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High TROP-2 expression as a predictor of poor neoadjuvant chemotherapy response in luminal B breast cancer: a retrospective clinicopathological study

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Abstract

Purpose Trophoblast cell surface antigen 2 (TROP-2) is a type I transmembrane glycoprotein that is expressed on the cell surface. It is overexpressed in various epithelial malignancies. Due to its protumoral biological effects and its role as a target receptor for antibody–drug conjugates, TROP-2 is of particular clinical interest. This study aims to investigate the relationships between TROP-2 expression, clinicopathological parameters, and response to neoadjuvant chemotherapy in invasive breast carcinomas.

Methods TROP-2 expression was evaluated by immunohistochemically from 211 cases of invasive breast carcinoma. The H-score was used in the TROP-2 assessment. Cases with a score of 0-200 were considered low, and cases with a score above 200 were considered high TROP-2 expression.

Results High TROP-2 expression was significantly associated with HER2 negativity ($p=0.019$), lymph node metastasis ($p=0.016$), and a poor response to neoadjuvant chemotherapy (RCB-II/III) ($p=0.01$). Multivariate analysis revealed that molecular subtype, stromal tumor-infiltrating lymphocytes, and high TROP-2 expression were independent predictors of neoadjuvant chemotherapy response.

Conclusion High TROP-2 expression was found to be associated with adverse clinicopathological parameters and poor response to neoadjuvant chemotherapy, and was identified as an independent predictive biomarker for neoadjuvant response. The lower pathological complete response rates observed in luminal B molecular subtype breast carcinomas with high TROP-2 expression suggest that TROP-2-targeting agents should be investigated more thoroughly in the neoadjuvant therapy setting, particularly in LB subtype cases. Furthermore, assessing TROP-2 expression in each case will aid in optimal patient selection for treatment and contribute to the personalization of oncological therapy.

Keywords TROP-2 expression, Neoadjuvant chemotherapy response, Breast carcinomas, Molecular subtype

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Introduction

Trophoblast cell surface antigen 2 (TROP-2), an integral component of the EpCAM family, is a type I transmembrane glycoprotein that is encoded by the TACSTD2 gene. It is located on the outer surface of the cell membrane and is associated with intracellular Ca^{2+} signaling and the activation of proliferative pathways, such as MAPK and PI3K/AKT. It is expressed at low levels in many healthy epithelial cells and contributes to cellular proliferation, adhesion and tissue regeneration. In malignant epithelial tumors, TROP-2 is often overexpressed and has a predominantly protumoral effect, promoting tumor cell growth, movement, infiltration, the process by which cells change from a epithelial to a mesenchymal state (EMT), and anti-apoptotic effects [1–4].

TROP-2 expression has two distinct clinical and biological implications. Firstly, the TROP-2 glycoprotein itself exerts intrinsic protumoral biological effects on tumor cells. Secondly, its high expression on tumor cells serves as a specific gateway, facilitating the intracellular delivery of chemotherapeutic agents.

Antibody drug conjugates targeting the TROP-2 receptor, such as sacituzumab govitecan (SG), have been shown to improve survival in patients with advanced metastatic triple-negative (TN) and hormone receptor-positive / human epidermal growth factor receptor 2 (HER2)-negative breast carcinoma, and their use has been approved by the US Food and Drug Administration [5, 6]. The therapeutic mechanism of SG does not involve the direct inhibition of TROP-2-mediated biological processes. Instead, its antitumor activity results from the induction of DNA damage by the cytotoxic load delivered intracellularly as a topoisomerase I inhibitor.

Despite the well-established protumoral activity of high TROP-2 expression in tumor cells, its adequacy as an independent prognostic marker and its impact on the response to neoadjuvant chemotherapy (NAC) remain controversial. The proliferative and anti apoptotic effects of high TROP-2 expression have a reverse effect on the NAC response. It is thought that the predominance of these effects varies case by case basis, depending on the level of TROP-2 expression and the tumor's molecular and microenvironmental characteristics.

In this study, we aimed to investigate TROP-2 expression rates across different molecular subtypes of invasive breast carcinoma, their association with clinicopathological parameters, their relationship with the immune microenvironment, and their effect on response to NAC.

Materials and methods

Case selection and inclusion criteria

The electronic medical database of our institution was reviewed retrospectively to identify patients diagnosed with invasive breast carcinoma via core needle biopsy between January 2014 and December 2024, and who underwent definitive surgical treatment (mastectomy or breast-conserving surgery) at our institution. Patients received standard NAC regimens, which typically consisted of combinations of anthracyclines and taxanes (such as cyclophosphamide, doxorubicin and paclitaxel). For patients with HER2-positive disease, targeted therapy with trastuzumab, with or without pertuzumab, was administered alongside the taxane component of the NAC regimen, in line with clinical guidelines.

Patients with metastatic disease at diagnosis, those who developed a second primary malignancy after diagnosis, patients who died within the first month following diagnosis, and patients with incomplete or unavailable follow-up data were excluded from the study. After applying these criteria, 211 breast carcinoma cases were included in the study. Clinical data, including age, pretreatment tumor size, NAC regimen, recurrence / metastasis status, and survival outcomes, were obtained from the hospital's electronic database.

Hematoxylin and eosin (H&E) and immunohistochemically stained slides from core needle biopsies and resection specimens, as well as paraffin blocks containing pretreatment biopsy tissue, were retrieved from the pathology archives. Pathological variables, including histological type, histological grade, tumor size, angiolymphatic invasion, and axillary lymph node status, were obtained from the pathology reports of both the initial biopsy and the surgical specimen.

Morphological and immunohistochemical evaluation

Morphological and immunohistochemical evaluations were independently and blindly performed by two pathologists (OO and ÇÖ) using an Olympus BX-51 light microscope (Olympus Corporation, Tokyo, Japan; ocular 22 mm). When the scores were not in agreement, a multi-headed microscope was used to re-evaluate the slides to reach a consensus. H&E-stained sections and immunohistochemically stained slides from core needle biopsy specimens were re-evaluated for estrogen receptor (ER) (anti-ER, clone SP1, REF: 790–4324, Ventana), progesterone receptor (PR) (anti-PR, clone 1E2, REF: 790–2223, Ventana), HER2 (anti-HER2/neu, clone 4B5, REF: 790–2991, Ventana) and Ki-67 (anti-Ki-67, clone 30 – 9, REF: 790–4286, Ventana). Nuclear staining in ≥ 10% of carcinoma cells was considered positive for ER and PR expression [7].

For human epidermal growth factor receptor 2 (HER2) evaluation, cases showing intense complete membranous staining in ≥ 10% of tumor cells (score 3+) by immunohistochemistry or cases with equivocal (score 2+) immunohistochemical results accompanied by gene amplification detected by silver in situ hybridization were considered HER2-positive [8]. The Ki-67 proliferation index was

assessed by manually estimating the average percentage of positively stained tumor nuclei in biopsy specimens. Accordingly, cases with a Ki-67 proliferation index of 20% or more were classified as having a high Ki-67 proliferation index [9].

Histological tumor types were classified according to the World Health Organization (WHO) classification of breast tumors, and nuclear grade was determined using the Nottingham histological grading system. Based on the results of immunohistochemical analyses of ER, PR, HER2 and Ki-67, tumors were categorized into surrogate molecular subtypes as follows: Luminal A (LA) (ER+, PR+/−, HER2−, low Ki-67); Luminal B (LB) (ER+, PR+/−, HER2 + or ER+, PR+/−, HER2 − with high Ki-67); HER2-enriched (HER2) (ER−, PR−, HER2+); and triple-negative (TN) (ER−, PR−, HER2−) [10, 11].

