Original paper

TROP-2 expression in triple-negative and human epidermal growth factor receptor 2 enriched breast cancers and its relationship with clinicopathologic parameters

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TROP-2 is a transmembrane calcium signaling molecule that is detected at a high rate (63%) in breast cancers. There are conflicting data on its relationship with subtypes, clinical, and pathological data in breast cancer.

TROP-2 expression levels were evaluated by immunohistochemistry, and the H-score method was used to analyze the data. This evaluation was conducted on a total of 79 patients diagnosed with triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2) positive (HER2-E) breast cancer. The study also investigated the relationship between TROP-2 expression levels and the clinical-pathological features observed in patients diagnosed with TNBC and HER2-E. A total of 62 TNBC (78.5%) and 17 HER2-E (21.5%) cases were analyzed in the study.

The presence of high TROP-2 (H-score > 100) was detected in 87% of the TNBC group and 94% of the HER2-E group.

Among the pathological parameters, only low H-score values were found to have a statistically significant correlation with mucinous morphology; however, no significant correlation was found with other pathological parameters, including CerbB2 expression status. No significant relationship was found between H-score and clinical parameters. Furthermore, TROP-2 expression in HER2-E cancers is notably elevated. Further studies with larger series are required to clarify expression rates in mucinous tumors.

Key words: breast cancer, immunohistochemistry, TROP-2, Sacituzumab govitecan.

Introduction

Breast cancer is the second most common type of cancer worldwide after lung cancer. Estimates for 2023 suggested there would be 297,790 new cases of invasive breast cancer, and approximately 43,700 breast cancer-related deaths [1]. These figures highlight the necessity of ongoing initiatives to develop and enhance treatment approaches for breast cancer.

Antibody-drug conjugates (ADCs) are a new class of anticancer drugs that are promising cancer treatments and have ushered in a new era of remark-

able achievements [2]. Several ADC formats such as bispecific, conditionally active, immune-stimulating, protein-degrader or dual-drug ADCs, have been developed, and each enables the selective delivery of highly cytotoxic payloads to tumors [3]. Sacituzumab govitecan is an antibody-drug conjugate composed of an anti-trophoblast cell surface antigen 2 (TROP-2) antibody coupled to SN-38, the active metabolite of irinotecan and a topoisomerase I inhibitor. Sacituzumab govitecan has received the Food and Drug Administration (FDA) approval for adult patients with locally advanced or metastatic triple-negative breast cancer (TNBC) and hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who meet specific criteria.

TROP-2, the monoclonal antibody to which the drug binds, is a transmembrane calcium signal transducer that is highly expressed in multiple tumor types, especially breast cancer (> 90%) [4]. Although FDA approval was granted independently of tumor TROP-2 expression, only a limited number of recent studies have correlated TROP-2 expression with clinical and prognostic parameters in breast tumors [5]. In the literature, there are different results regarding the relationship between TROP-2 expression and clinicopathological and prognostic factors. While some studies have found membranous and/or cytoplasmic TROP-2 expression to be associated with clinicopathological factors, no significant relationship was found in some other publications [6–9].

In studies investigating TROP-2 expression across different molecular subtypes of breast cancer, it was detected in all groups, but showed higher expression in TNBCs compared to other groups [10]. Most of the studies with TROP-2 are in TNBCs with aggressive prognosis and without targeted therapies. In contrast, there are very few studies investigating the frequency of TROP-2 expression and its relationship with prognostic factors in the HER2-enriched breast cancer (HER2-E) group.

We aimed to evaluate TROP-2 expression in TNBC and HER2-E breast cancer, determine differences in expression between the two groups, and to investigate potential associations with clinico-pathological features and survival outcomes.

Material and methods

Patient characteristics

Patients diagnosed with stage 1–4 TNBC and HER2-E in our institution between 2016 and 2024 were included in the study. Those without samples in the pathology archive were excluded. Patients were grouped according to the World Health Organization classification [11]. All patients were estrogen receptor (ER) and progesterone receptor (PR) negative by immunohistochemistry (IHC). Triple-negative breast cancer cases are patients who, in addition to being ER and PR negative, have HER2 expression of 0 or +1 by IHC, or have HER2 expression of +2 by IHC but no amplification detected by fluorescence *in situ* hybridization (FISH). Patients in the HER2-E group had an IHC HER2 expression of +3 or an IHC expression of +2 with FISH-detected amplification.

