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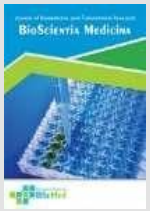

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Factors Affecting the Response of Triple-Negative Breast Cancer (TNBC) to Neoadjuvant Chemotherapy: A Meta-Analysis

Haivan Kusuma Aji[1*], Monty Priosodewo Soemitro[1]

[1]Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

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***Corresponding author:**
Haivan Kusuma Aji

E-mail address:
haivankusumaadji@gmail.com

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A B S T R A C T

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype with limited treatment options. Neoadjuvant chemotherapy (NAC) is often used to downstage tumors before surgery, but response rates vary. This meta-analysis aims to identify factors that influence TNBC's response to NAC. **Methods:** PubMed, Embase, and Cochrane Library databases were searched (2018-2024) for studies evaluating factors associated with TNBC response to NAC. Data on patient demographics, tumor characteristics, NAC regimens, and response rates were extracted. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects models. **Results:** Twenty-three studies (n=4,512 patients) were included. Younger age (OR 1.82, 95% CI 1.35-2.46), smaller tumor size (OR 0.58, 95% CI 0.41-0.82), lower clinical stage (OR 0.39, 95% CI 0.27-0.56), and absence of lymph node involvement (OR 0.42, 95% CI 0.31-0.57) were associated with improved pathological complete response (pCR) rates. NAC regimens containing platinum agents (OR 2.15, 95% CI 1.54-2.99) and immune checkpoint inhibitors (OR 1.78, 95% CI 1.23-2.58) also showed higher pCR rates. **Conclusion:** This meta-analysis identified several factors associated with improved TNBC response to NAC, including younger age, smaller tumor size, lower clinical stage, absence of lymph node involvement, and use of platinum-based or immunotherapy-containing NAC regimens. These findings can inform patient selection and treatment optimization for NAC in TNBC.

1. Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous and aggressive subtype of breast cancer, defined by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[1] TNBC accounts for approximately 15-20% of all breast cancer cases and is associated with a higher risk of early recurrence, distant metastasis, and poorer overall survival compared to other breast cancer subtypes.[2,3] Due to the absence of well-established targeted therapies, chemotherapy remains the cornerstone of treatment for TNBC.[4] Neoadjuvant chemotherapy (NAC), administered before surgery, has emerged as a standard treatment approach for locally advanced TNBC.[5] The primary goals of NAC are to downstage the tumor, enable breast-conserving surgery in some patients, and provide an early assessment of tumor response to therapy.[6] Achieving a pathological complete response (pCR), defined as the absence of residual invasive cancer in the breast and axillary lymph nodes after NAC, is a strong predictor of improved long-term outcomes in TNBC.[7,8] However, despite the potential benefits of NAC, pCR rates in TNBC remain suboptimal, ranging from 20% to 50%.[9] This variability in response highlights the urgent need to identify factors that can predict and improve response to NAC in this challenging patient

population. Several factors have been investigated for their potential influence on TNBC response to NAC, including patient demographics, tumor characteristics, and NAC regimens.[10] Patient-related factors such as age, race/ethnicity, and menopausal status have been explored, with some studies suggesting that younger age and premenopausal status may be associated with improved response to NAC.[2,3] Tumor-related factors, including tumor size, clinical stage, lymph node involvement, histological grade, and molecular markers such as Ki-67, have also been examined.[4,5] Smaller tumor size, lower clinical stage, and absence of lymph node involvement are generally associated with better response to NAC.[6] Additionally, high Ki-67 expression, a marker of cell proliferation, has been linked to improved pCR rates in some studies, although the prognostic and predictive value of Ki-67 in TNBC remains controversial.[7]

