

Ki-67 Expression and Rates of Pathologic Complete Response in T1cN0M0 Triple-Negative Breast Cancer: A National Cancer Database Analysis

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Abstract

Purpose

Treatment sequencing for T1cN0M0 triple-negative breast cancer (TNBC) remains controversial because neoadjuvant chemotherapy (NACT) has not demonstrated improved overall survival (OS) compared to adjuvant chemotherapy (ACT). Using pathologic complete response (pCR) as an early, positive prognostic indicator, this study evaluates how Ki-67 expression levels impact pCR rates in T1cN0M0 TNBC to identify patients who benefit most from upfront chemotherapy.

Methods

The National Cancer Database (NCDB) was queried (2018–2022) for female patients aged ≥ 18 with T1N0M0 TNBC undergoing chemotherapy and surgery. Patients were grouped into NACT or ACT cohorts and balanced using inverse probability of treatment weighting (IPTW). Cox multivariate analysis evaluated OS predictors, while logistic regression identified factors associated with pCR. A ROC curve was created for Ki-67 expression in the setting of pCR and the maximum Youden index established a threshold value.

Results

An analysis of 8,831 patients from the NCDB found no significant difference in OS between NACT and ACT, but multivariate analysis revealed lymphovascular invasion (LVI), invasive lobular subtype (ILC), and mixed invasive lobular/ductal subtype were associated with worse OS. In the NACT group, there was a 3.59 HR for worse OS in non-pCR patients compared to those achieving pCR. Ki-67 expression was strongly associated with pCR rates, with Ki-67 $\geq 45.8\%$ yielding a 45.3% pCR rate compared to 21.8% for Ki-67 $< 45.8\%$.

Conclusion

Although OS did not differ between NACT and ACT in T1cN0M0 TNBC, achieving pCR after NACT significantly improved survival. A Ki-67 threshold of $\geq 45.8\%$ predicted higher pCR rates and can guide patient selection for upfront chemotherapy.

Introduction

Breast cancer is one of the most diagnosed cancers globally, resulting in high morbidity and mortality [1]. Triple-negative breast cancer (TNBC), an aggressive subtype of breast cancer defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, accounts for approximately 15% of all new breast cancer cases [2, 3]. The invasive

nature of TNBC, high rates of recurrence, and low response to therapeutics contribute to its poor prognosis [3]. Chemotherapy remains a cornerstone of systemic therapy for TNBC, but the optimal sequencing of treatment interventions in early-stage disease continues to be debated [4]. The role of neoadjuvant chemotherapy (NACT) versus adjuvant chemotherapy (ACT) in patients with small, node-negative tumors remains unclear [5].

For patients with T1cN0M0 TNBC, prior research has not demonstrated a significant, consistent overall survival (OS) advantage with NACT compared with ACT [6]. However, there is evidence that NACT may offer several potential benefits in the management of early-stage TNBC [7]. Pathologic complete response (pCR) following NACT has emerged as an early, positive prognostic indicator for favorable long-term outcomes in TNBC and is commonly used to stratify prognosis and guide post-neoadjuvant treatment decisions [8]. However, not all patients derive equal benefit from NACT, and reliable predictors of pCR in early-stage TNBC are incompletely defined.

Ki-67 is a nuclear protein expressed during cellular proliferation and has been widely studied as a prognostic and predictive biomarker in breast cancer [9]. Higher Ki-67 expression has been associated with increased chemosensitivity in TNBC, yet its clinical utility in guiding treatment sequencing, especially in T1cN0M0, remains uncertain [10]. Ki-67 thresholds that meaningfully discriminate likelihood of pCR in this population have not been established, limiting its integration into clinical decision-making.

This study aimed to evaluate the association between Ki-67 expression and pCR among patients undergoing NACT, and the impact Ki-67 expression may have on the rate of pCR in the T1cN0M0 TNBC population. Using a large national database, we sought to compare survival outcomes between NACT and ACT, identify predictors of pCR, and determine a clinically relevant Ki-67 threshold to aid in selecting appropriate candidates for upfront chemotherapy.

Materials and Methods

Data was obtained from the National Cancer Database (NCDB) 2022 Participant User File, a nationwide oncology registry jointly sponsored by the American College of Surgeons and the American Cancer Society. The NCDB captures approximately 70% of newly diagnosed malignancies in the United States from more than 1,500 Commission on Cancer-accredited facilities. This study was approved by the Johns Hopkins Institutional Review Board (IRB00363497).

Adult female patients aged 18 years and older, diagnosed with clinical T1cN0M0 TNBC between 2018 and 2022, were identified from the NCDB. Patients who underwent both chemotherapy and breast surgery were included. Patients with missing treatment sequence information, unknown survival data, metastatic disease, or incomplete pathologic response data were excluded from the corresponding analyses (Fig. 1).