Patient and tumor characteristics were retrieved from the clinical database and medical records, such as age, tumor size, histological subtype, tumor grade, multifocality, presence of ductal carcinoma *in situ* (DCIS), grade of DCIS, lymphovascular invasion (LVI), perineural invasion (PNI), tumor necrosis, lymph node involvement, Ki-67 proliferation index, presence of metastasis, data on relapse and survival.

Immunohistochemistry protocol

In tru-cut biopsies, all tissue in formalin-fixed paraffin-embedded (FFPE) tumor blocks was used for IHC analysis. Representative areas from primary tumors in resection specimens were selected in hematoxylin/eosin-stained sections, and 6-mm cores were obtained and arrayed in a macroarray block. Five-μm thick slides of FFPE tumor blocks for tru-cut biopsies and macroarray blocks were used for IHC analyses. We assessed TROP-2 expression by IHC on the Ventana Automated IHC Stainer (Ventana, Roche). Ratio of 1 : 300 dilution of rabbit monoclonal anti-TROP-2 antibody (Clone: ZR388, ZETA) was used, pre-treated for 20 min at pH 9, and incubated for 30 min. Placental tissue was used as a positive control.

Evaluation of TROP-2 expression

The H-score method is widely used in IHC assessment, particularly for tumors with heterogeneous staining patterns, as it considers both staining intensity and percentage. This approach is commonly applied to evaluate TROP-2 expression in the literature.

Firstly, the staining pattern of TROP-2 (cytoplasmic and/or membranous) was evaluated. Although there are very few publications in the literature that acknowledge the importance of cytoplasmic expression [12] (Figure 1I), membranous staining was evaluated in our study and only cytoplasmic staining was excluded from the evaluation due to the protein being localized to the membrane and the fact that membrane staining is considered important in most publications in the literature [13, 14].

The presence of membranous complete and/or incomplete staining of invasive tumoral cells was evaluated. Tumors considered positive were divided into 3 groups as weak, moderate, and strong membranous positive according to the staining intensity. Staining intensity was evaluated as negative, weak, intermediate, and strong (Figure 1A–H).