Stromal tumor infiltrating lymphocytes (sTILs) as indicators of the tumor immune microenvironment were evaluated according to the 2014 criteria proposed by the International TILs Working Group (ITILWG) [12]. Accordingly, areas of necrosis and artifacts, as well as inflammatory cells associated with benign breast tissue or surrounding in situ carcinoma, were excluded from the evaluation of H&E-stained sections from core needle biopsy specimens. The proportions of lymphocytes and plasma cells in the tumor stroma were assessed. Mean sTILs density was recorded in 10%-increments. Cases with < 10% sTILs were classified as low, those with 20–40% as intermediate, and those with > 40% as high (Figs. 1 and 2). For statistical analyses, cases were divided into two groups: low sTILs and high sTILs (including the intermediate and high groups). This was done to achieve more balanced group distributions.

For TROP-2 immunohistochemistry, a mouse monoclonal anti-TROP-2 antibody (clone B-9; Santa Cruz Biotechnology, Dallas, TX, USA; catalogue no. sc-376746) was used at a dilution of 1:100. Immunohistochemical staining was performed using the Roche / Ventana BenchMark Ultra IHC Stainer (Tucson, AZ, USA). TROP-2 expression was evaluated using the histological score (H-score), which incorporates both staining intensity and extent [13]. Staining intensity was graded on a scale of 0 to 3 (none, weak, moderate, or strong) and the percentage of tumor cells at each intensity level was recorded (Figs. 3, 4, 5 and 6). The H-score was calculated by multiplying each intensity score by its corresponding percentage of stained cells and summing the results. Cases with an H-score of > 200 were classified as having high TROP-2 expression, while those with an H-score of 0–200 were classified as having low expression [13, 14].

Assessment of response to neoadjuvant chemotherapy

During routine pathological evaluation, surgical resection specimens (mastectomy or breast-conserving surgery) obtained after NAC were fixed in 10% neutral buffered formalin for 24–48 h. In cases with a grossly identifiable tumor, at least three tissue blocks were sampled. In cases without a grossly identifiable tumor, the

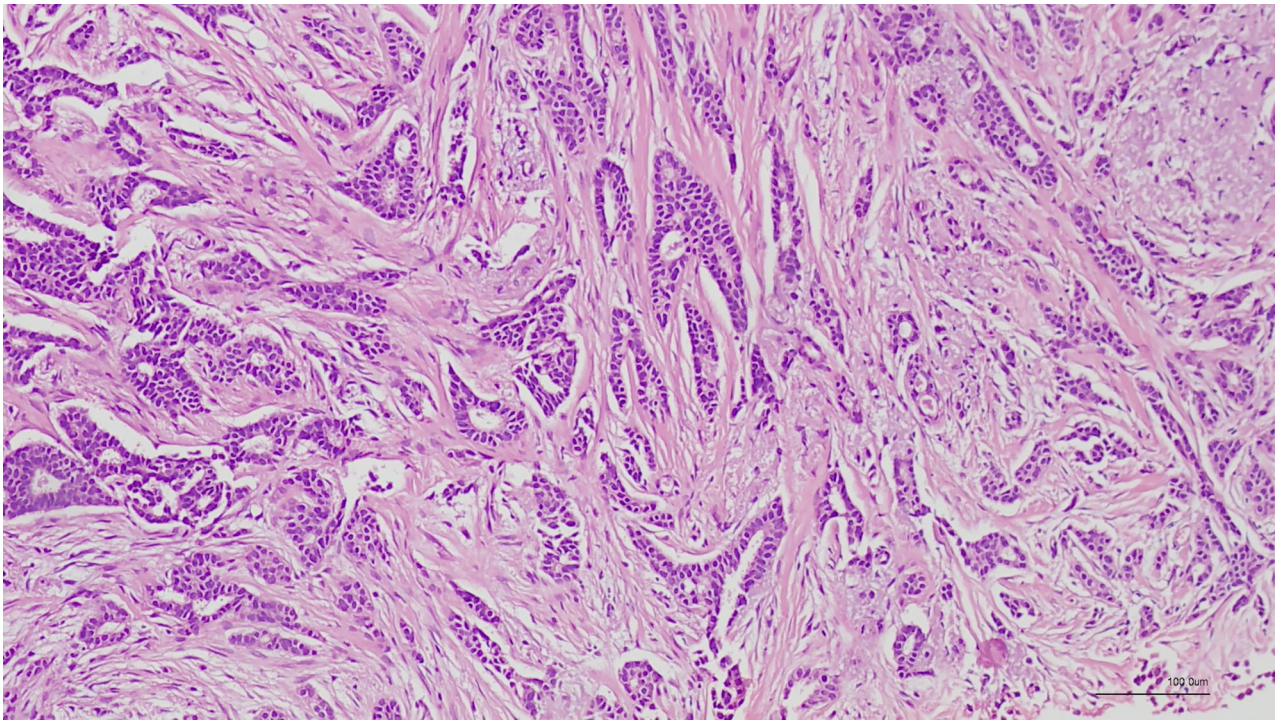


Fig. 1 Invasive breast carcinoma, low stromal tumor infiltrating lymphocytes (H&E x 100)

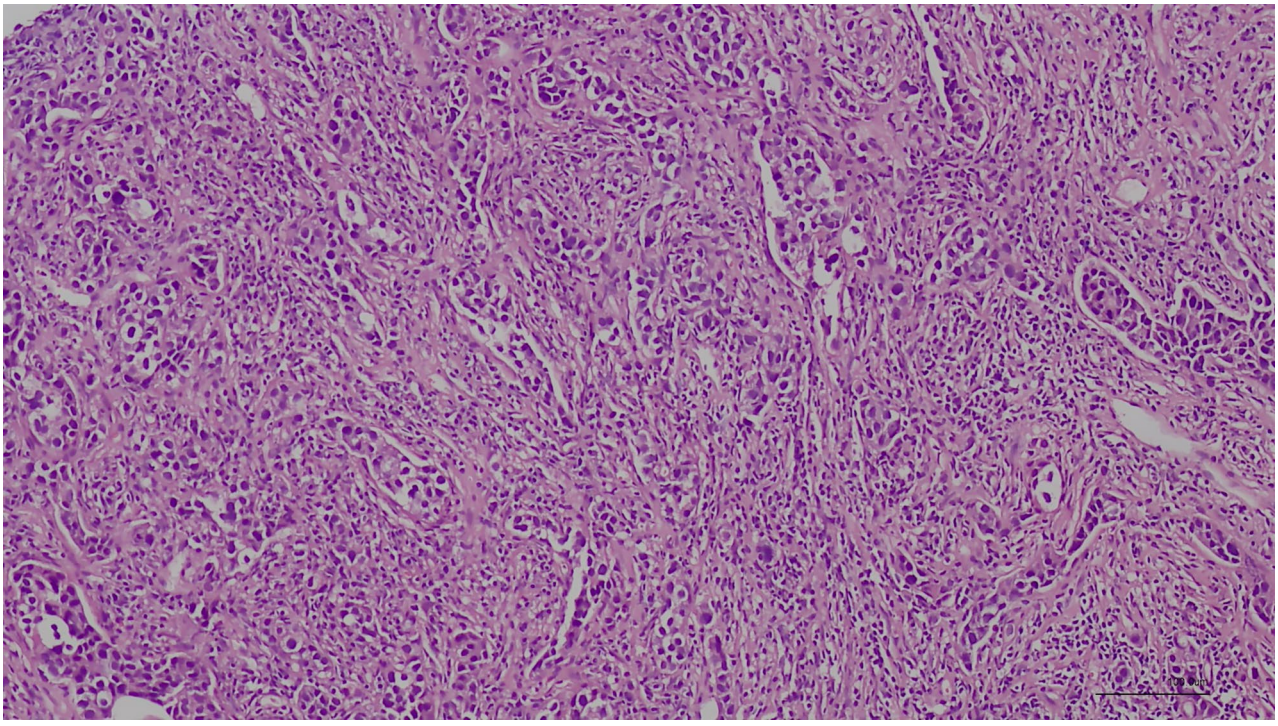


Fig. 2 Invasive breast carcinoma, high stromal tumor infiltrating lymphocytes (H&E x 100)