Patients were categorized into NACT and ACT cohorts based on the sequence of systemic therapy relative to surgery. Baseline demographic, clinicopathologic, and treatment-related variables were collected, including age, race, tumor grade, lymphovascular invasion (LVI), histologic subtype, and Ki-67 proliferation index. The primary outcome was overall survival (OS), and secondary outcomes included pCR and predictors of pCR among patients receiving NACT. pCR was defined as ypT0N0M0 on final surgical pathology following completion of neoadjuvant chemotherapy. Baseline characteristics between the NACT and ACT cohorts were compared using chi-square tests for categorical variables and t-tests for continuous variables, as appropriate.

To reduce selection bias and account for baseline differences between treatment groups, inverse probability of treatment weighting (IPTW) based on propensity scores was performed. Propensity scores were generated using logistic regression incorporating clinically relevant covariates, including age, race, tumor grade, lymphovascular invasion (LVI), histologic subtype, and Ki-67 expression level. Kaplan-Meier survival analysis was used to compare overall survival (OS) between the NACT and ACT groups before and after IPTW adjustment. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors associated with OS. Among patients receiving NACT, univariable and multivariable logistic regression analyses were performed to identify factors associated with pathologic complete response (pCR), with results reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Among patients receiving NACT, additional analyses were performed comparing patients who achieved pCR with those who did not. Univariable and multivariable logistic regression analyses were conducted to identify factors associated with achievement of pCR, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). Ki-67 expression was analyzed both as a categorical variable divided into quintiles and as a continuous variable for receiver operating characteristic (ROC) curve analysis. The optimal Ki-67 cutoff for predicting pCR was determined using the maximum Youden Index. All statistical analyses were performed using Stata version 18 (StataCorp LLC, College Station, TX). A p-value ≤ 0.05 was considered statistically significant.

Results

Upon querying the NCDB for female patients ≥ 18 years of age with T1cN0M0 TNBC who underwent both chemotherapy and surgery between 2018 and 2022, we obtained a total of 8831 patients with a mean age of 60.0 ± 11.9 years. Prior to matching with IPTW, there were a total of 3563 (40.35%) patients in the NACT group and 5268 (59.65%) patients in the ACT group. After IPTW, a pseudo-population of 2666 (38.95%) patients undergoing NACT and 4177 (61.05%) patients undergoing ACT was established (Table 1).

Table 1. Baseline characteristics of study data obtained from the National Cancer Data Base before and after IPTW matching

Characteristic	Before matching		After matching	
	NACT	ACT	NACT	ACT
Total, n (%)	3563 (40.35%)	5268 (59.65%)	2666 (38.95%)	4177 (61.05%)
Sex	Female	Female	Female	Female
Age, mean (SD)	56.60 (12.02)	62.33 (11.23)	56.04 (12.03)	62.02 (11.27)
<i>Race</i>				
White	2649 (74.35%)	3831 (72.72%)	2000 (75.02%)	3069 (73.47%)
African American	698 (19.59%)	1138 (21.60%)	511 (19.17%)	873 (20.90%)
Asian	10 (0.28%)	21 (0.40%)	8 (0.30%)	16 (0.38%)
Other	70 (1.96%)	99 (1.88%)	49 (1.84%)	83 (1.99%)
Unknown	136 (3.82%)	179 (3.40%)	98 (3.68%)	136 (3.26%)
Tumor characteristics				
<i>Histology</i>				
Invasive ductal carcinoma	3439 (96.52%)	4869 (92.43%)	2567 (96.29%)	3876 (92.79%)
Invasive lobular carcinoma	24 (0.67%)	82 (1.56%)	16 (0.60%)	65 (1.56%)
Mixed IDC/ILC	21 (0.59%)	42 (0.80%)	19 (0.71%)	32 (0.76%)
Mucinous/signet ring carcinoma	1 (0.03%)	3 (0.06%)	1 (0.04%)	3 (0.07%)
Other histology	78 (2.19%)	272 (5.16%)	63 (2.36%)	201 (4.81%)
<i>Grade</i>				
Grade 1	36 (1.01%)	114 (2.16%)	33 (1.24%)	88 (2.11%)
Grade 2	740 (20.77%)	1266 (24.03%)	552 (20.71%)	1003 (24.01%)
Grade 3	2596 (72.86%)	3352 (63.63%)	1925 (72.21%)	2628 (62.92%)
Unknown	191 (5.36%)	536 (10.17%)	156 (5.85%)	458 (10.96%)
<i>Lymphovascular invasion</i>				
Not present	2267 (63.63%)	4020 (76.31%)	1680 (63.02%)	3157 (75.58%)
Present/identified	172 (4.83%)	707 (13.42%)	134 (5.03%)	552 (13.22%)
Unknown	1124 (31.55%)	541 (10.27%)	852 (33.08%)	468 (11.20%)
<i>Ki-67 expression level</i>				
0–20%	390 (10.95%)	835 (15.85%)	305 (11.44%)	668 (15.99%)
21–40%	610 (17.12%)	1096 (20.80%)	435 (16.32%)	873 (20.90%)
41–60%	677 (19.00%)	998 (18.94%)	511 (19.17%)	797 (19.08%)
61–80%	1032 (28.96%)	1288 (24.45%)	778 (29.18%)	1013 (24.25%)
81–100%	854 (23.97%)	1051 (19.95%)	637 (23.89%)	826 (19.77%)
Vital status				
Dead	131 (4.91%)	279 (6.68%)	—	—
Alive	2535 (95.09%)	3896 (93.32%)	—	—
Follow-up, months, mean (SD)	37.4 (14.6)	39.9 (16.1)	—	—