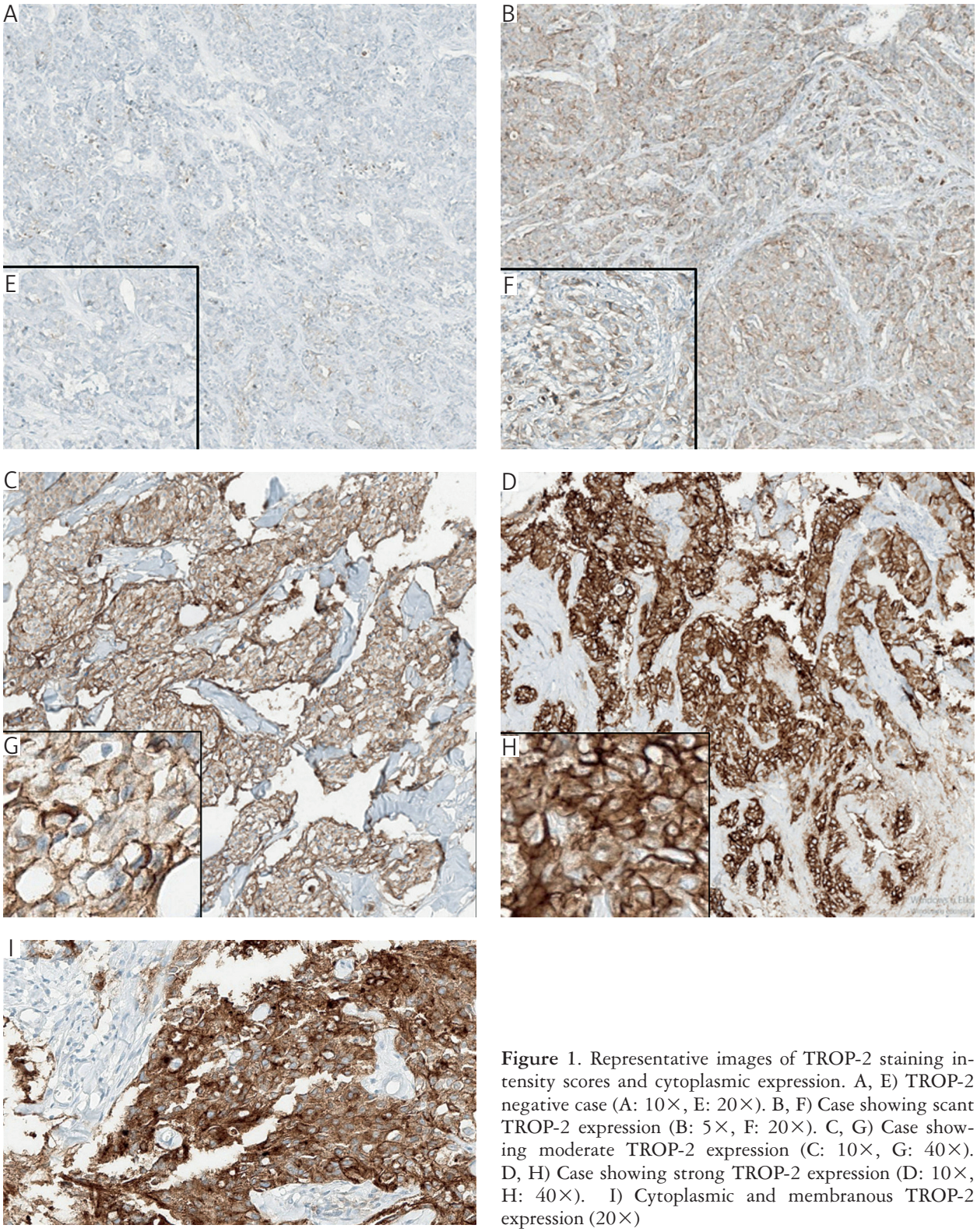

Figure 1. Representative images of TROP-2 staining intensity scores and cytoplasmic expression. A, E) TROP-2 negative case (A: 10×, E: 20×). B, F) Case showing scant TROP-2 expression (B: 5×, F: 20×). C, G) Case showing moderate TROP-2 expression (C: 10×, G: 40×). D, H) Case showing strong TROP-2 expression (D: 10×, H: 40×). I) Cytoplasmic and membranous TROP-2 expression (20×)

The H-score method was used to evaluate staining. H-score considers staining intensity and the percentage of cells at that intensity. H-scores were calculated using the following formula: H-score = (3 × % cells with strong intensity staining) + (2 × % cells with moderate intensity staining) + (1 × % cells with mild intensity staining) [15]. The H-score scale range is 0–300, with specific Trop-2 expression categories assigned: Trop-2 negative/low is classified as an H-score of 0 to < 100, Trop-2 medium is an H-score of 100–200, and Trop-2 high is an H-score > 200–300.

Scoring and grading were performed separately by three pathologists, who were unaware of the clinical and histopathological data.

Statistical analysis

All statistical analysis was conducted using SPSS 20.0 statistical software (SPSS Inc., USA). The correlations between TROP-2 expression and pathologic features (histological type of tumor, grade, presence and grade of concomitant DCIS, LVI, PNI, tumor necrosis, HER2 expression status) were analyzed using the χ^2, contingency and/or Phi correlation test. One-way ANOVA, Kruskal-Wallis and point-biserial correlation coefficient analyses were performed to statistically evaluate the relationship between Ki-67 proliferation index and H-score. Chi-square, contingency correlation, Phi correlation, one-way ANOVA, Kruskal-Wallis, were applied to evaluate the relationship between clinical parameters (stage at diagnosis, presence of recurrence/progression, time between diagnosis and recurrence, survival, time between initial diagnosis and death) and TROP-2 expression scoring values. $P < 0.05$ was considered statistically significant.

Results

Patients

Overall, 79 patients were identified through our electronic data search (Table I). A total of 79 patients were included for IHC analyses. Of the TNBC cases that underwent IHC analysis, 34% ($n = 27$) were tru-cut biopsy and 66% ($n = 52$) were excision material. While 78.5% ($n = 62$) of the patients had TNBC, 21.5% ($n = 17$) were from the HER2-E breast cancer group. While 29% ($n = 5$) of the HER2-E group had tru-cut biopsy and 71% ($n = 12$) were excision material, 35% ($n = 22$) of the TNBC cases had tru-cut biopsy and 65% ($n = 40$) were excision material. The mean age at diagnosis was 50.6 (min 25 – max 79).