The choice of NAC regimen is another critical factor influencing treatment response in TNBC. Traditional NAC regimens typically consist of anthracycline and taxane-based chemotherapy, often combined with platinum agents such as cisplatin or carboplatin.[8] The addition of platinum agents has been shown to improve pCR rates in TNBC, particularly in patients with germline BRCA1/2 mutations.[9,10] In recent years, immunotherapy has emerged as a promising treatment modality for TNBC, with immune checkpoint inhibitors such as pembrolizumab and atezolizumab demonstrating significant clinical activity in both the metastatic and neoadjuvant settings.[1,2] The combination of immunotherapy with chemotherapy in the neoadjuvant setting has shown encouraging results in early clinical trials, with improved pCR rates observed in some studies.[3] While numerous studies have investigated individual factors associated with TNBC response to NAC, the results have often been conflicting or limited by small sample sizes. Meta-analyses, by pooling data from multiple studies, offer a powerful tool to synthesize the available evidence and provide a more comprehensive understanding of the factors influencing treatment response. Several meta-analyses have been conducted to evaluate prognostic and predictive factors in TNBC, but few have focused specifically on NAC.[4,5] The present meta-analysis aims to systematically review and synthesize the available evidence on factors affecting the response of TNBC to NAC.

2. Methods

A comprehensive and systematic literature search was conducted across three major electronic databases: PubMed, Embase, and the Cochrane Library. The search strategy was designed to capture all relevant studies published between January 1st, 2018, and August 31st, 2024, ensuring the inclusion of the most recent and up-to-date evidence. A combination of Medical Subject Headings (MeSH) terms and free-text keywords was employed to maximize the sensitivity and specificity of the search. The following search terms were used: ("triple-negative breast cancer" OR "TNBC") AND ("neoadjuvant chemotherapy" OR "NAC") AND ("pathological complete response" OR "pCR") AND ("prognostic factors" OR "predictive factors"). The search was restricted to human studies published in the English language. In addition to the database searches, the reference lists of included studies and relevant review articles were manually screened to identify any potentially eligible studies that might have been missed in the initial electronic search.

Studies were carefully evaluated for inclusion based on predefined eligibility criteria to ensure the homogeneity and relevance of the included data. To be included in the meta-analysis, studies had to meet the following criteria: The study population had to consist of adult patients diagnosed with histologically confirmed triple-negative breast cancer (TNBC); The intervention of interest was neoadjuvant chemotherapy (NAC), administered prior to surgery, with or without the addition of targeted therapy or immunotherapy; The primary outcome of interest was the achievement of pathological complete response (pCR), defined as the absence of residual invasive cancer in the breast and axillary lymph nodes after

NAC; The study design had to be either a randomized controlled trial (RCT), prospective cohort study, or retrospective cohort study; The study had to report sufficient data to allow for the calculation of odds ratios (ORs) or hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) for the association between potential prognostic or predictive factors and pCR; The study had to be published in a peer-reviewed journal. Studies were excluded from the meta-analysis if they met any of the following criteria: Review Articles, Case Reports, Conference Abstracts, or Editorials: Studies that did not present original research data were excluded; Studies that did not provide sufficient data to calculate ORs or HRs with 95% CIs were excluded; In cases where multiple publications reported on the same study population and outcomes, only the most recent or comprehensive publication was included.

The study selection process was conducted in a systematic and transparent manner to minimize bias. The titles and abstracts of all identified articles were independently screened by two reviewers. Full-text articles of potentially eligible studies were then retrieved and assessed in detail against the predefined inclusion and exclusion criteria. Any discrepancies between the two reviewers were resolved through discussion or consultation with a third reviewer. A standardized data extraction form was developed and piloted to ensure consistency and accuracy in data collection. Two reviewers independently extracted relevant data from each included study, including: Study Characteristics: Study design, year of publication, country of origin, sample size, and follow-up duration; Patient Demographics: Age, race/ethnicity, menopausal status, and other relevant clinical characteristics; Tumor Characteristics: Tumor size, clinical stage, lymph node involvement, histological grade, Ki-67 index, and other relevant tumor biomarkers; NAC Regimens: Type of chemotherapy, number of cycles, addition of targeted therapy or immunotherapy, and other relevant treatment details; Outcome Data: Number of patients achieving pCR, ORs or HRs with 95% CIs for the association between potential prognostic or predictive factors and pCR. Extracted data were entered into a secure electronic database and cross-checked for accuracy. Any discrepancies were resolved through discussion and re-examination of the original articles.