Kaplan-Meier analysis before and after matching exhibited no significant difference in OS between the NACT and ACT groups (Figure 2). Multivariate analysis demonstrated that lymphovascular invasion (LVI) HR 2.48 (95%CI 1.82-3.38, $p<0.001$), invasive lobular subtype HR 2.33 (95% CI 1.00-5.43, $p=0.050$), and mixed invasive lobular/ductal carcinoma subtype HR 5.94 (95% CI 2.66-13.27, $p<0.001$) were predictors of worse OS. Both grade II disease HR 3.40 (95% CI 1.04-11.13, $p=0.043$) and grade III disease HR 3.79 (95%CI 1.18-12.17, $p=0.025$) were found to be significant for worse OS on univariate analysis, but not significant on multivariate analysis (Table 2).

Figure 2. Kaplan-Meier survival curves of neoadjuvant and adjuvant chemotherapy groups (A) before and (B) after matching with IPTW. No significant difference in OS before matching ($p=0.63$) or after IPTW-adjustment ($p=0.79$).

Table 2. Univariate and multivariate analysis performed to calculate hazard ratios (HR) for demographic factors and tumor characteristics with regard to overall survival (OS).

Characteristic	Univariate		Multivariate	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Treatment group				
NACT (n = 2666, 38.95%)	Reference	—	Reference	—
ACT (n = 4177, 61.05%)	1.05 (0.82–1.33)	0.72	0.97 (0.74–1.26)	0.79
Demographics				
<i>Age</i>				
<50	Reference	—	Reference	—
≥50	NA	NA	NA	NA
<i>Race</i>				
White	Reference	—	Reference	—
African American	1.03 (0.79–1.33)	0.82	1.04 (0.77–1.41)	0.78
Asian	1.18 (0.27–5.08)	0.82	1.99 (0.49–8.02)	0.34
Other	NA	NA	NA	NA
Unknown	NA	NA	NA	NA
Tumor characteristics				
<i>Histology</i>				
Invasive ductal carcinoma	Reference	—	Reference	—
Invasive lobular carcinoma	1.95 (0.96–4.00)	0.066	2.33 (1.00–5.43)	0.05
Mixed IDC/ILC	5.09 (2.44–10.62)	<0.001	5.94 (2.66–13.27)	<0.001
Mucinous/signet ring carcinoma	4.92 (0.55–44.19)	0.16	4.29 (0.54–33.97)	0.17
Other histology	1.18 (0.63–2.22)	0.61	1.01 (0.47–2.18)	0.98
<i>Grade</i>				
Grade 1	Reference	—	Reference	—
Grade 2	3.40 (1.04–11.13)	0.043	3.19 (0.76–13.41)	0.11
Grade 3	3.79 (1.18–12.17)	0.025	3.81 (0.91–16.00)	0.068
Unknown	Excluded	—	Excluded	—
<i>Lymphovascular invasion</i>				
Not present	Reference	—	Reference	—
Present/identified	2.36 (1.78–3.15)	<0.001	2.48 (1.82–3.38)	<0.001
Unknown	1.13 (0.84–1.53)	0.43	1.20 (0.87–1.66)	0.28
<i>Ki-67 expression level</i>				
0–20%	Reference	—	Reference	—
21–40%	1.26 (0.84–1.90)	0.26	1.28 (0.79–2.06)	0.31
41–60%	0.98 (0.64–1.49)	0.92	1.12 (0.69–1.83)	0.64
61–80%	1.35 (0.92–1.99)	0.13	1.52 (0.94–2.46)	0.089
81–100%	1.17 (0.79–1.75)	0.42	1.34 (0.81–2.20)	0.25
Response to neoadjuvant chemotherapy				
pCR achieved	Reference	—	Reference	—
Non-pCR	3.59 (1.95–6.62)	<0.001	3.58 (1.91–6.71)	<0.001