In the distribution according to diagnostic groups, 43% ($n = 34$) were classified as invasive ductal carcinoma-NST, 5% ($n = 4$) as showing apocrine differentiation, 4% ($n = 3$) as metaplastic (1 adenosquamous and 2 squamous carcinoma), 45.5% ($n = 36$) as invasive ductal carcinoma-NST showing medullary-like pattern and 2.5% ($n = 2$) as mucinous carcinoma.

In 85% ($n = 67$) of the patients, the tumor was grade 3, in 14% ($n = 11$) it was grade 2, and in 1% ($n = 1$) it was grade 1. Concomitant ductal carcinoma *in situ* was detected in 38% ($n = 30$) of the patients and of these, 77% ($n = 23$) had grade 3, 20% ($n = 6$) had grade 2, and 3% ($n = 1$) had grade 1. In patients whose excision material was evaluated, the mean tumor diameter was 3.2 cm (0.7–16 cm). Macro-metastasis was observed in 34.6% ($n = 18$). The mean number of metastatic LNs was 5 (min 1 – max 18). Lymphovascular invasion was detected in 44% ($n = 23$) of the patients, and PNI was detected in 6% ($n = 3$). The average Ki-67 proliferation index was 56%.

In 70 patients, the stage at diagnosis was known. 44 (63%) of these patients were in the early stage and 26 (37%) were in the advanced stage. Of these 70 patients, 8 (11.5%) had metastatic disease (stage 4) at the time of diagnosis. Only 1 of these patients belonged to the HER2-E group, while 7 of them were TNBC.

Because 62 of 79 (78%) patients were followed up in our hospital, neoadjuvant/adjuvant treatment protocol, presence of recurrence/progression, time between diagnosis and recurrence, metastatic treatment protocol, and survival data are available. Since 62 of 79 patients were followed up in our institution, 78% of the patients had information about the neoadjuvant/adjuvant treatment protocol. The most common neo/adjuvant treatment protocol used in TNBC patients (77.4%, $n = 48$) was AC + T (adriamycin, cyclophosphamide, and docetaxel/paclitaxel). In addition, 2 patients (3.2%) received AC (adriamycin and cyclophosphamide) and 1 patient (1.6%) received adjuvant capecitabin. In the HER2-E group, 7 patients (11.2%) received AC + TH (doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab), 3 patients (5%) received paclitaxel and trastuzumab, and 1 (1.6%) patient received AC + PTT (adriamycin and cyclophosphamide + docetaxel pertuzumab trastuzumab).

The recurrence/progression rate was 30% ($n = 20$). Recurrence/progression occurred in 7 (16%) of 44 early-stage patients. Recurrence/progression data were available for 24 of 26 advanced-stage patients, and 8 (33.3%) of them developed recurrence/progression. Recurrence-free survival in locally early-stage patients was calculated as 43 months (min 4 – max 96). The median overall survival for all patients was 33 months (min 1 – max 96).

In 19 (30%) of 62 patients, metastasis developed.

Evaluation of TROP-2 expression

While 4 cases (5%) were TROP-2-negative, TROP-2 staining was observed in 75 cases (95%) at varying rates (Figure 2). All 4 TROP-2-negative cases were TNBC, and 3 were invasive ductal carcinoma-NST (2 had medullary-like patterns). 1 case was mucinous carcinoma-type B.

Of the 17 HER2-E breast cancer samples, 12 (70.5%) had an H-score of (+3), 4 (23.5%) had an H-score of (+2), and 1 (6%) had an H-score of (+1).

Of the 62 TNBC samples, 35 (56%) had an H-score of 3, 19 (31%) had an H-score of 2, and 4 (6.5%) had an H-score of 1. In 4 cases (6.5%), no staining was detected and considered negative.

There was no statistically significant difference between H-score and CerbB2 expression status.

Relationship between TROP-2 expression and pathological data

In the analyses performed with H-score, statistically significant correlations were found between histological subtype and H-score ($p < 0.05$).