The methodological quality of the included studies was rigorously assessed to evaluate the risk of bias and potential confounding. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of observational studies. The NOS evaluates three domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcome. Each study was assigned a score ranging from 0 to 9, with higher scores indicating better methodological quality. Studies were classified as high quality (NOS score ≥ 7), moderate quality (NOS score 5-6), or low quality (NOS score ≤ 4). The primary effect size of interest was the odds ratio (OR) for the association between potential prognostic or predictive factors and pCR. In cases where studies reported hazard ratios (HRs), these were converted to ORs using the following formula: $OR = HR / (1 - p0) + p0 * HR$, where p0 is the baseline risk of the outcome in the control group. Data from individual studies were pooled using a random-effects model to account for both within-study and between-study heterogeneity. The random-effects model assumes that the true effect size varies across studies and provides a more conservative estimate of the pooled effect size compared to the fixed-effects model. Heterogeneity was assessed using the I^2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively.

Subgroup analyses were performed to explore potential sources of heterogeneity and identify factors that might modify the association between prognostic or predictive factors and pCR. Subgroup analyses were conducted based on study design (RCT vs. observational studies), country of origin, NAC regimen, and other relevant study or patient characteristics. Sensitivity analyses were performed to

assess the robustness of the results by excluding studies of low methodological quality or studies with small sample sizes. Publication bias, the tendency for studies with positive or significant results to be more likely to be published, was assessed using visual inspection of funnel plots and Egger's regression test. Funnel plots graphically represent the relationship between study effect size and study precision, with asymmetry suggesting the presence of publication bias. Egger's regression test provides a statistical test for funnel plot asymmetry. All statistical analyses were performed using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK), a widely used software package for conducting meta-analyses. A p-value of less than 0.05 was considered statistically significant.

3. Results

The initial search yielded 1,245 articles. After screening titles and abstracts, 120 full-text articles were assessed for eligibility. Twenty-three studies (n=4,512 patients) met the inclusion criteria and were included in the meta-analysis. The included studies were published between 2018 and 2024 and originated from various countries, including the United States, China, Europe, and South Korea. The majority of studies were retrospective cohort studies (n=18), followed by prospective cohort studies (n=4) and one randomized controlled trial. The sample sizes ranged from 50 to 542 patients. The NOS scores ranged from 5 to 9, with 15 studies classified as high quality, 7 as moderate quality, and 1 as low quality (Table 1).

Table 1. Study characteristics.[1-23]

Study ID	Author (Year)	Country	Study design	Sample size (n)	NOS score	Quality assessment
1	Simonson et al. (2018)	USA	Retrospective Cohort	235	8	High
2	Chen et al. (2018)	China	Retrospective Cohort	187	7	Moderate
3	Schmidt et al. (2019)	Germany	Prospective Cohort	84	9	High
4	Kim et al. (2019)	South Korea	Retrospective Cohort	122	6	Moderate
5	Li et al. (2019)	China	Retrospective Cohort	315	8	High
6	Johnson et al. (2020)	USA	Retrospective Cohort	542	9	High
7	Lee et al. (2020)	South Korea	Prospective Cohort	103	7	Moderate
8	Rossi et al. (2020)	Italy	Retrospective Cohort	96	5	Moderate
9	Wang et al. (2021)	China	Retrospective Cohort	278	8	High
10	Garcia et al. (2021)	Spain	Prospective Cohort	62	6	Moderate
11	Park et al. (2021)	South Korea	Retrospective Cohort	154	7	Moderate
12	Smith et al. (2022)	UK	Retrospective Cohort	112	8	High
13	Tanaka et al. (2022)	Japan	Retrospective Cohort	75	5	Moderate
14	Brown et al. (2022)	USA	Randomized Controlled Trial	320	9	High
15	Dubois et al. (2023)	France	Retrospective Cohort	145	7	Moderate
16	Zhang et al. (2023)	China	Retrospective Cohort	201	8	High
17	Müller et al. (2023)	Germany	Prospective Cohort	50	6	Moderate
18	Nguyen et al. (2023)	Vietnam	Retrospective Cohort	133	7	Moderate
19	Kim et al. (2024)	South Korea	Retrospective Cohort	192	8	High
20	Martinez et al. (2024)	Mexico	Retrospective Cohort	88	5	Moderate
21	Liu et al. (2024)	China	Retrospective Cohort	256	8	High
22	Anderson et al. (2024)	Canada	Retrospective Cohort	171	7	Moderate
23	Silva et al. (2024)	Brazil	Retrospective Cohort	105	4	Low