The NACT group was then further divided into a pCR group with 1359 patients and a non-pCR group with 2204 patients. As compared to the group who achieved pCR, the non-pCR group was found to have worse OS with HR 3.59 (95%CI 1.95-6.62, $p < 0.001$) (Table 2). With regard to predictive factors for pCR, univariable logistic regression demonstrated that age > 50 OR 0.68 (95% CI 0.55-0.84, $p < 0.001$) was

associated with lower rates of pCR while grade III disease OR 3.57 (95% CI 1.21-10.54, p=0.021) was associated with higher rates of pCR. However, on multivariate analysis, these differences were no longer found to be significant. On univariate analysis, LVI was found to have decreased rates of pCR with OR 0.41 (95% CI 0.25-0.67, p<0.001), but there was insufficient data to run a multivariate analysis. All Ki-67 expression levels above the lowest quintile had an increased rate of pCR with Ki-67 21-40% OR 1.68 (95%CI 1.09-2.59, p=0.018), Ki-67 41-60% OR 3.52 (95%CI 2.33-5.33, p<0.001), Ki-67 61-80% OR 4.09 (95%CI 2.73-6.12, p<0.001), and Ki-67 81-100% OR 4.45 (95%CI 2.94-6.74, p<0.001), on multivariate analysis (Table 3).

Table 3. Secondary analysis of the NACT group divided into pCR and non-pCR groups. Univariate and multivariate logistic regression performed to obtain odds ratios (OR) of demographic factors and tumor characteristics related to achieving pCR.

Characteristic	Univariate		Multivariate	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
<i>N</i> = 3563 patients <i>pCR</i> = 1359 patients <i>Non-pCR</i> = 2204 patients				
Demographics				
<i>Age</i>				
<50	Reference	—	Reference	—
≥50	0.68 (0.55–0.84)	<0.001	0.86 (0.68–1.08)	0.19
<i>Race</i>				
White	Reference	—	Reference	—
African American	0.98 (0.80–1.20)	0.81	0.88 (0.70–1.11)	0.30
Asian	0.80 (0.20–3.19)	0.75	0.86 (0.20–3.78)	0.85
Other	0.70 (0.38–1.30)	0.26	0.90 (0.46–1.76)	0.76
Unknown	NA	NA	NA	NA
Tumor characteristics				
<i>Histology</i>				
Invasive ductal carcinoma	Reference	—	Reference	—
Invasive lobular carcinoma	Not enough data	NA	NA	NA
Mixed IDC/ILC	0.43 (0.12–1.54)	0.19	0.60 (0.15–2.43)	0.48
Mucinous/signet ring carcinoma	Not enough data	NA	NA	0.11
Other histology	0.49 (0.24–1.00)	0.05	0.69 (0.32–1.47)	0.34
<i>Grade</i>				
Grade 1	Reference	—	Reference	—
Grade 2	1.49 (0.50–4.46)	0.47	1.21 (0.39–3.77)	0.74
Grade 3	3.57 (1.21–10.54)	0.021	1.87 (0.61–5.78)	0.28
Unknown	Excluded	—	Excluded	—
<i>Lymphovascular invasion</i>				
Not present	Reference	—	Reference	—
Present/identified	0.41 (0.25–0.67)	<0.001	Not enough data, high unknown	NA
Unknown	Excluded	—	Excluded	—
<i>Ki-67 expression level</i>				
0–20%	Reference	—	Reference	—
21–40%	1.99 (1.31–3.02)	0.001	1.68 (1.09–2.59)	0.018
41–60%	4.49 (3.02–6.67)	<0.001	3.52 (2.33–5.33)	<0.001
61–80%	5.41 (3.69–7.93)	<0.001	4.09 (2.73–6.12)	<0.001
81–100%	6.00 (4.07–8.85)	<0.001	4.45 (2.94–6.74)	<0.001

Based on the maximum Youden Index, the optimal cutoff for Ki-67 expression was found to be 45.8%, with Ki-67 expression <45.8% having a pCR rate of 21.8% and Ki-67 ≥45.8% having a pCR rate of 45.3% (Chi² *p* value <0.001) (Figure 3).

Figure 3. Receiver operating characteristic (ROC) curve used to calculate the maximum Youden Index (*J* = sensitivity + specificity -1).

Discussion

This study examined the survival outcomes of T1cN0M0 TNBC patients who underwent surgery with neoadjuvant or adjuvant chemotherapy, and analyzed the clinicopathological features associated with achieving pCR. Overall, OS did not differ between NACT and ACT, pCR following NACT was associated with improved survival, and Ki-67 expression emerged as the strongest predictor of pCR.

