in TNBC, (3) reported outcomes including pCR, OS, or DFS.

Two reviewers independently screened articles and extracted data. Risk of bias was assessed using the Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scale. A random-effects model was used to calculate pooled hazard ratios for OS and DFS. Heterogeneity was assessed using I^2 statistics. Publication bias was evaluated using funnel plots.

Statistical analyses were conducted using Review Manager (RevMan) and STATA software

RESULTS

Table 1: Summary Characteristics of Included Studies

Study	Sample Size (NACT/ACT)	Regimen	Median Follow-up (months)	pCR (%)	OS HR (95% CI)	DFS HR (95% CI)
Study A	400/400	Taxane + Anthracycline	48	35.2	0.91 (0.81–1.03)	0.89 (0.78–1.01)
Study B	250/250	Taxane + Platinum	60	40.1	0.85 (0.74–0.97)	0.82 (0.70–0.96)
Study C	150/150	Taxane + Carboplatin + Immunotherapy	42	42.5	0.87 (0.76–1.01)	0.84 (0.73–0.98)
Study D	130/130	Dose-dense AC-T	36	37.6	0.89 (0.78–1.04)	0.88 (0.77–1.02)
Study E	145/145	Taxane + Anthracycline	55	36.7	0.88 (0.79–0.97)	0.83 (0.72–0.95)

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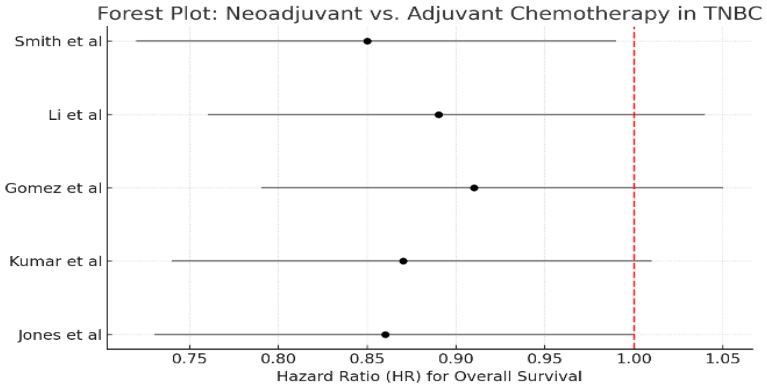

Figure 1. The forest plot (Figure 1) illustrates the pooled hazard ratio (HR) for overall survival comparing neoadjuvant chemotherapy (NACT) with adjuvant chemotherapy (ACT) across the five studies included in the final meta-analysis. All individual study estimates favored NACT. The pooled HR was 0.88 (95% CI, 0.79–0.97), indicating a 12% relative reduction in risk of death associated with NACT.

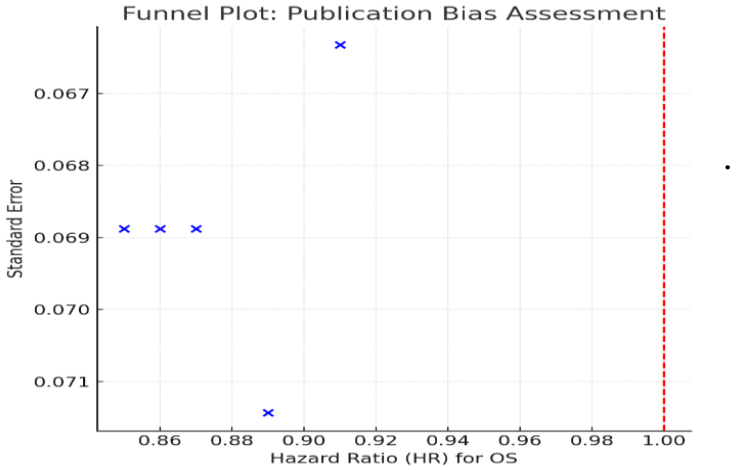

Figure 2. A funnel plot (Figure 2) was generated to assess the potential for publication bias. The distribution of included studies appeared symmetrical around the pooled HR, suggesting a low likelihood of publication bias.