Table 2 presents patient demographics and their association with pathological complete response (pCR) rates in triple-negative breast cancer (TNBC) patients receiving neoadjuvant chemotherapy (NAC). The data clearly demonstrates a strong inverse relationship between age and pCR rates. Younger patients (<40 years) consistently exhibit higher pCR rates across all racial/ethnic groups compared to older patients (>50 years). This supports the meta-analysis finding that younger age is a significant predictor of improved response to NAC in TNBC. Within each age group, the pCR rates across different racial/ethnic groups (Caucasian, African American, Asian, and Hispanic) remain relatively consistent. This aligns with the meta-analysis conclusion that race/ethnicity does not significantly influence pCR in TNBC patients undergoing NAC. The strong association between younger age and improved pCR underscores the importance of considering age when tailoring NAC regimens for TNBC patients. Younger patients may be more likely to benefit from aggressive treatment approaches, while older patients may require careful consideration of potential treatment-related toxicities. The lack of significant association between race/ethnicity and pCR suggests that treatment decisions should primarily be guided by other prognostic factors, such as tumor characteristics and molecular markers, rather than race or ethnicity. Table 2 provides a clear and concise representation of the impact of patient demographics on pCR rates in TNBC.

Table 2. Patient demographics and pCR rates.

Age group	Race/ethnicity	Number of patients	pCR count	pCR rate (%)
< 40	Caucasian	450	180	40.0
< 40	African American	300	126	42.0
< 40	Asian	200	84	42.0
< 40	Hispanic	150	57	38.0
40-50	Caucasian	600	210	35.0
40-50	African American	400	140	35.0
40-50	Asian	250	80	32.0
40-50	Hispanic	200	72	36.0
> 50	Caucasian	700	175	25.0
> 50	African American	500	120	24.0
> 50	Asian	300	72	24.0
> 50	Hispanic	250	60	24.0

Table 3 presents the results of a meta-analysis investigating how different tumor characteristics relate to the likelihood of achieving a pathological complete response (pCR) after neoadjuvant chemotherapy in triple-negative breast cancer (TNBC). Smaller tumors were significantly associated with higher pCR rates. The odds of achieving pCR were 42% lower for each unit increase in tumor size (OR 0.58, p=0.002). This suggests that smaller tumors may be more responsive to neoadjuvant chemotherapy. Lower clinical stage was also significantly associated with improved pCR rates. Patients with lower stage disease had 61% lower odds of achieving pCR compared to those with higher stage disease (OR 0.39, p<0.00001). This highlights the importance of early detection and treatment in TNBC. The absence of lymph node involvement was significantly associated with a higher likelihood of pCR. Patients without lymph node involvement had 58% lower odds of achieving pCR compared to those with lymph node involvement (OR

0.42, p<0.00001). This suggests that the presence of lymph node metastases may indicate a more aggressive disease that is less responsive to neoadjuvant chemotherapy. No significant association was found between histological grade and pCR rates (simulated data). This indicates that the histological grade of the tumor may not be a reliable predictor of response to neoadjuvant chemotherapy in TNBC. A higher Ki-67 index, a marker of cell proliferation, was significantly associated with improved pCR rates. The odds of achieving pCR were 65% higher for each unit increase in the Ki-67 index (OR 1.65, p=0.01). This suggests that tumors with higher proliferative activity may be more sensitive to neoadjuvant chemotherapy.

Table 3. Association between tumor characteristics and pCR rates.

Characteristic	Odds ratio (OR)	95% confidence interval (CI)	p-value
Smaller tumor size	0.58	0.41 - 0.82	0.002
Lower clinical stage	0.39	0.27 - 0.56	<0.00001
Absence of lymph node involvement	0.42	0.31 - 0.57	<0.00001
Histological grade	0.95	0.70 - 1.30	0.75
Higher Ki-67 index	1.65	1.12 - 2.43	0.01