On Cox multivariate analysis, lymphovascular invasion, invasive lobular carcinoma subtype, and mixed invasive lobular/ductal subtypes were associated with worse OS. LVI, which reflects tumor cell invasion into the blood and/or lymphatic systems, is a well-established adverse prognostic factor associated with increased metastatic potential and poorer oncologic outcomes [11, 12]. Given its association with worse OS, it was anticipated that LVI would also correlate with lower rates of pCR. However, while LVI demonstrated statistical significance on univariate analysis, incomplete data within the NCDB limited the current study's multivariate analysis.

Similarly, hormone receptor-positive invasive lobular carcinoma, compared to invasive ductal carcinoma, usually portends a more favorable early prognosis [13]. Triple negative invasive lobular carcinoma (TN-ILC) in recent studies, however, tends to have lower Ki-67, lower pCR rates, and worse survival despite seemingly indolent histologic features [14, 15]. Additionally, the diagnosis of invasive lobular carcinoma is more susceptible to initial radiographic underestimation, particularly in the absence of preoperative MRI, which may partially contribute to poorer outcomes observed in this group [16, 17].

Zheng et al. (2025) performed a parallel population-based analysis of patients with T1cN0M0 TNBC using the SEER database (2010–2020), and similarly found no significant difference in OS between NACT and ACT groups [18]. Importantly, both studies demonstrated that patients who achieved pCR following NACT had significantly better OS (HR 0.429, 95% CI 0.242–0.762) compared to those unable to achieve pCR [18]. In a notable difference, Zheng et al. identified younger age and grade III disease as independent predictors of pCR on multivariate analysis. While these variables were significant on univariate analysis in the present study, they did not remain significant on multivariate analysis. This discrepancy may be explained by the inclusion of Ki-67 in the present study's model, which is not available in the SEER database. Younger patients and high-grade TNBC are both known to exhibit higher proliferative indices, suggesting that Ki-67 expression itself may represent a more direct biologic predictor of achieving pCR. Consistent with this hypothesis, we found increasing Ki-67 expression was strongly associated with achieving pCR across all quintiles above the reference group. Using the maximum Youden index, the present study identified an optimal Ki-67 threshold of 45.8%, with patients below this threshold achieving a pCR rate of 21.8% compared to a pCR of 45.3% among patients with a Ki-67 $\geq$ 45.8%.

Importantly, the present study expands upon the above findings by identifying a Ki-67 threshold specific to the T1cN0M0 population, a subgroup that has not been previously well characterized. Despite current

guidelines recommending NACT for $\geq T2$ TNBC lesions [19], 40.35% of this study population still underwent chemotherapy prior to surgery (Table 1). Tumor characteristics and patient demographics undoubtedly played a role in decision-making, but these elements and their respective contributions have been incompletely defined. The findings of this study suggest that Ki-67 may serve as a clinically useful biomarker that may refine the selection of patients most likely to benefit from upfront chemotherapy.

Limitations

There were some limitations to this study. First, there was inherent selection bias due to the retrospective nature of this study. Although IPTW was used to reduce confounding, unmeasured and/or missing variables including patients' germline BRCA mutation status, patient performance status, as well as the type, dose, and duration of treatment may have influenced treatment allocation and outcome. Patients' treatments may be further affected by their treatment tolerance, physician preference, and/or institutional treatment patterns, for which current national databases do not account.

There were multiple limitations as a result of using the NCDB. The NCDB is a hospital-based registry capturing data from the Commission on Cancer-accredited facilities, and as such may not be fully representative of the general US cancer population [20, 21]. The NCDB also contains a substantial degree of missing or incomplete data for certain clinicopathologic variables. In the current study, this was particularly relevant for the LVI analysis where insufficient data precluded multivariate evaluation of its association with pCR. Additionally, the NCDB does not undergo central pathology review, which is important given the well-described interobserver variability and lack of assay standardization when it comes to Ki-67 evaluation [22].

Importantly, the NCDB does not detail chemotherapy regimens, including the treatment type, dose, or completion rates, and does not adequately capture the utilization of modern immunotherapy. This latter point is particularly relevant given that pembrolizumab combined with neoadjuvant chemotherapy is now the standard of care for high-risk early-stage TNBC following the KEYNOTE-522 trial, which demonstrated significantly improved pCR rates with pembrolizumab-chemotherapy compared to chemotherapy alone (64.8% vs. 51.2%, respectively) [23].

Notably, pembrolizumab was approved by the FDA in July 2021, and the current study period (2018–2022) straddles this time point [24]. Earlier years of the present cohort almost certainly did not include checkpoint inhibitors in their systemic therapies. This may explain, at least in part, why the observed pCR rate in this study was lower than the ~ 65% reported in contemporary studies incorporating checkpoint inhibitors. Similarly, KEYNOTE-522 showed that there was a significant OS benefit with a 5-year OS of 86.6% vs. 81.7% with the use of pembrolizumab, emphasizing the importance of accounting for immunotherapy when evaluating OS as an endpoint for future analyses [25].