Table I. Clinicopathological characteristics of patients and tumors

Parameters	HER2-E			TNBC		
Total number of patients, *N* (%)	17 (21.5)			62 (78.5)		
Median age at diagnosis (min – max)	50 (34–73)			48 (25–79)		
	Early stage	**Locally advanced/metastatic stage**		**Early stage**	**Locally advanced/metastatic stage**	
Clinical stage, *n* (%)*	8 (53)	7 (47)		36 (65)	19 (35)	
Median survival time (min – max)	55.8 months (14.5–96.3)			29.2 months (0.5–96)		
Relapse/progression, *n* (%)	7 (43.5)			13 (54.5)		
Pathological characteristics						
The nature of the biopsy analyzed, *n* (%)	Tru-cut Bx	Excision		Tru-cut Bx	Excision	
Diagnosis, *n* (%)	5 (29)	12 (71)		22 (35)	40 (65)	
Invasive ductal carcinoma-NST, *n* (%)	13 (76)			21 (34)		
Invasive ductal carcinoma-NST with medullary-like pattern, *n* (%)	3 (18)			33 (53)		
Invasive ductal carcinoma-NST with apocrine differentiation, *n* (%)	1 (6)			3 (5)		
Metaplastic carcinoma, *n* (%)	0 (0)			3 (5)		
Mucinous carcinoma, *n* (%)	0 (0)			2 (3)		
Multifocality, *n* (%)	2 (18)			7 (17.5)		
Tumor grade, *n* (%)	G1	G2	G3	G1	G2	G3
	0 (0)	4 (24)	13 (76)	1 (2)	7 (11)	54 (87)
Presence of DCIS accompanying invasive tumor, *n* (%)	11 (65)			19 (31)		
DCIS grade, *n* (%)	G1	G2	G3	G1	G2	G3
	0 (0)	1 (9)	10 (91)	1 (5)	5 (27)	13 (68)
Median tumor size (mm) at diagnosis (min – max)**	20 (4–60)			25 (5–160)		
Number of cases with SLNB or AD, *n* (%)	10 (59)			37 (60)		
Number of cases with lymph node metastasis	ITC	M1	M2	ITC	M1	M2
	1	2	4	0	1	13
Perineural invasion, *n* (%)	1 (6)			2 (3)		
Lymphovascular invasion, *n* (%)	8 (47)			16 (26)		
Presence of tumor necrosis, *n* (%)	4 (24)			21 (34)		
Median Ki-67 proliferation index (min – max)	40 (15–75)			70 (5–100)		

AD – axillary disection, DCIS – ductal carcinoma in situ, G1 – grade 1, G2 – grade 2, G3 – grade 3, HER2-E – human epidermal growth factor receptor 2 enriched breast cancer, ITC – isolated tumor cell, M1 – micrometastasis, M2 – macrometastasis, NST – no special type, SLNB – sentinel lymhp node biopsy, TNBC – triple negative breast cancer