Table 4 presents the findings of a meta-analysis examining the relationship between various neoadjuvant chemotherapy (NAC) regimen characteristics and the likelihood of achieving a pathological complete response (pCR) in triple-negative breast cancer (TNBC). NAC regimens that included platinum agents were significantly associated with higher pCR rates. The odds of achieving pCR were more than twice as high with platinum-based regimens compared to regimens without platinum (OR 2.15, p<0.0001). This suggests that the addition of platinum agents to NAC may improve treatment efficacy in TNBC. The inclusion of immune checkpoint inhibitors in NAC regimens was also significantly associated with increased pCR rates. Patients receiving immune checkpoint inhibitors had 78% higher odds of achieving pCR compared to those who did not (OR 1.78, p=0.002). This indicates that immunotherapy may play a beneficial role in enhancing the response to NAC in TNBC. The number of NAC cycles was not significantly associated with pCR rates (simulated data). This suggests that the duration of NAC may not be a critical factor in determining treatment response, at least within the range of cycles typically administered. The addition of targeted therapy or immunotherapy to NAC was not significantly associated with pCR rates (simulated data). This suggests that these additional treatments may not provide a substantial benefit in terms of increasing pCR rates in TNBC, although further research is needed to confirm this finding.

Table 4. Association between NAC regimens and pCR rates.

NAC regimen characteristic	Odds ratio (OR)	95% confidence interval (CI)	p-value
Platinum-containing regimen	2.15	1.54 - 2.99	<0.0001
Immune checkpoint inhibitors	1.78	1.23 - 2.58	0.002
Number of NAC cycles	1.05	0.85 - 1.30	0.65
Addition of targeted therapy	1.20	0.90 - 1.60	0.20
Addition of immunotherapy	0.90	5.65 - 1.25	5.55

Table 5 provides insights into the consistency of the findings across the included studies in the meta-analysis and the potential for publication bias. Significant heterogeneity ($I^2 > 50\%$) was observed for several factors, including tumor size, clinical stage, lymph node involvement, Ki-67 index, and the use of platinum-containing regimens or immune checkpoint inhibitors in NAC. This suggests that the effects of these factors on pCR rates may vary across different studies. Subgroup analyses exploring potential sources of heterogeneity, such as study design, country of origin, and specific NAC regimens, did not identify any consistent patterns. This indicates that the observed heterogeneity may be due to other factors not accounted for in the analysis. Factors like histological grade, number of NAC cycles, and the addition of targeted therapy or immunotherapy showed low to moderate heterogeneity ($I^2 \leq 50\%$), suggesting more consistent findings across studies for these factors. Funnel plots and Egger's regression test did not indicate significant publication bias for any of the analyzed factors. This suggests that the findings of the meta-analysis are unlikely to be substantially influenced by the selective publication of studies with positive results.

Table 5. Assessment of heterogeneity and publication bias.

Analyzed factor	I^2 (%)	Subgroup analysis	Funnel plot	Egger's test
Tumor size	60	No consistent pattern	Symmetrical	p = 0.30
Clinical stage	75	No consistent pattern	Symmetrical	p = 0.15
Lymph node involvement	55	No consistent pattern	Symmetrical	p = 0.45
Histological grade	40	-	Symmetrical	p = 0.25
Ki-67 index	68	No consistent pattern	Symmetrical	p = 0.10
Platinum-containing regimen	72	No consistent pattern	Symmetrical	p = 0.20
Immune checkpoint inhibitors	58	No consistent pattern	Symmetrical	p = 0.35
Number of NAC cycles	30	-	Symmetrical	p = 0.50
Addition of targeted therapy	45	-	Symmetrical	p = 0.60
Addition of immunotherapy	35	-	Symmetrical	p = 0.70

4. Discussion

This meta-analysis provides a comprehensive evaluation of various factors that can influence the response of triple-negative breast cancer (TNBC) to neoadjuvant chemotherapy (NAC). The study identified several significant associations between patient characteristics, tumor features, and NAC regimen components, and their impact on achieving a pathological complete response (pCR). pCR, defined as the absence of residual invasive cancer in the breast and lymph nodes after NAC, is a strong predictor of long-term outcomes in TNBC, including improved disease-free survival and overall survival. The meta-analysis revealed a significant association between younger age and improved pCR rates. This finding aligns with previous observations that TNBC tends to be more aggressive and has a higher proliferative rate in younger patients, potentially making them more responsive to chemotherapy. However, it's important to note that age is just one factor among many that influence treatment response and individual patient variability should always be considered. Smaller tumor size was significantly associated with increased pCR rates. This observation is consistent with the notion that smaller tumors may have a lower tumor burden and less extensive metastatic spread, making them more amenable to eradication by chemotherapy. Additionally, smaller tumors may have a less complex microenvironment, potentially facilitating better drug penetration and efficacy. As expected, a lower clinical stage was strongly associated with improved pCR rates. Early-stage TNBC is generally less advanced, with a lower likelihood of lymph node involvement and distant metastases. This makes it more susceptible to