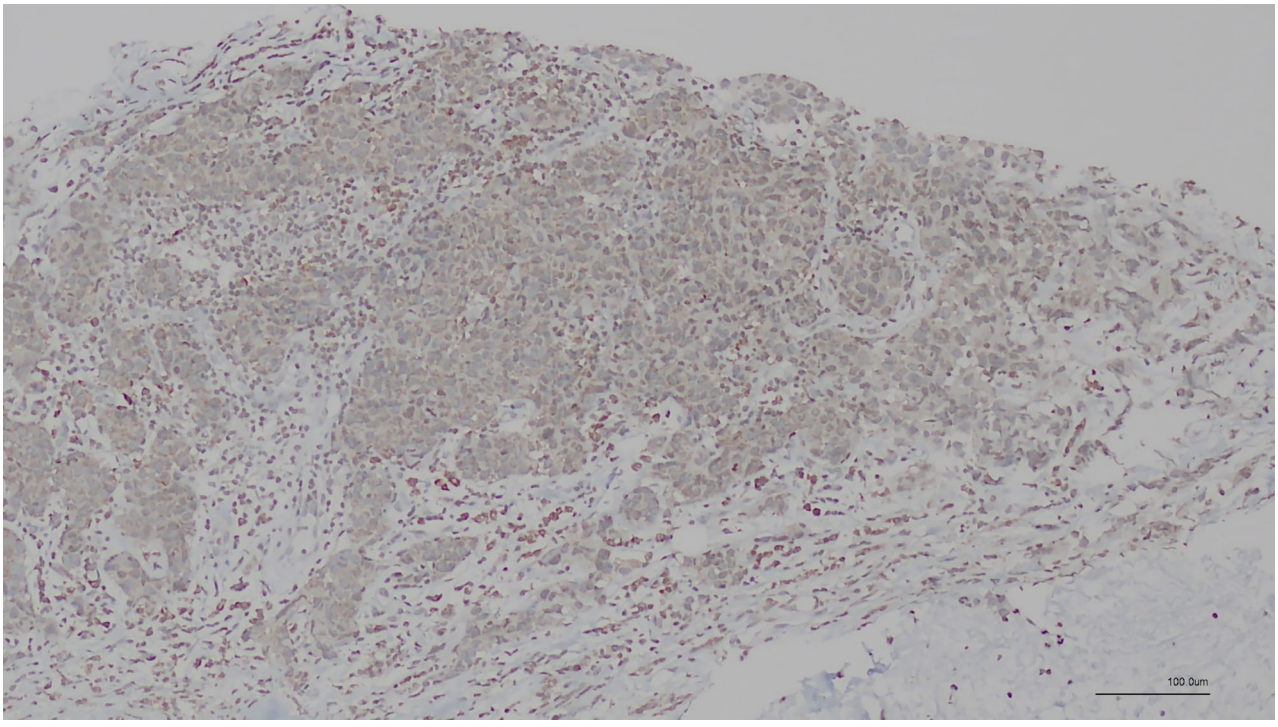


Fig. 3 Invasive breast carcinoma, TROP-2 immunohistochemical staining, none (x 100)

entire radiologically defined tumor bed and all fibrotic areas were extensively sampled.

The pathological response to NAC was assessed using the Residual Cancer Burden (RCB) scoring system [15]. The RCB score was calculated using the RCB calculator, taking into account the size of the primary tumor bed, tumor cellularity, the proportion of in situ carcinoma, the presence of lymph node metastasis, and the

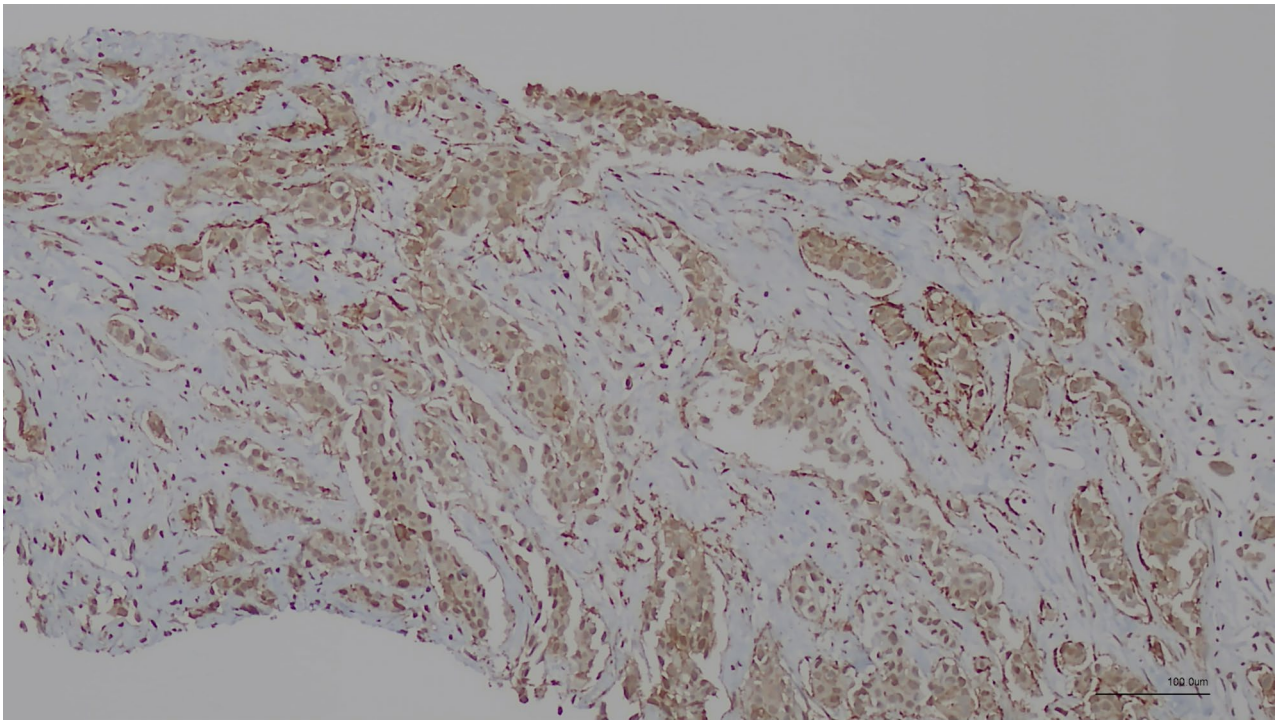


Fig. 4 Invasive breast carcinoma, TROP-2 immunohistochemical staining, weak intensity (x 100)