Long-term follow up data was also limited, as Ki-67 data had only begun to be incorporated in the NCDB starting in 2018, restricting this study period from 2018–2022. Finally, this study focused exclusively on T1cN0M0 disease. As such, it is difficult to determine whether the observed association between Ki-67

expression and pCR was driven solely by tumor biology vs. if it was also influenced by the relatively narrow tumor size range examined.

Conclusions

While OS was not significantly different for NACT and ACT in T1cN0M0 TNBC, pCR following NACT was associated with improved OS compared to the non-pCR group. LVI, invasive lobular subtype, and mixed invasive lobular/ductal subtype were associated with worse OS. Age < 50 and high-grade disease were not found to be associated with increased achievement of pCR, but each quintile of Ki-67 expression above reference value was determined to be significant. Ki-67 expression $\geq 45.8\%$ was associated with significantly higher rates of pCR and this value. In addition to the consideration of multiple clinical factors, this Ki-67 threshold may help identify which patients with T1cN0M0 TNBC may be most likely to achieve pCR, and therefore derive the greatest benefit from a neoadjuvant approach.

Future Directions

Prospective studies are needed to validate the prognostic and clinical utility of using a Ki-67 threshold in patients with early-stage TNBC in guiding treatment decisions. These would allow for more detailed data capturing of patients' systemic therapy regimens and treatment adherence, and importantly incorporate immunotherapy data. Expanding the study population to include T2 and higher tumors could help elucidate whether Ki-67 and pCR is driven purely by tumor biology vs. whether the interplay between proliferative index and tumor burden may make a significant difference in response.

Further investigations looking more closely at triple negative invasive lobular subtypes (TN-ILC) is also warranted. Although this is a rare subtype and makes up a small proportion of the present study cohort, it is associated with significantly worse OS. Expanding the data set to include additional years and tumor stages may provide enough numbers to better characterize treatment response and outcomes in this population.

Finally, the integration of Ki-67 with other emerging biomarkers such as PD-L1, stromal tumor-infiltrating lymphocytes, and/or genomic signatures may improve the accuracy of future pCR predictive models and aid in selecting which patients with early-stage TNBC may benefit most from neoadjuvant therapy.

Declarations

Competing interests:

The authors have no relevant financial or non-financial interests to disclose

Ethics approval:

This study was approved by the Johns Hopkins Institutional Review Board (IRB00363497).

Consent to participate:

Given the retrospective nature of the study using population-based data, the requirement for written informed consent was waived.

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Author Contribution

AV: writing- original draft. FS: formal analysis, methodology. SD: writing- review and editing. CS: writing- review and editing. PR: visualization. IS: visualization. AS: writing- review and editing. CSM: conceptualization, writing- review and editing. OS: conceptualization, writing- review and editing. All authors have read and agreed to the final version of the manuscript

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Data Availability

The data that support the findings of this study are available from the National Cancer Database (NCDB). Restrictions apply to the availability of this data, which is not publicly available. Data is, however, available from the authors upon reasonable request and with the permission of the American College of Surgeons (ACS) and the Commission on Cancer (CoC).