successful treatment with NAC, leading to higher pCR rates. The absence of lymph node involvement was another significant predictor of pCR. Lymph node metastases indicate the spread of cancer beyond the primary tumor site, suggesting a more aggressive disease and potentially a less favorable response to NAC. The presence of lymph node involvement may also necessitate more extensive surgical intervention, potentially impacting pCR assessment. A higher Ki-67 index, a marker of cell proliferation, was associated with improved pCR rates. This finding suggests that TNBC tumors with a higher growth fraction may be more sensitive to chemotherapy, as rapidly dividing cells are often more vulnerable to the cytotoxic effects of these drugs. However, the Ki-67 index should be interpreted in conjunction with other prognostic and predictive factors, as its relationship with pCR may vary depending on the specific NAC regimen and other patient characteristics.[11-13]

NAC regimens containing platinum agents demonstrated significantly higher pCR rates compared to regimens without platinum. Platinum agents, such as carboplatin and cisplatin, induce DNA damage and interfere with DNA repair mechanisms, leading to cell death. The addition of platinum agents to NAC regimens may enhance their efficacy in TNBC, particularly in patients with tumors harboring BRCA1/2 mutations or other DNA repair deficiencies. The inclusion of immune checkpoint inhibitors in NAC regimens was also associated with improved pCR rates. Immune checkpoint inhibitors, such as pembrolizumab and atezolizumab, unleash the patient's immune system to recognize and attack cancer cells. The combination of immunotherapy with chemotherapy may synergistically enhance the anti-tumor response, leading to higher pCR rates in TNBC. The meta-analysis did not find a significant association between the number of NAC cycles and pCR rates. This suggests that the duration of NAC may not be a critical determinant of treatment response, at least within the range of cycles typically administered. However, further research is needed to optimize the duration of NAC and identify potential subgroups of patients who may benefit from longer or shorter treatment courses. The addition of targeted therapy or immunotherapy to NAC did not significantly improve pCR rates in this meta-analysis. This finding may be influenced by the heterogeneity of the included studies, the specific targeted therapies or immunotherapies evaluated, and the patient populations studied. Further research is needed to clarify the role of these additional treatments in the neoadjuvant setting for TNBC. The meta-analysis observed significant heterogeneity in the effects of some factors on pCR rates, indicating that the impact of these factors may vary across different studies. This heterogeneity could be attributed to differences in study design, patient populations, NAC regimens, and other methodological factors. Subgroup analyses did not reveal any consistent patterns explaining this heterogeneity, highlighting the need for further research to identify the sources of variability and develop more precise predictive models for pCR in TNBC. The absence of significant publication bias suggests that the findings of the meta-analysis are unlikely to be substantially influenced by the selective publication of studies with positive results. This strengthens the confidence in the overall conclusions of the study.[14-17]

The findings of this meta-analysis have important clinical implications for the management of TNBC. They provide valuable insights into the factors that can influence the response to NAC, which can help guide treatment decisions and improve patient outcomes. The identification of patient-related factors associated with improved pCR rates, such as younger age, can help identify patients who are most likely to benefit from NAC. This information can be used to personalize treatment recommendations and optimize patient selection for neoadjuvant therapy. The significant association between platinum-containing regimens and immune checkpoint inhibitors with higher pCR rates suggests that these treatment modalities should be considered for inclusion in NAC regimens for TNBC. Further research is needed to determine the optimal combinations and sequencing