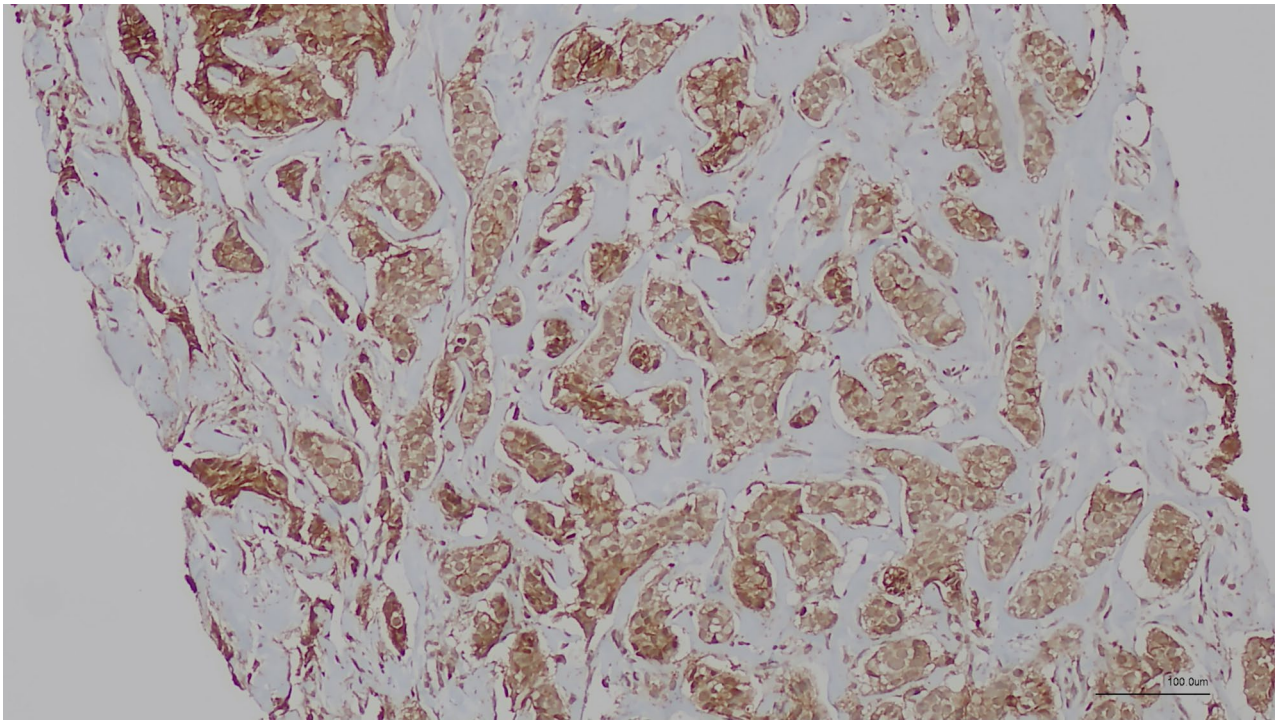


Fig. 5 Invasive breast carcinoma, TROP-2 immunohistochemical staining, moderate intensity (x 100)

size of metastatic deposits within lymph nodes. Based on the calculated RCB score, cases were classified into four categories: RCB-0, RCB-I, RCB-II, and RCB-III. Cases with an RCB score of 0 were considered to achieve a pathological complete response (pCR). For statistical analysis, patients were grouped into two categories: a good response group (RCB-0 and RCB-I), and a poor response group (RCB-II and RCB-III).

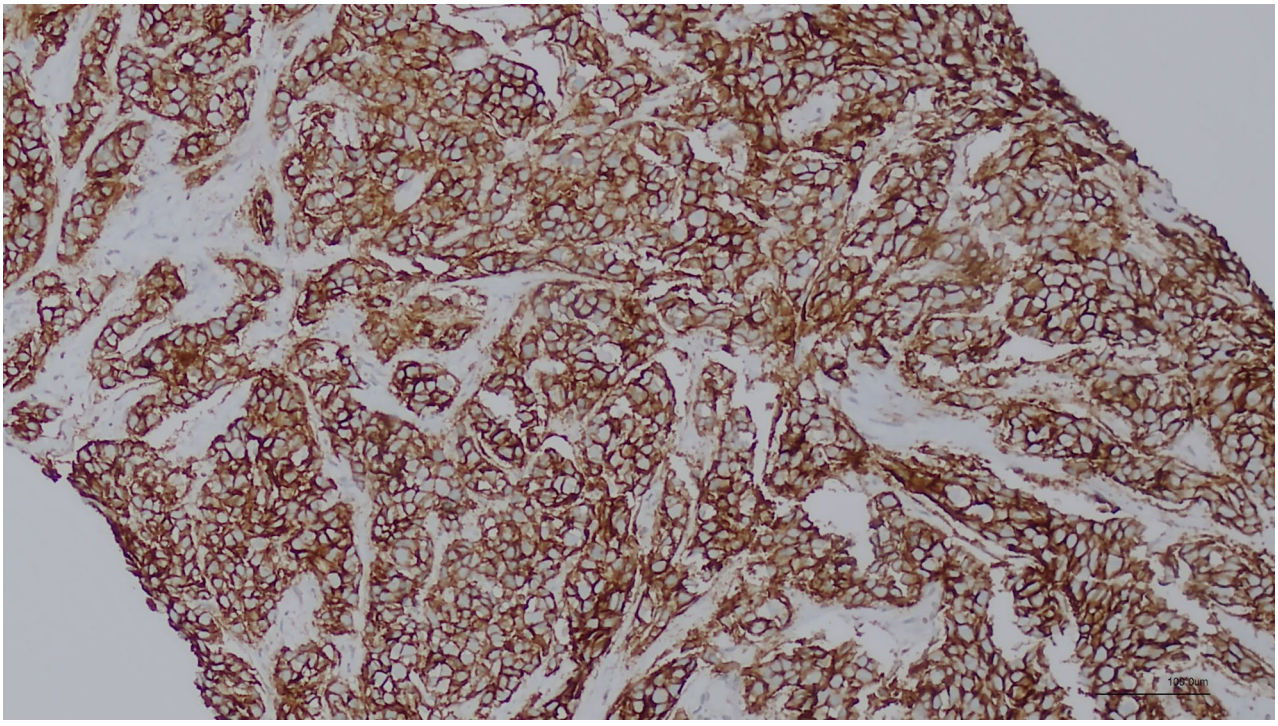


Fig. 6 Invasive breast carcinoma, TROP-2 immunohistochemical staining, strong intensity (x 100)

Outcomes

Disease-free survival (DFS) was defined as the period between the date of surgery and the first detection of disease recurrence or distant metastasis, as evidenced by radiological or pathological findings. Overall survival (OS) was defined as the time from the date of diagnosis to death from any cause or to the date of the last follow-up visit.

Statistical analysis

A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 29; IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages. The relationships between TROP-2 expression, RCB status (0, I vs. II, III) and clinicopathological variables were assessed using the chi-square test or Fisher's exact test, as appropriate. To identify factors associated with residual cancer burden (RCB), an initial univariate logistic regression analysis was performed. Variables with p-values < 0.10 in the univariate analysis were then included in a multivariate logistic regression model using a backward stepwise method to identify independent predictors of RCB. Results were reported as odds ratios (OR) with 95% confidence intervals (CIs).

Results

General clinicopathological characteristics

All 211 patients included in the study were female, with a mean age of 58 years (range 28–92 years). Histologically, 188 cases (89%) were classified as invasive breast carcinoma, no special type (NST), while the remaining 23 cases (11%) represented other subtypes, including invasive lobular, mucinous, and micropapillary carcinomas. The pathological tumor stage was pT1 in 66 cases, pT2 in 128 cases, and pT3 in 17 cases. According to surrogate molecular subtyping, 39 cases were classified as LA, 120 as LB, 29 as HER2, and 23 as TN breast carcinoma. Low sTILs were observed in 101 cases, while 110 cases showed high sTILs.