** Clinical stage data could not be obtained in 2 early stage cases and 7 advanced stage cases.*

*** In patients with multifocal tumors, the largest tumor diameter was included in the calculation.*

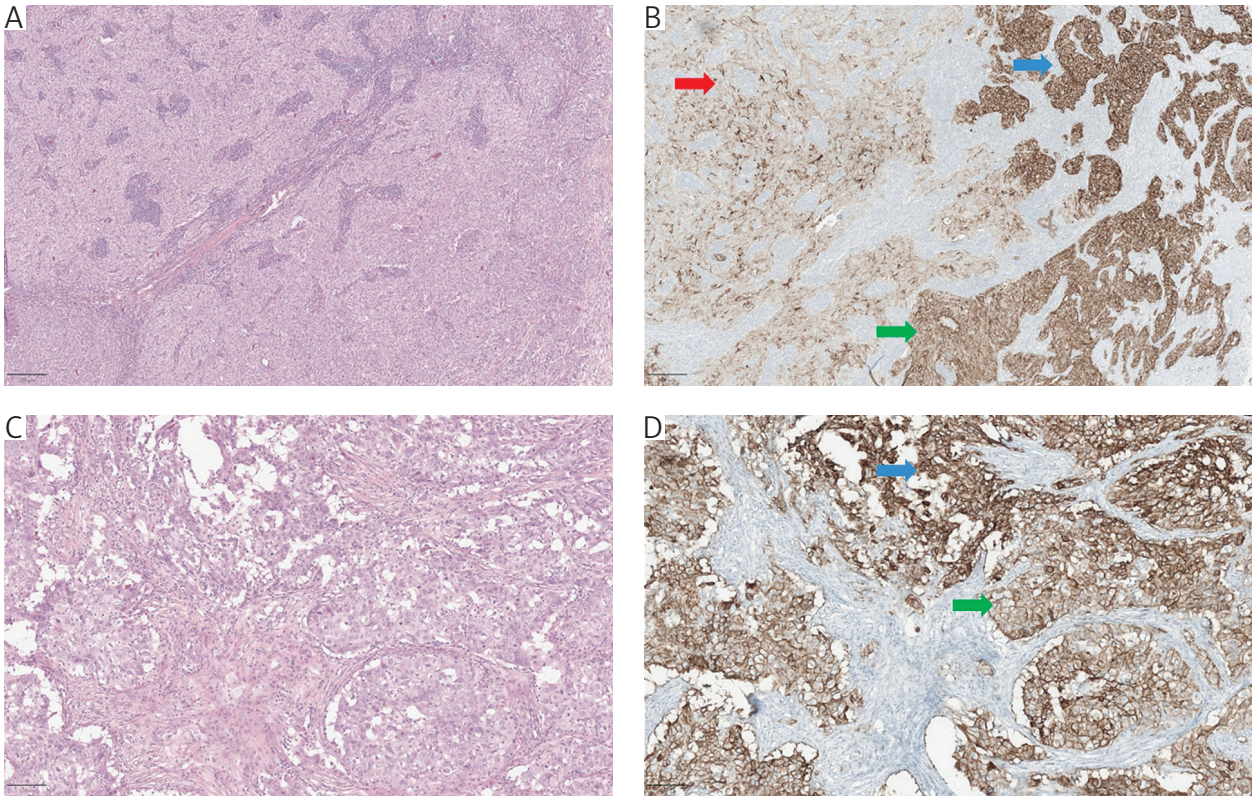

Figure 2. Representative examples of tumors showing different staining intensities. **A**) Hematoxylin and eosin (HE) section of the tumor specimen with scant, moderate, and strong TROP-2 expression (10×). **B**) Different areas of staining in the tumor (red arrow indicates scant, green arrow indicates moderate, blue arrow indicates strong positive areas, 10×). **C**) HE section of the tumor specimen with moderate and strong TROP-2 expression (10×). **D**) Different areas of staining in the tumor (green arrow indicates moderate, blue arrow indicates strong positive areas, 10×)

H-score was 1 in 10 (12.7%), 2 in 22 (27.8%), and 3 in 47 (59.5%) of 79 cases. Except for tumors containing mucinous/mucinous component, H-score 3 was the highest in all other types, while H-score 1 was found in tumors containing mucinous/mucinous component. Because the mucinous tumors generally exhibit luminal characteristics, only 2 mucinous tumors with TNBC characteristics could be included in the study. Although the number of cases in this group was small, the group that created a statistically significant difference in the relationship between subtypes and H-score was tumors containing mucinous/mucinous components ($p = 0.012$).

However, no significant correlation was found between H-score and tumor diameter, tumor grade, concomitant DCIS, DCIS grade, Ki-67 proliferation index, tumor necrosis, presence of LVI or PNI.

Relationship between TROP-2 expression and clinical data

TROP-2 H-score was found to be (+3) in 6 (75%) and (+2) in 2 of 8 patients (7 with TNBC, 1 with HER2-E) who had metastatic disease at the time of diagnosis.

According to the clinical stage, 44 (63%) of the patients were in the locally early stage (stage 1 and 2A), while 26 (37%) were in the locally advanced/metastatic disease (stage 2B, 3, and 4). The H-score was (+3) in 29 (66%) of 44 patients, (+2) in 8 of 44 (18%), (+1) in 4 of 44 (9%) and negative in 3 of 44 (7%). When the H-score values of 26 locally advanced/metastatic cases are analyzed, 15 cases (58%) are (+3), 9 cases (35%) are (+2), 1 case (3.5%) is (+1), and 1 case (3.5%) is negative.

H-score (+3) and (+2) values were found in 82% ($n = 37$) of locally early-stage patients, whereas this rate was 93% ($n = 24$) in locally advanced/metastatic disease patients. Both values were high, and there was no statistically significant difference in H-score values between early and advanced/metastatic disease patients. However, while 3 negative cases (7%) were found in the early-stage group, this rate was 3.5% ($n = 1$) in the other group. Although negative H-score values were higher in locally early-stage patients than in locally advanced/metastatic disease patients, no statistically significant relationship was observed.