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Figures

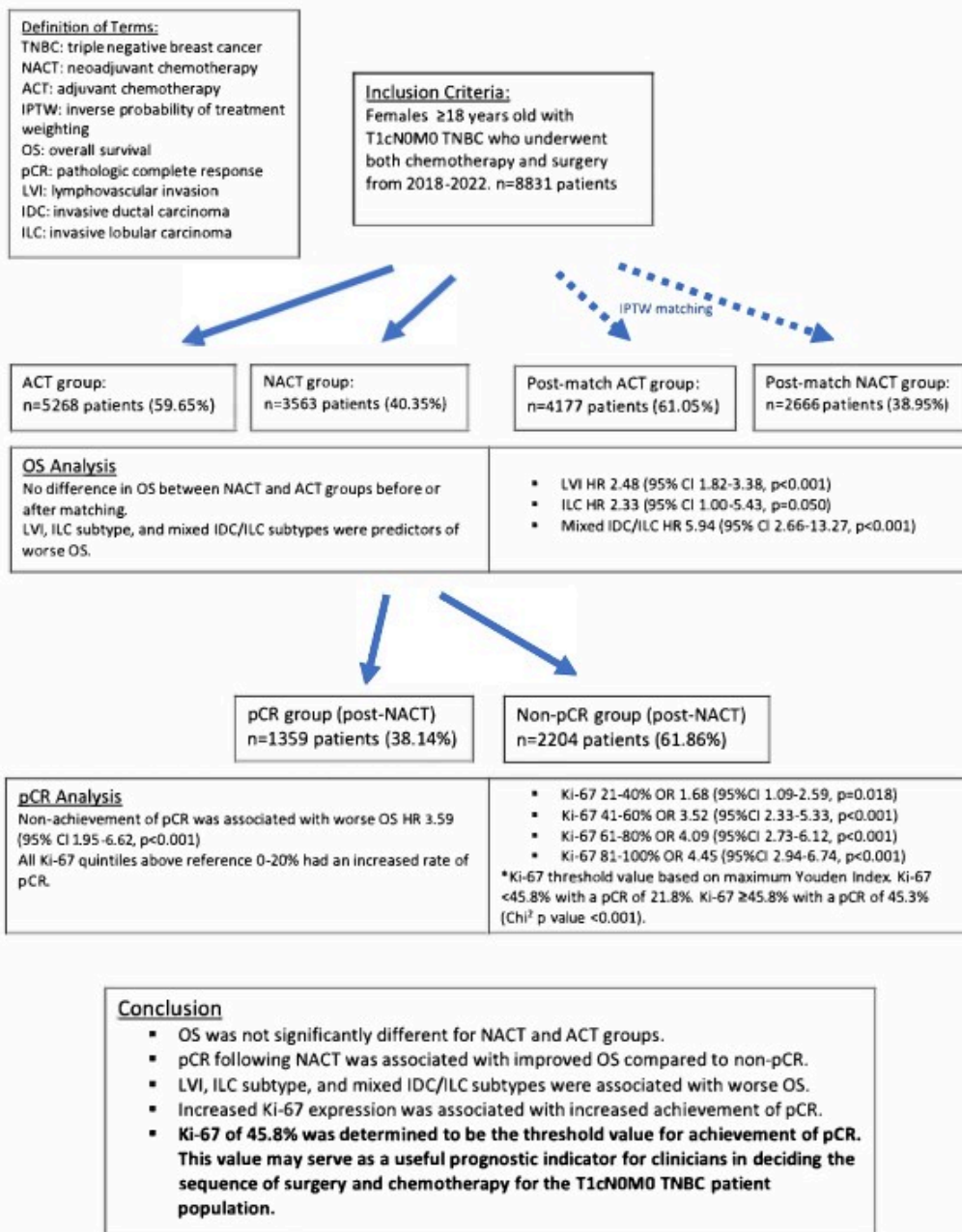


Figure 1

Flowsheet of study design

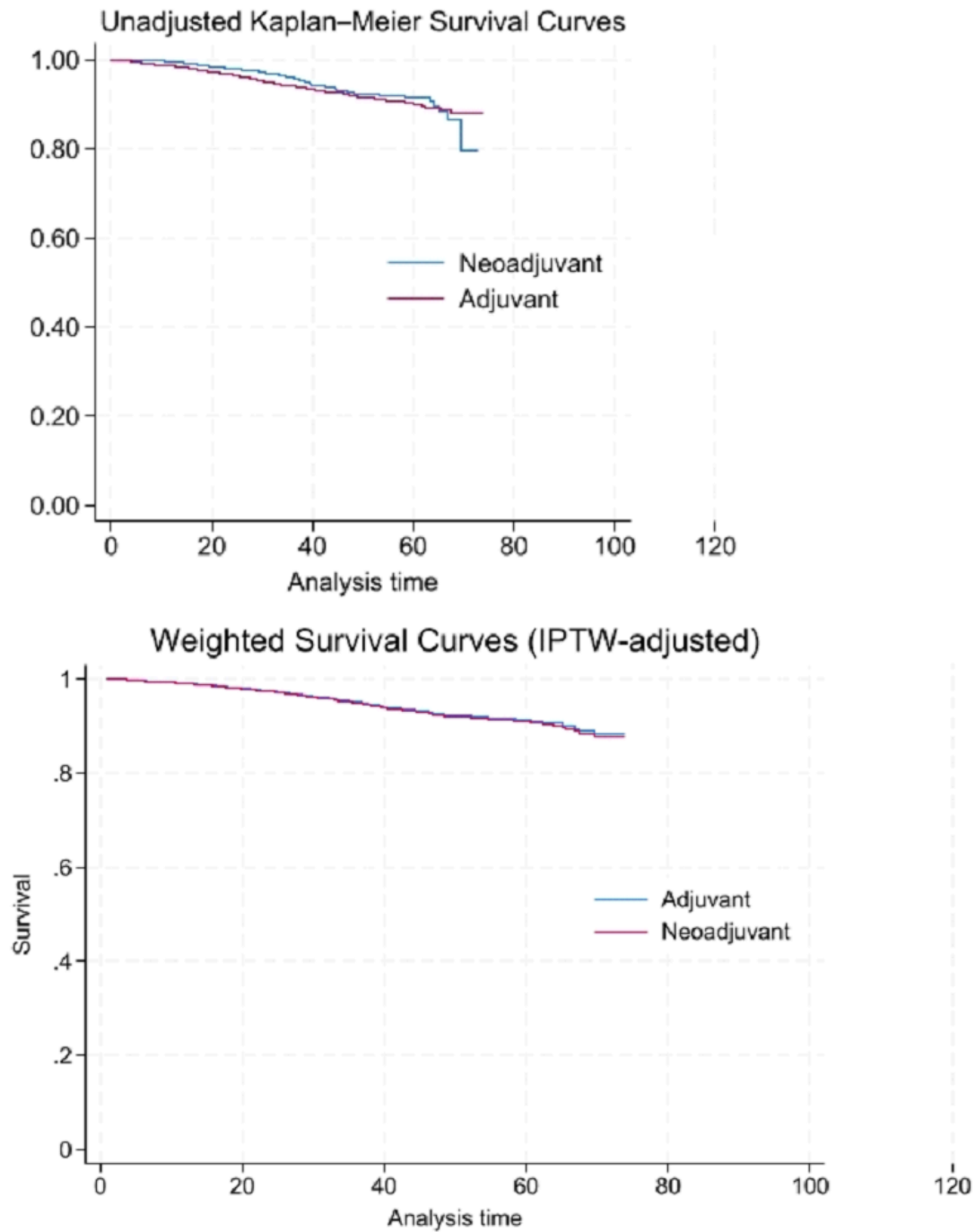


Figure 2

Kaplan-Meier survival curves of neoadjuvant and adjuvant chemotherapy groups (A) before and (B) after matching