TROP-2 expression and associated clinicopathological parameters

The associations between TROP-2 expression and clinicopathological parameters are summarized in Table 1. Immunohistochemical evaluation of TROP-2 demonstrated a predominantly cytoplasmic and membranous staining pattern in most cases. Of the 211 cases examined, high TROP-2 expression was observed in 124 cases (58.7%), while 87 cases (41.3%) exhibited low expression. H-score distribution revealed 13 cases with scores of 100 or less, 74 cases with scores between 101 and 200, and 134 cases with scores of over 200. The high TROP-2 expression rates by molecular subtype were 69%

Table 1 Trop-2 expression and associated clinicopathological parameters

		TROP-2 expression				
		Low		High		
		Count	Column *N* %	Count	Column *N* %	*P* value
Molecular subtype	LA	12	13.8	27	21.8	0.087
	LB	51	58.6	69	55.6	
	HER2	17	19.5	12	9.7	
	TN	7	8.0	16	12.9	
sTILs	Low	40	46.0	61	49.2	0.645
	High	47	54.0	63	50.8	
Pathologic stage (diameter)	1	28	32.2	38	30.6	0.827
	2	51	58.6	77	62.1	
	3	8	9.2	9	7.3	
Position	Left	39	44.8	78	62.9	0.009
	Right	48	55.2	46	37.1	
Nuclear grade	1	1	1.1	3	2.4	0.181
	2	67	77.0	81	65.3	
	3	19	21.8	40	32.3	
Estrogen receptor	Negative	24	27.6	27	21.8	0.332
	Positive	63	72.4	97	78.2	
Progesterone receptor	Negative	37	42.5	39	31.5	0.099
	Positive	50	57.5	85	68.5	
HER 2 status	Negative	45	51.7	84	67.7	0.019
	Positive	42	48.3	40	32.3	
Ki- 67 proliferation index	Low	20	23.0	32	25.8	0.64
	High	67	77.0	92	74.2	
Angiolymphatic invasion	Negative	69	79.3	92	74.2	0.39
	Positive	18	20.7	32	25.8	
Perineural invasion	Negative	81	93.1	119	96.0	0.367
	Positive	6	6.9	5	4.0	
Lymph node metastasis	Negative	56	64.4	59	47.6	0.016
	Positive	31	35.6	65	52.4	
RCB G	RCB 0,1	45	51.7	42	33.9	0.01
	RCB 2,3	42	48.3	82	66.1	
Metastasis	Negative	72	82.8	96	77.4	0.343
	Positive	15	17.2	28	22.6	
Survival Status	Alive	80	92.0	112	90.3	0.684
	Dead	7	8.0	12	9.7	

Abbreviations: LA Luminal A, *LB* Luminal B, *HER2* Human epidermal receptor 2, *TN* Triple negative, *sTILs* Stromal tumor infiltrating lymphocytes, *RCB G* Residual cancer burden group

in LA, 57% in LB, 41% in HER2, and 70% in TN breast carcinoma.

Although higher levels of TROP-2 expression were proportionally more common in the LA and TN molecular subtypes, this difference was not statistically significant ($p = 0.087$). However, when cases were examined based solely on HER2 expression and high TROP-2 expression, HER2 negativity was found to be significantly associated with high TROP-2 expression ($p = 0.019$).

Specifically, high TROP-2 expression was observed to be associated with lymph node metastasis ($p = 0.016$), tumor position (left-sided) ($p = 0.009$), and poor treatment response (RCB-II/III) ($p = 0.01$); while no statistically significant association was found between high TROP-2 expression and molecular subtype ($p = 0.087$), ER expression ($p = 0.332$) or PR expression ($p = 0.099$), Ki-67 proliferation index ($p = 0.64$), sTILs ($p = 0.645$), metastasis development ($p = 0.343$), or survival outcomes ($p = 0.684$).

Response to neoadjuvant chemotherapy

In the entire study cohort, a complete pathological response (RCB-0) was achieved in 72 cases (34%), while a good response to NAC (RCB-0/1) was observed in 87 cases (41%). Cases with high TROP-2 expression showed a complete pathological response rate of 25% and a good response rate of 33%. Among cases with low TROP-2 expression, the complete response rate was 42.5%, and

the good response rate was 51.7%. Tumors with high TROP-2 expression had lower rates of both complete pathological response (RCB-0) and good treatment response (RCB-0/I), and this difference was statistically significant ($p = 0.01$).

Clinicopathological markers associated with RCB are shown in Table 2. Accordingly, a statistically significant association was found between RCB and high TROP-2 expression ($p = 0.01$), molecular subtype ($p < 0.001$), sTILs ($p < 0.001$), ER and PR expression ($p < 0.001$), HER2 expression ($p < 0.001$), Ki-67 proliferation index ($p < 0.001$), angiolymphatic invasion ($p < 0.001$), and metastasis development ($p < 0.001$).

When analyzed by molecular subtypes, the overall pathological complete response rates were 8% for luminal A (LA), 28% for luminal B (LB), 86% for HER2, and 43% for TN breast carcinomas. In cases with high TROP-2 expression, the pathological complete response rates were 7% in LA, 19% in LB, 83% in HER2, and 43% in TN tumors. Although a proportional decrease in treatment response was observed in LA, LB, and HER2 molecular subtype breast carcinomas with high TROP-2 expression, a statistically significant difference was detected only in LB molecular subtype cases ($p = 0.027$).

Univariate analysis revealed significant correlations between NAC response and high TROP-2 expression ($p = 0.01$), molecular subtype ($p < 0.001$), sTILs ($p < 0.001$), Ki-67 proliferation index ($p < 0.001$) (Table 3). Multivariate analysis revealed that molecular subtype (OR: 0.167; 95% CI: 0.080–0.349), sTILs (OR: 0.468; 95% CI:

Table 2 Residual cancer burden group and associated clinicopathological parameters

		RCB Groups				
		RCB 0,1		RCB 2,3		
		Count	Column *N* %	Count	Column *N* %	*P* value
Molecular subtype	LA	5	5.7	34	27.4	< 0.001
	LB	43	49.4	77	62.1	
	HER2	27	31.0	2	1.6	
	TN	12	13.8	11	8.9	
TROP-2 expression	Low	45	51.7	42	33.9	0.01
	High	42	48.3	82	66.1	
Tumor infiltrating lymphocytes	Low	29	33.3	72	58.1	< 0.001
	High	58	66.7	52	41.9	
Pathologic stage (diameter)	1	32	36.8	34	27.4	0.338
	2	48	55.2	80	64.5	
	3	7	8.0	10	8.1	
Position	Left	51	58.6	66	53.2	0.438
	Right	36	41.4	58	46.8	
Nuclear grade	1	2	2.3	2	1.6	0.308
	2	56	64.4	92	74.2	
	3	29	33.3	30	24.2	
Estrogen receptor	Negative	37	42.5	14	11.3	< 0.001
	Positive	50	57.5	110	88.7	
Progesterone receptor	Negative	50	57.5	26	21.0	< 0.001
	Positive	37	42.5	98	79.0	
HER 2 status	Negative	30	34.5	99	79.8	< 0.001
	Positive	57	65.5	25	20.2	
Ki- 67 proliferation index	Low	9	10.3	43	34.7	< 0.001
	High	78	89.7	81	65.3	
Angiolymphatic invasion	Negative	79	90.8	82	66.1	< 0.001
	Positive	8	9.2	42	33.9	
Perineural invasion	Negative	85	97.7	115	92.7	0.129
	Positive	2	2.3	9	7.3	
Lymph node metastasis	Negative	82	94.3	33	26.6	< 0.001
	Positive	5	5.7	91	73.4	
Metastasis	Negative	79	90.8	89	71.8	< 0.001
	Positive	8	9.2	35	28.2	
Survival Status	Alive	82	94.3	110	88.7	0.166
	Dead	5	5.7	14	11.3	