Recurrence/progression rate

A total of 69 out of 79 breast carcinoma cases were included in the analysis. The rate of cases with recurrence/progression was 29% ($n = 20$).

Table II. TROP-2 expression levels in triple-negative breast cancer and human epidermal growth factor receptor 2 enriched breast cancer in the literature

Tumor group	Study group (year)	Number of cases	H-score 3, *n* (%)	H-score 2, *n* (%)	H-score 1, *n* (%)	H-score negative, *n* (%)
TNBC	Lai *et al*. [18]*	35	25 (71)	9 (26)	0 (0)	1 (3)
	Aslan *et al*. [19]**	28	(93)	N/A		N/A
	Mertens *et al*. [20]	25	17 (68)	5 (20)	2 (8)	1 (4)
	Izci *et al*. [7]	589	97 (16.5)	149 (25.3)		343 (58.2)
	Jeon *et al*. [9]****	807	151 (18.7)			656 (81.3)
	Bardia *et al*. [15]	290	157 (54)	74 (25.5)		59 (20.5)
	Van Bockstal *et al*. [14]	33	26 (79)	4 (12)		3 (9)
	Kıvrak *et al*.	62	35 (56)	19 (31)	4 (6.5)	4 (6.5)
HER2-E	Lai *et al*. [18]	7	3 (43)	4 (57)	0	0
	Aslan *et al*. [19]**	35	(74)	N/A		N/A
	Mertens *et al*. [20]	19	10 (52.6)	8 (42.1)	0	1 (5.3)
	Gion *et al*. [17]***	41	10 (24.4)	14 (34.1)		17 (41.4)
	Van Bockstal *et al*. [14]	13	10 (77)	3 (23)		0
	Kıvrak *et al*. (current study)	17	12 (70.5)	4 (23.5)		1 (6)

HER2-E – human epidermal growth factor receptor 2 enriched breast cancer, N/A – no available, TNBC – triple negative breast cancer
** In this study, TROP-2 expression in tumors was performed by considering only the staining intensity independent of the expression percentage.*
*** In this study, TROP-2 expression in tumors was performed by considering only the staining intensity independent of the expression percentage. In the literature, only the percentage of tumors with strong TROP2 expression is given and other rates could not be reached. Additionally, the HER2-positive group in the study includes both the luminal B group (n = 8) and the HER2-E group (n = 27).*
**** In this study, TROP2 expression cut-offs are different from other studies (H-score: 1: 1–9, 2: 10–49, 3: ≥ 50). Additionally, the patient group included in the study comprises Luminal B and HER2-E patients.*
***** In this study, moderate-to-strong membranous expression of TROP-2 in at least 10% of tumor cells was considered 'high' TROP-2 expression.*

Table III. H-score according to TROP-2 expression

H-score			
n = 3 (%)	*n* = 2 (%)	*n* = 1 (%)	*n* = 0 (%)
12 (70.5)	4 (23.5)	1 (6)	0 (0)
H-score			
n = 3 (%)	*n* = 2 (%)	*n* = 1 (%)	*n* = 0 (%)
35 (56)	19 (31)	4 (6.5)	4 (6.5)

TROP-2 expression was evaluated in three groups based on the H-score (0–100, 101–200, 201–300). In the univariate logistic regression analysis, no significant relationship was found between TROP-2 H-score level and recurrence/progression ($\chi^2 = 0.345$, df = 2, $p = 0.842$). The explanatory power of the model was low (Nagelkerke $R^2 = 0.007$), and the model fit was considered good according to the Hosmer-Lemeshow test ($p = 1.000$).

The likelihood of recurrence/progression in the TROP-2 H-score 101–200 group was 0.70 times (OR = 0.703, 95% CI: 0.129–3.844) that of the 0–100 group, and 1.23 times higher (OR = 1.231, 95% CI: 0.352–4.305) in the 201–300 group.

However, these differences were not statistically significant ($p = 0.685$ and $p = 0.745$, respectively).