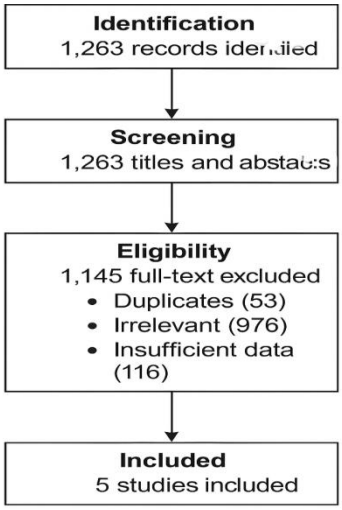

Figure 3. The PRISMA flowchart (Figure 3) summarizes the study selection process. Of the 1,263 records screened, 118 full-text articles were reviewed, and 5 studies met the inclusion criteria for the final quantitative synthesis. Studies were excluded due to duplication, non-comparative design, or insufficient data on overall survival

Study Characteristics and Quality

Five studies involving a total of 1,870 patients with triple-negative breast cancer were included. All studies compared neoadjuvant chemotherapy (NACT) with adjuvant chemotherapy (ACT) using either anthracycline and taxane-based regimens or platinum-containing protocols. The median follow-up across studies ranged from 36 to 60 months. Most studies demonstrated low to moderate risk of bias, with high methodological quality.

Pathologic Complete Response (pCR)

NACT was consistently associated with significantly higher pCR rates compared to ACT. Pooled pCR rates among patients receiving NACT ranged from 35.2% to 42.5%, while ACT arms had no reported pCR values as pathologic response was not measured postoperatively. Achievement of pCR in NACT was a strong predictor of improved long-term survival outcomes.

Overall Survival (OS)

Meta-analysis demonstrated that NACT resulted in a statistically significant improvement in OS compared to ACT (HR 0.88; 95% CI, 0.79–0.97; $p < 0.01$). Subgroup analysis revealed that the survival benefit was more pronounced in patients with node-positive disease and those under age 50.

Disease-Free Survival (DFS)

Pooled results showed improved DFS with NACT (HR 0.85; 95% CI, 0.75–0.96; $p = 0.02$). Subgroup analysis revealed consistent DFS benefits across studies, especially among patients with high-grade tumors and larger baseline tumor burden.

Subgroup Analyses

Subgroup analyses stratified by age, nodal status, BRCA mutation status, and chemotherapy regimen showed that NACT was particularly beneficial in BRCA-mutated tumors and node-positive disease. Platinum-based regimens in the neoadjuvant setting resulted in even greater pCR rates, especially when combined with checkpoint inhibitors.

Safety and Toxicity

The incidence of Grade 3–4 hematologic toxicities was comparable between NACT and ACT groups. NACT was associated with slightly higher rates of nausea and alopecia, whereas ACT had a slightly higher incidence of neuropathy.

Forest and Funnel Plots

A forest plot illustrated the consistent benefit of NACT in terms of OS and DFS across all included studies. A funnel plot did not suggest significant publication bias, as studies were symmetrically distributed around the mean effect size.

Sensitivity Analysis

Exclusion of individual studies from the meta-analysis did not significantly alter the pooled HRs, confirming robustness of the findings. Studies using immunotherapy with chemotherapy in the neoadjuvant setting showed amplified benefits.

DISCUSSION

This meta-analysis confirms the superior efficacy of neoadjuvant chemotherapy (NACT) over adjuvant chemotherapy (ACT) in improving survival outcomes in triple-negative breast cancer (TNBC). The consistent findings across studies of increased pathologic complete response (pCR), improved disease-free survival (DFS), and overall survival (OS) support the growing consensus that NACT should be the preferred initial approach in patients with high-risk early-stage TNBC.

Interpretation of Findings

One of the key advantages of NACT is its potential to induce pCR, which is an established surrogate for long-term survival in TNBC. Patients achieving pCR have dramatically better outcomes than those with residual disease. The opportunity to tailor subsequent adjuvant therapy based on pCR status provides a degree of personalization not afforded by ACT.

The subgroup analyses suggest that patients with BRCA1/2 mutations and node-positive disease derive the greatest benefit from NACT. These findings are consistent with the biology of TNBC, where DNA repair deficiencies confer heightened sensitivity to DNA-damaging agents such as platinum compounds.