Abbreviations: RCB G Residual cancer burden group, *LA* Luminal A, *LB* Luminal B, *HER2* Human epidermal receptor 2, *TN* Triple negative

Table 3 Logistic regression analysis of the residual cancer burden groups

	Univariate Analysis				Multivariate Analysis			
			95% C.I. for OR				95% C.I. for OR	
	p	OR	Lower	Upper	*p*	Exp(B)	Lower	Upper
Age	0.324	1.012	0.988	1.037				
High TROP-2 expression	0.010	2.092	1.193	3.667	0.015	2.159	1.161	4.013
Molecular subtype	< 0.001	0.144	0.071	0.294	< 0.001	0.167	0.080	0.349
Tumor infiltrating lymphocytes	< 0.001	0.361	0.204	0.639	0.017	0.468	0.251	0.872
Pathologic stage (diameter) (2 vs. 1)	0.142	1.569	0.860	2.861				
Pathologic stage (diameter) (3 vs. 1)	0.591	1.345	0.457	3.958				
Position (Right vs. left)	0.438	1.245	0.716	2.166				
Nuclear grade (2 vs. 1)	0.625	1.643	0.225	11.993				
Nuclear grade (3 vs. 1)	0.974	1.034	0.136	7.840				
Perineural invasion	0.130	3.326	0.701	15.791				

High TROP-2 expression, Molecular subtype and Tumor infiltrating lymphocytes variables selected for covariates

Abbreviations: OR" (Odds Ratio) ve "*%95 CI*" (Confidence Interval)

0.251–0.872), and high TROP-2 expression (OR: 2.159; 95% CI: 1.161–4.013) were independent predictors of NAC response (Table 3).

High TROP-2 expression was associated with a generally worse NAC response in breast carcinomas and was an independent predictor of NAC response. However, the association between high TROP-2 expression and a poor NAC response reached statistical significance only within the LB molecular subtype.

Survival analysis

The mean follow-up period for the cases was 40 months (range, 6-141 months). During the follow-up period, distant metastasis developed in 43 patients, and death occurred in 19 patients during this period. No significant association was found between high TROP-2 expression and OS or DFS (Figs. 7 and 8). Pathological parameters associated with survival included sTILs ($p = 0.004$), lymph node metastasis ($p = 0.035$), and metastasis development ($p < 0.001$) (Table 4). In multivariate analysis, metastasis was independent risk factors for OS (Table 5), whereas lymph node metastasis was an independent risk factor for DFS.

Discussion

Breast carcinomas are histologically and molecularly heterogeneous tumors, and TROP-2 expression may vary across molecular subtypes. Despite the observed differences in TROP-2 expression among molecular subtypes and its known associations with tumor progression-related biological features, the clinical utility of TROP-2 as an independent prognostic / predictive biomarker in breast carcinoma remains controversial. In the present study, high TROP-2 expression (H-score > 200) was observed in 58.7% of the 211 cases of breast carcinoma. High TROP-2 expression occurred more frequently in the TN and LA molecular subtypes than in the HER2 and LB molecular subtypes, however, these differences were not statistically significant ($p = 0.087$). High TROP-2 expression was significantly associated with HER2 negative status, lymph node metastasis, and poorer response to NAC. In contrast, no statistically significant association was identified between TROP-2 expression and sTILs, nuclear grade, histological subtype, OS or DFS. In multivariate analysis, high TROP-2 expression, molecular subtype, and sTILs were identified as independent predictive markers of NAC response. High TROP-2 expression has been identified as a factor that negatively affects the response to standard chemotherapy, particularly in LB molecular subtype breast carcinomas.

Interestingly, our study observed a significant correlation between TROP-2 expression and tumor location, suggesting that TROP-2 may play a role in tumor location. High TROP-2 expression was detected in left-sided breast carcinomas ($p = 0.009$). However, no association was observed between tumor location and age or tumor size. The association between high TROP-2 expression and left-sided tumors could not be explained by biology in our cohort. This finding may be a coincidental result of the retrospective nature of our study. It should be considered a novel observation requiring further confirmation in larger, independent studies.

In our study, changes in NAC response due to high TROP-2 expression were most frequently observed in LB molecular subtypes ($p = 0.027$). Luminal B molecular subtype cases with high TROP-2 expression had a lower pathological complete response rate compared to LB cases with low TROP-2 expression (19% vs. 28%). This supports the possibility of evaluating the use of TROP-2-targeted agents in neoadjuvant therapy in LB molecular subtype breast carcinoma cases with high TROP-2 expression in the future.

Previous studies have reported varying results regarding the effect of high TROP-2 expression on treatment

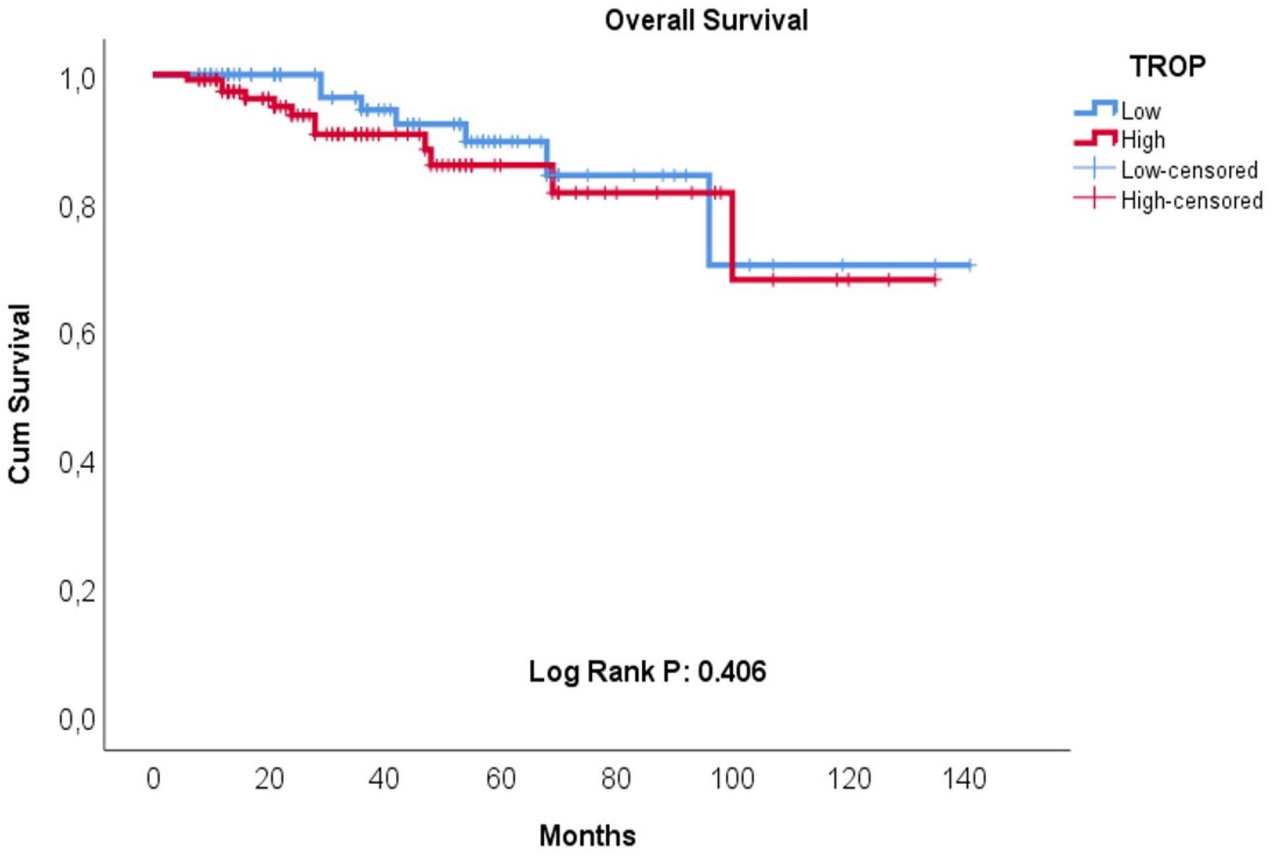


Fig. 7 Kaplan Meier overall survival curves for TROP-2 expression

response in breast carcinomas, and similarly, the distribution across molecular subtypes has varied. Mertens et al. demonstrated that breast carcinomas generally exhibit moderate to high TROP-2 expression regardless of molecular subtypes [16]. In contrast, Aslan et al. [17] reported higher TROP-2 expression levels in TN breast carcinomas, while Vidula et al. [2] reported higher TROP-2 expression levels in TN and LA molecular subtypes.