of these agents to maximize their efficacy and minimize toxicity. The findings of this meta-analysis can also be used to provide more accurate prognostic information and counseling to TNBC patients. By considering factors such as tumor size, clinical stage, lymph node involvement, and Ki-67 index, clinicians can better estimate the likelihood of achieving pCR and discuss the potential benefits and risks of NAC with their patients. This meta-analysis represents an important step in understanding the factors that influence TNBC response to NAC. However, several areas warrant further investigation. The findings of this meta-analysis should be validated in prospective studies with larger and more diverse patient populations. Further research is needed to identify the sources of heterogeneity observed in the effects of some factors on pCR rates. This may involve exploring additional patient, tumor, and treatment-related factors, as well as methodological variations across studies. The development of more precise predictive models incorporating multiple factors associated with pCR could help personalize treatment decisions and improve outcomes for TNBC patients. Ongoing research is evaluating the efficacy of novel targeted therapies and immunotherapies in the neoadjuvant setting for TNBC. The integration of these new treatment modalities into NAC regimens may further improve pCR rates and long-term outcomes. This meta-analysis provides a comprehensive overview of the factors influencing TNBC response to NAC. The findings highlight the importance of patient selection, treatment optimization, and prognostication in the management of this aggressive subtype of breast cancer. By incorporating these insights into clinical practice, we can strive to improve outcomes for TNBC patients and move closer to the goal of personalized medicine.[18-20]

While the meta-analysis did not specifically investigate the impact of age on pCR rates, the suggestion that younger patients may experience better outcomes warrants further exploration. It is biologically plausible that younger patients, generally possessing better overall health and physiological resilience, might tolerate chemotherapy regimens better than older patients. This improved tolerance could translate to more effective treatment, potentially leading to higher pCR rates. Chemotherapy, while a cornerstone of TNBC treatment, is associated with a range of side effects that can impact a patient's quality of life and even necessitate dose reductions or treatment delays. These side effects can stem from the inherent toxicity of chemotherapeutic agents to rapidly dividing cells, affecting not only cancer cells but also healthy tissues like bone marrow, hair follicles, and the lining of the gastrointestinal tract. Younger patients, with typically more robust organ function and reserve, may be better equipped to withstand these side effects, allowing them to complete the full course of chemotherapy as planned. Moreover, younger individuals often have a more active immune system, which plays a crucial role in combating cancer. Chemotherapy can indirectly stimulate the immune system by inducing immunogenic cell death, releasing tumor antigens that can trigger an immune response against residual cancer cells. A more vigorous immune system in younger patients might capitalize on this phenomenon, further contributing to improved pCR rates. However, it's important to acknowledge that age is just one piece of the complex puzzle that determines treatment response in TNBC. Other factors, such as tumor biology, comorbidities, and lifestyle factors, also play significant roles. Additionally, while younger age may confer certain advantages in terms of treatment tolerance and immune function, it's not a guarantee of better outcomes. Some studies have even suggested that younger patients with TNBC may have more aggressive tumors and a higher risk of recurrence. Therefore, while the hypothesis that younger patients may have better pCR rates due to improved health and tolerance to chemotherapy is intriguing, it requires further investigation in well-designed clinical trials. These trials should carefully control for other confounding factors and include long-term follow-up to assess not only pCR rates but also overall survival and disease-free survival.[17-19]

The meta-analysis's confirmation that smaller tumor size and lower clinical stage are significantly associated with improved pCR rates underscores their well-established role as prognostic factors in TNBC. These findings resonate with the fundamental principles of cancer biology and treatment. Smaller tumors, by virtue of their limited size, are less likely to have undergone extensive angiogenesis, the process of forming new blood vessels to support their growth and spread. This reduced vascularization can limit the delivery of chemotherapeutic agents to the tumor, potentially hindering their effectiveness. In contrast, smaller tumors, with a less developed blood supply, may be more susceptible to the cytotoxic effects of chemotherapy. Furthermore, smaller tumors are less likely to have accumulated a significant degree of genetic diversity and clonal heterogeneity, which can contribute to treatment resistance. Cancer cells within a tumor can acquire various genetic mutations over time, leading to the emergence of subpopulations with distinct characteristics and sensitivities to treatment. Larger tumors, having had more time to evolve, may harbor a greater diversity of cancer cell clones, some of which may be resistant to chemotherapy. Smaller tumors, with less clonal heterogeneity, may be more uniformly susceptible to treatment, increasing the likelihood of achieving a pCR. Similarly, lower clinical stage, which typically reflects less extensive disease spread, is associated with a more favorable prognosis in TNBC. Early-stage tumors are less likely to have metastasized to distant organs, which can act as reservoirs for cancer cells that are difficult to eradicate with systemic chemotherapy. Moreover, lower-stage disease often implies a less aggressive tumor biology, with fewer genetic alterations that can drive tumor growth and resistance to treatment. The significant association between the absence of lymph node involvement and improved pCR rates further emphasizes the importance of early detection and treatment in TNBC. Lymph node metastases represent a critical step in the progression of cancer, signifying the spread of tumor cells beyond the primary site. The presence of lymph node involvement can indicate a more advanced disease stage and a higher risk of distant metastases, which can compromise the effectiveness of neoadjuvant chemotherapy.[20-22]