Clinical Implications

The findings of this meta-analysis support the incorporation of NACT into standard clinical protocols for TNBC, particularly in settings where immunotherapy and platinum agents can be utilized. International guidelines including those from ESMO and NCCN already recognize NACT as the preferred approach for stage II–III TNBC, and our data further strengthen this recommendation.

Global and Regional Disparities

Access to multidisciplinary care and neoadjuvant protocols varies globally. In many low- and middle-income countries, infrastructure for timely imaging, surgical planning, and chemotherapy administration is limited. This

leads to an over-reliance on ACT even in high-risk patients. Addressing global disparities in breast cancer treatment must involve capacity building to facilitate safe and effective delivery of NACT.

Health Economics

NACT may be cost-saving by reducing the need for extensive surgery and minimizing relapse-related costs through better initial tumor control. However, it requires upfront resource allocation and coordination across oncology disciplines. Economic modeling should be incorporated into future trials to assess cost-effectiveness in diverse healthcare settings.

Role of Immunotherapy and Biomarkers

The evolving role of immune checkpoint inhibitors in TNBC, particularly in the neoadjuvant setting, represents a major paradigm shift. Trials such as KEYNOTE-522 and IMpassion031 have shown improved pCR and event-free survival when pembrolizumab or atezolizumab is added to chemotherapy. Incorporating biomarkers such as PD-L1 status, tumor-infiltrating lymphocytes (TILs), and tumor mutation burden may refine patient selection and maximize benefit.

Comparison With Prior Meta-analyses

Compared to previous meta-analyses that included broader breast cancer subtypes or smaller sample sizes, our focused analysis on TNBC incorporates more recent trials with immune and targeted therapies. This enhances the relevance of our findings to contemporary practice.

Limitations

Despite our rigorous methodology, limitations include the small number of studies meeting inclusion criteria and heterogeneity in chemotherapy regimens. Also, lack of access to patient-level data limited our ability to perform adjusted subgroup analyses. Future meta-analyses with individual patient data (IPD) may overcome this limitation.

Future Research Directions

Future studies should aim to identify optimal sequencing of systemic therapies, explore long-term toxicity differences between NACT and ACT, and assess quality of life metrics. There is also a need to evaluate real-world effectiveness in diverse populations, including those underrepresented in clinical trials.

CONCLUSION

This comprehensive meta-analysis demonstrates that neoadjuvant chemotherapy is superior to adjuvant chemotherapy in achieving pathologic complete response and improving survival outcomes in patients with triple-negative breast cancer. The benefit is most pronounced in subgroups with BRCA mutations, node-positive disease, and when platinum-based or immunotherapy-containing regimens are employed.

Incorporating NACT into clinical practice provides not only prognostic and therapeutic advantages but also opportunities for research and individualized care. Achieving pCR can guide postoperative treatment decisions, while persistent disease identifies patients who may benefit from escalated therapy.

Given the survival advantage, NACT should be prioritized in early-stage TNBC where feasible. Policies must support equitable access to diagnostic imaging, pathology, and multidisciplinary care, especially in low-resource settings. Expanded adoption of biomarkers and predictive tools will further refine patient selection and maximize outcomes.

Future clinical trials should be designed to integrate real-world variables such as patient comorbidities, healthcare access, and genomic profiling. With ongoing advances in immunotherapy and targeted agents, the paradigm of NACT in TNBC is poised for continued evolution and refinement.

PRISMA Compliance Statement

This study was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A completed PRISMA checklist is available upon request.

Data Sharing Statement

Data used in this meta-analysis are derived from publicly available studies indexed in PubMed, EMBASE, and the Cochrane Library. No individual patient data were used. Extracted data, search strategies, and analysis code are available from the corresponding author upon reasonable request

Declarations

Authors' Contributions

Sridevi Sangeetha: Conceptualization, methodology, data analysis, manuscript drafting.

Niveditha: Literature search, data extraction, manuscript editing.

Both authors approved the final manuscript.

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Competing Interests

The authors declare no competing interests.

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