Similarly, studies investigating the relationship between TROP-2 expression and response to NAC have yielded inconsistent results. Elghazawy et al. reported no significant association between TROP-2 expression and response to NAC in hormone receptor-positive (HR+), HER2-negative breast carcinoma [18]. Similarly, Izci et al. did not observe a significant relationship between high TROP-2 expression and pathological complete response following NAC in TN molecular subtypes of breast carcinoma [13]. In contrast, another study demonstrated that high TROP-2 expression was associated with a worse response to NAC in HER2-positive breast carcinoma [19].

Different results have been reported regarding the relationship between high TROP-2 expression and survival outcomes. In one study, high TROP-2 expression was associated with improved survival in TN breast carcinomas [20]. In contrast, other studies have reported that high TROP-2 expression in breast carcinomas is associated with worse OS and DFS [21–24]. Despite studies reporting positive or negative effects on survival, others have not found a significant relationship between TROP-2 expression and survival [13, 25–27].

The variability in prognostic and predictive findings reported in the literature may be attributed to several methodological and biological factors. These include the use of different TROP-2 immunohistochemical antibody clones from various manufacturers, heterogeneity in TROP-2 expression assessment methods (e.g., immunohistochemistry versus genetic analyses), and the application of different cut-off values across studies. Additionally, discrepancies may be due to differences in sample size, pathological stage, and the distribution of molecular subtypes among study cohorts. In conclusion, to reach consensus on the prognostic and predictive significance of high TROP-2 expression, standardization of scoring and grading systems, along with studies with larger case numbers and longer follow-up periods, is needed.

High TROP-2 expression, frequently observed in tumor cells, presents a clinically significant therapeutic

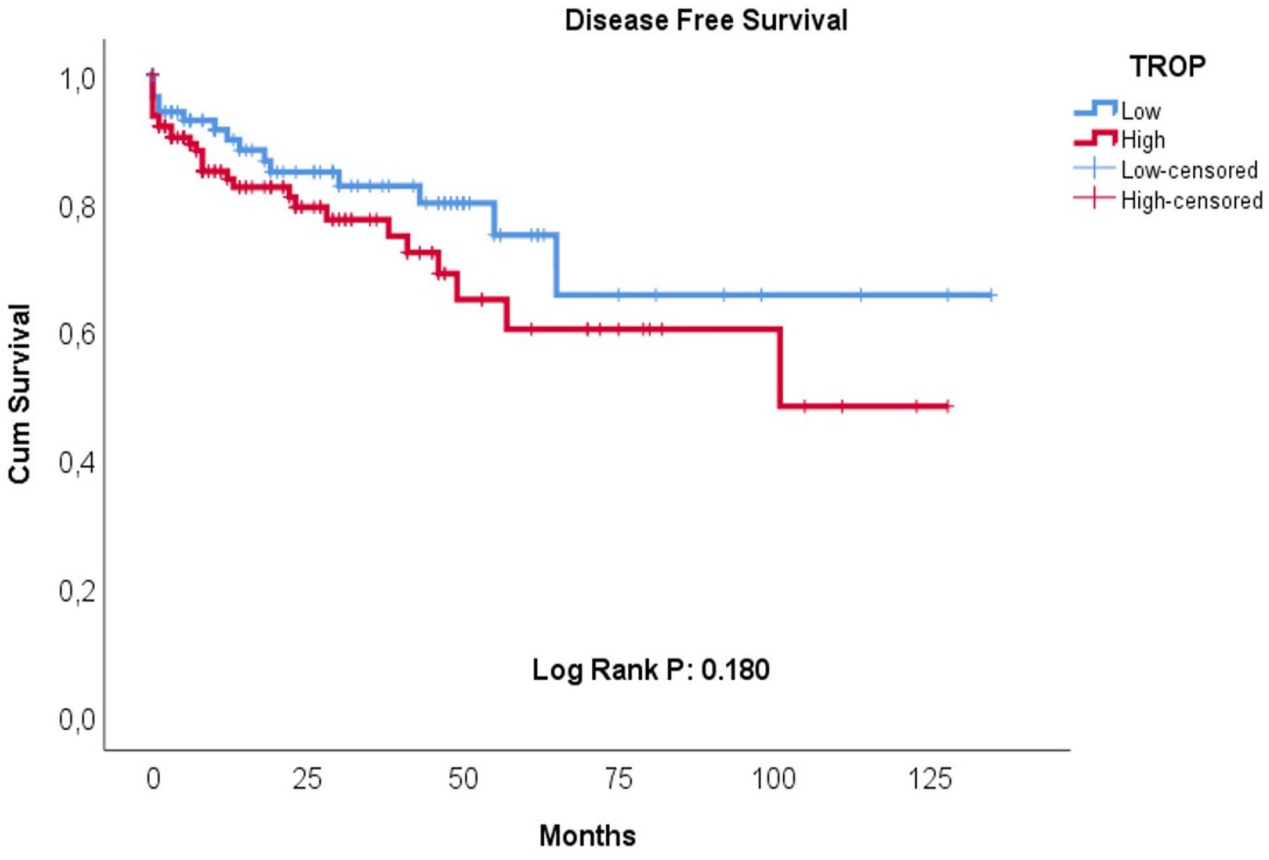


Fig. 8 Kaplan Meier disease-free survival curves, TROP-2 expression

opportunity. Sacituzumab govitecan is an antibody-drug conjugate consisting of a monoclonal antibody linked to a cytotoxic chemotherapeutic agent. Its clinical efficacy has been well established, particularly in patients who have previously received treatment for metastatic TN breast cancer, and it has been incorporated into clinical practice in recent years [5, 28].

Although SG is expected to be more effective in tumors with high TROP-2 expression, clinical and preclinical data suggest that it may also be effective in tumors with low TROP-2 expression [14]. This phenomenon, known as the bystander effect, enables the cytotoxic payload to diffuse into neighboring tumor cells with low or heterogeneous TROP-2 expression. Consequently, SG may retain antitumor activity even in biologically heterogeneous tumors [29]. In this context, Bardia et al. reported that SG significantly improved median OS compared to the control group in patients with high TROP-2 expression. SG also provided a clinical benefit to patients with low TROP-2 expression, likely due to the bystander effect [28].