with IPTW. No significant difference in OS before matching ($p=0.63$) or after IPTW-adjustment ($p=0.79$).

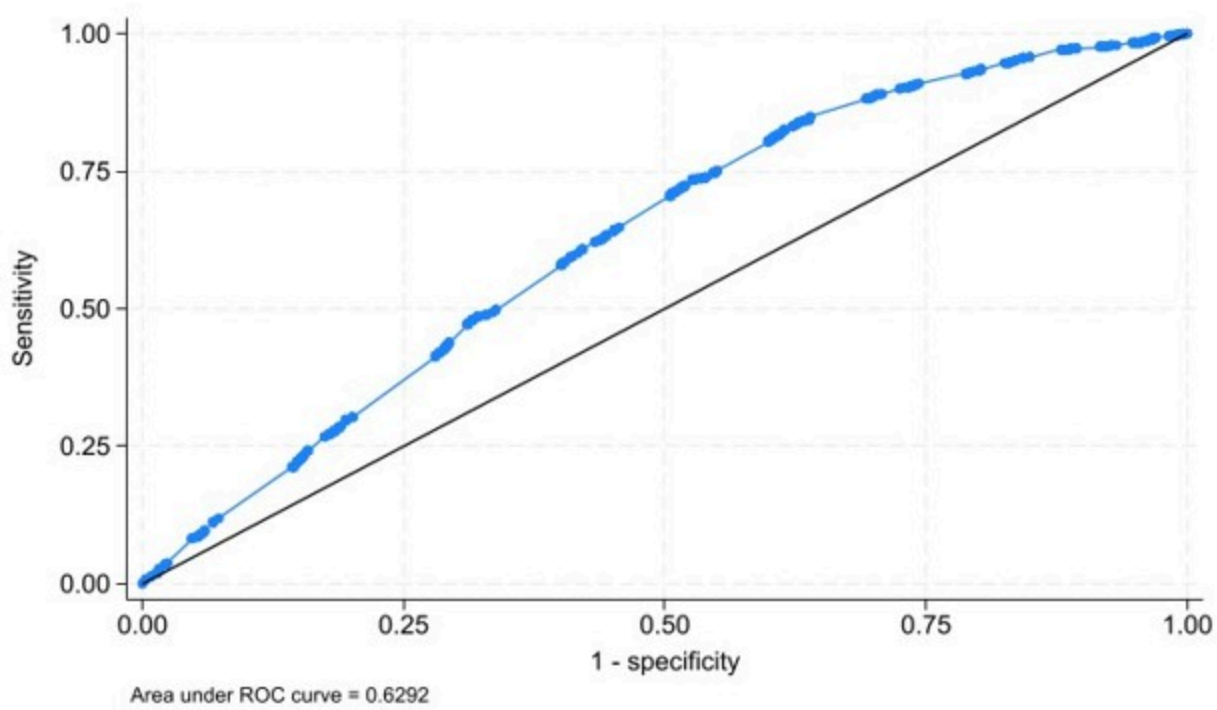


Figure 3

Receiver operating characteristic (ROC) curve used to calculate the maximum Youden Index ($J = \text{sensitivity} + \text{specificity} - 1$).