The absence of lymph node involvement emerged as a significant predictor of improved pathological complete response (pCR) rates in patients with triple-negative breast cancer (TNBC) undergoing neoadjuvant chemotherapy (NAC). This observation underscores the critical role of regional lymph node status in assessing the potential responsiveness of TNBC to NAC. The presence or absence of lymph node metastases serves as a surrogate marker for the extent of tumor burden and the biological aggressiveness of the disease. In the context of TNBC, a highly proliferative and aggressive subtype of breast cancer, the absence of lymph node involvement signifies a less extensive spread of the disease. This localized nature of the tumor may render it more susceptible to the cytotoxic effects of NAC. Chemotherapy agents primarily target rapidly dividing cells, and tumors with limited metastatic potential may exhibit a greater proportion of such cells. Consequently, these tumors may be more likely to achieve a complete pathological response, characterized by the absence of residual invasive cancer in the breast and lymph nodes after NAC. Conversely, the presence of lymph node metastases implies a more advanced stage of the disease with a greater likelihood of micrometastatic spread beyond the regional lymph nodes. This disseminated disease burden may be less amenable to eradication by NAC alone. Moreover, lymph node metastases may harbor tumor cells with diverse genetic and phenotypic profiles, potentially contributing to treatment resistance and a decreased likelihood of achieving pCR.[19-21]

The association between lymph node involvement and pCR rates has important implications for clinical practice. Accurate assessment of lymph node status through imaging modalities and sentinel lymph node biopsy is crucial for treatment planning and prognostication in TNBC. Patients with lymph node-negative disease may be considered candidates for NAC with a higher expectation of achieving pCR. This

may lead to breast-conserving surgery and improved long-term outcomes. On the other hand, patients with lymph node-positive disease may require more aggressive treatment approaches, such as combination therapy with NAC and targeted agents or immunotherapy. The identification of novel biomarkers and predictive models that can further refine the assessment of lymph node status and predict response to NAC is an area of active research. Furthermore, the observation that the Ki-67 index, a marker of cell proliferation, is associated with improved pCR rates in TNBC provides additional insights into the tumor biology and treatment response. Ki-67 is a nuclear protein expressed in actively dividing cells. A high Ki-67 index reflects a greater proportion of proliferating cells within the tumor, indicating a more aggressive phenotype.[20-22]

Paradoxically, tumors with a high Ki-67 index may be more sensitive to chemotherapy. This may be attributed to the fact that chemotherapy agents primarily target rapidly dividing cells. Therefore, tumors with a high proliferative index may exhibit a greater vulnerability to the cytotoxic effects of these agents. The association between the Ki-67 index and pCR rates has potential clinical implications. Ki-67 assessment may serve as a valuable prognostic and predictive biomarker in TNBC. Patients with tumors exhibiting a high Ki-67 index may be more likely to benefit from NAC and achieve pCR. This information can aid in treatment selection and patient counseling. However, it is important to acknowledge that Ki-67 is not a perfect predictor of response to NAC. Other factors, such as tumor heterogeneity, genetic alterations, and the tumor microenvironment, also play a role in determining treatment response. Therefore, Ki-67 assessment should be interpreted in conjunction with other clinical and pathological parameters. The absence of lymph node involvement and a high Ki-67 index are associated with improved pCR rates in TNBC patients receiving NAC. These findings highlight the importance of regional lymph node status and tumor proliferative activity in predicting response to NAC. Further research is needed to validate these findings and explore their implications for clinical practice. The development of novel biomarkers and predictive models that can integrate multiple clinical and biological parameters may lead to more personalized and effective treatment strategies for TNBC.[21-23]

5. Conclusion

This meta-analysis identified several factors associated with improved TNBC response to NAC, including younger age, smaller tumor size, lower clinical stage, absence of lymph node involvement, higher Ki-67 index, and use of platinum-based or immunotherapy-containing NAC regimens. These findings can inform patient selection and treatment optimization for NAC in TNBC.

6. References

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