The current clinical application of SG follows a "one-size-fits-all" approach, since TROP-2 testing is not required for its administration in metastatic settings. However, our study contributes to the ongoing discussion about this potential paradox in precision medicine. While high TROP-2 expression is generally observed in breast carcinomas, TROP-2 negativity can be seen in some histological subtypes, particularly in metaplastic breast carcinoma [13, 30]. Furthermore, as with ER, PR, and HER2, TROP-2 expression levels can change over time and during treatment. The possibility of reduced or absent therapeutic response in these cases, when considered alongside the risk of treatment-related side effects such as neutropenia, diarrhea, nausea, and alopecia, suggests that pre-treatment TROP-2 receptor status assessment may be clinically significant.

We believe that checking TROP-2 levels before treatment can help clinicians see which patients will benefit the most. This can help them plan a treatment for each patient and see how well it will work over time. From a health economics perspective, the additional cost of TROP-2 immunohistochemical staining is minimal compared to the total cost of oncological treatment.

Our findings demonstrate that high TROP-2 expression, particularly in LB molecular subtype breast carcinoma cases, is associated with a poor response to standard NAC regimens. This suggests that considering TROP-2 expression, along with molecular subtype and sTILs, which are other factors predicting neoadjuvant

Table 4 Overall survival and associated clinicopathological parameters

		Overall Survival				
		0		1		
		Count	Column *N* %	Count	Column *N* %	*P* value
High TROP-2 expression	Low	80	41.7	7	36.8	0.684
	High	112	58.3	12	63.2	
Molecular subtype	LA	34	17.7	5	26.3	0.511
	LB	110	57.3	10	52.6	
	HER2	28	14.6	1	5.3	
	TN	20	10.4	3	15.8	
Tumor infiltrating lymphocytes	Low	86	44.8	15	78.9	0.004
	High	106	55.2	4	21.1	
Pathologic stage (diameter)	1	63	32.8	3	15.8	0.310
	2	114	59.4	14	73.7	
	3	15	7.8	2	10.5	
Position	Left	106	55.2	11	57.9	0.822
	Right	86	44.8	8	42.1	
Nuclear grade	1	4	2.1	0	0.0	0.351
	2	132	68.8	16	84.2	
	3	56	29.2	3	15.8	
Estrogen receptor	Negative	47	24.5	4	21.1	1.000
	Positive	145	75.5	15	78.9	
Progesterone receptor	Negative	70	36.5	6	31.6	0.673
	Positive	122	63.5	13	68.4	
HER 2 score	Negative	116	60.4	13	68.4	0.495
	Positive	76	39.6	6	31.6	
Ki- 67 proliferation index	1	45	23.4	7	36.8	0.262
	2	147	76.6	12	63.2	
Angiolymphatic invasion	Negative	150	78.1	11	57.9	0.085
	Positive	42	21.9	8	42.1	
Perineural invasion	Negative	182	94.8	18	94.7	1.000
	Positive	10	5.2	1	5.3	
Lymph node metastasis	Negative	109	56.8	6	31.6	0.035
	Positive	83	43.2	13	68.4	
RCB Group	RCB 0,1	82	42.7	5	26.3	0.166
	RCB 2,3	110	57.3	14	73.7	
Metastasis	Negative	163	84.9	5	26.3	< 0.001
	Positive	29	15.1	14	73.7	

Abbreviations: RCB G Residual cancer burden group, *LA* Luminal A, *LB* Luminal B, *HER2* Human epidermal receptor 2, TN: Triple negative

response in LB subtype breast carcinoma cases, in pretreatment planning would be beneficial. Furthermore, it suggests that patients with high TROP-2 expression should be prioritized for neoadjuvant clinical trials involving TROP-2-targeted agents such as SG, rather than standard neoadjuvant therapy. Therefore, larger, prospective, multicenter studies are warranted to definitively establish TROP-2 as an independent biomarker in the neoadjuvant setting.

Conclusion

*The TROP-2 glycoprotein has two distinct clinical implications. First, it is significantly overexpressed in malignant cells compared to healthy tissues, making it a viable target for antibody-drug conjugates. Second, high TROP-2 expression in breast carcinomas is associated with response to neoadjuvant chemotherapy (NAC) and was identified as an independent predictive factor for treatment response in our study.

*In our study, high TROP-2 expression was associated with resistance to the standard NAC regimen, particularly in LB molecular subtype breast carcinoma cases, and was identified as an independent predictor factor for NAC response. Prioritization of these cases for neoadjuvant clinical trials involving TROP-2-targeting agents such as Sacituzumab Govitecan, should be considered compared to the standard NAC regimen. Further studies with a larger number of cases are needed to reach a definitive conclusion on this matter.

Table 5 Logistic regression analysis of the overall survival

	Univariate Analysis				Multivariate Analysis			
	p	HR	95,0% CI for HR		*p*	HR	95,0% CI for HR	
			Lower	Upper			Lower	Upper
High TROP-2 expression	0.410	1.482	0.582	3.773				
AGE	0.401	1.017	0.978	1.058				
Molecular subtype	0.462	0.659	0.218	1.998				
Tumor infiltrating lymphocytes	0.035	0.304	0.101	0.918	0.189	0.470	0.152	1.450
Pathologic stage (diameter) (2 vs. 1)	0.261	2.049	0.586	7.165				
Pathologic stage (diameter) (3 vs. 1)	0.414	2.108	0.352	1.,634				
Position (Right vs. left)	0.586	0.776	0.312	1.933				
Angiolymphatic invasion	0.725	1.180	0.470	2.963				
Perineural invasion	0.580	0.565	0.075	4.276				
Lymph node metastasis	0.067	2.473	0.940	6.509	0.763	1.169	0.424	3.219
RCB (0, I vs. II, III)	0.183	2.004	0.721	5.571				
Metastasis	< 0.001	9.048	3.244	25.238	< 0.001	7.419	2.519	21.851

Tumor infiltrating lymphocytes, lymph node metastasis, and metastasis were selected for covariates

*Since high TROP-2 expression is not observed in all breast carcinoma cases, pre-treatment assessment of TROP-2 is crucial to identify patient subgroups that would benefit most from TROP-2 targeted therapies.

*Furthermore, although TROP-2 testing is not yet mandatory in clinical practice, its correlation with chemotherapy resistance suggests that TROP-2 scoring could serve as a valuable biomarker for improving personalized treatment strategies in the future.

Limitations

*This study is limited by its retrospective design. Additionally, a subset of the included cases had relatively short follow-up periods, which may limit the robustness of survival analyses. However, as the primary objective was to evaluate the association between TROP-2 expression and response to NAC (including recently diagnosed cases), it is unlikely to have substantially affected the main findings. Furthermore, including all four molecular subtypes strengthens the study and facilitates a more comprehensive understanding of how TROP-2 expression relates to NAC response in breast carcinoma.

*In our multivariate model, high TROP-2 expression emerged as a statistically significant independent predictor of NAC response. However, the relatively limited number of cases may not be sufficient to obtain specific results in breast carcinoma molecular subtypes. Therefore, although our results provide significant evidence for the predictive role of TROP-2 and are valuable for future studies, prospective multicenter studies with larger case numbers and longer follow-up periods are necessary to obtain definitive results.

Abbreviations

TROP-2	Trophoblast cell surface antigen 2
NAC	Neoadjuvant chemotherapy
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
LA	Luminal A
LB	Luminal B
TN	Triple negative
sTILs	Stromal tumor infiltrating lymphocytes
RCB	Residual cancer burden

Authors' contributions

All authors have made substantial contributions to the conception, design, acquisition of data, analysis, and interpretation of data, or have been involved in drafting the manuscript or revising it.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Recep Tayyip Erdoğan University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (2025/189). Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Patient confidentiality was strictly maintained by using de-identified archival data."

Consent for publication

Not applicable. The manuscript does not contain any individual person's data in any form.

Competing interests

The authors declare no competing interests.

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