Other clinical parameters

Information on the preoperative neoadjuvant treatment status of 13 patients in the HER2-E group is available: 4 (30%) received neoadjuvant treatment, while 9 (70%) did not. Of the 4 patients who received neoadjuvant treatment, 3 (75%) had H-score (+3) and 1 (25%) had H-score (+2). On the other hand, H-score was (+3) in 8 (89%) and (+2) in 1 (11%) of 9 patients who did not receive neoadjuvant treatment. There was no statistically significant difference between the two groups ($p > 0.05$).

In the TNBC group, information on the preoperative neoadjuvant treatment status of 54 patients is available. Nineteen (35%) of these patients received neoadjuvant treatment, while 35 (65%) did not. Of the 19 patients who received neoadjuvant treatment, 9 (47%) had H-score (+3), 8 (42%) had H-score (+2) and 2 (11%) had H-score 0. Of the 35 patients who did not receive neoadjuvant treatment, 22 (63%) had H-score (+3), 8 (23%) had H-score (+2), 3 (8%) had H-score (+1) and 2 (6%) had H-score 0.

No significant correlation was found between H-score and the recurrence-free survival, progression-free survival, and overall survival.

Discussion

TROP-2 expression levels

According to the studies in the literature, TROP-2 expression levels in TNBC and HER2-E breast cancers were evaluated with H-score. Although TROP-2 expression cut-offs differed in very few studies [16], a 3-scoring system was used, with scores generally grouped as low (0–100), medium (100–200), and high (200–300). There are conflicting data on TROP-2 expression levels in the literature. When tumors are divided into 2 groups as low (H-score 0 and 1) and high (H-score 2 and 3), a high expression rate in TNBCs is 18.7–100% and the low expression rate is 0–81.3%. When the first publications were excluded, a high rate of TROP-2 expression (88–100%) was found in TNBCs in studies conducted in 2024, including our study. Despite conflicting expression levels in the HER2-E group, high TROP-2 expression is predominantly observed. While the high TROP-2 expression rates vary between 58% and 100%, low TROP-2 expression rates vary between 0% and 41.4% (Table II). In our study, TROP-2 expression levels were high in both HER2-E and TNBC groups (Table II, III) [7, 9, 13, 14, 17–20]. Although most studies used the same H-score evaluation method, differences in antibody clones, staining, and evaluation procedures may have caused these conflicting results. If a consensus is reached in the literature on these variables and a cutoff point is established for positive values, the results of the studies can be compared more objectively.

In a study evaluating IHC expression of TROP-2 in tumor cells, membranous TROP-2 expression was found to be an unfavorable prognostic factor for overall survival, whereas cytoplasmic or nuclear TROP-2 expression was associated with a favorable prognosis [6]. In our study, we also found cytoplasmic and/or nuclear expression, but only membranous staining was considered.

The relationship between TROP-2 expression and pathological parameters

In the literature, few studies have examined the relationship between TROP-2 expression and clinical and pathological parameters.

In most of the limited number of studies, no significant correlation was found between TROP-2 expression and pathological parameters such as patient age, procedure type, tumor size, histologic type of tumor, histologic grade of tumor, Ki-67 index, LVI, or tumor or lymph node stage [20].

In contrast, two studies found that TROP-2 expression was associated with LVI, accompanying DCIS, nodal involvement, apocrine differentiation, the metaplastic subtype, and AR expression [7, 9].

In this study, the TROP-2 H-score showed a significant correlation only with the histological type (mucinous morphology) among the pathological parameters. Similar to the literature, no significant correlation was found with other pathological parameters. TROP-2 expression was found to be significantly lower (H-score 1) in mucinous tumors, although in small numbers. As ER and PR expression is detected in the majority of mucinous tumors, and as the focus of this study is HER2-E and TNBCs, only a small number of mucinous tumors could be included. Consequently, the findings of this study require validation in a larger series.

Most studies in the literature focus on TNBCs. In our study, TROP-2 expression was also evaluated in the HER2-E group in addition to TNBCs. Consistent with our finding that 94.5% of TNBC and HER2-E cases express TROP-2, Ambrogi *et al*. [6] and Mertens *et al*. [20] reported TROP-2 expression in a majority of breast cancers. Although there was no significant difference between the two groups, high TROP-2 expression was also detected in the HER2-E group.

The relationship between TROP-2 expression and clinical parameters

Numerous studies have found an association with clinical parameters (such as overall survival, disease-free survival and relapse-free survival, complete response rate), and high TROP-2 expression causes a decrease in all of these parameters [9, 16–18].

Conclusions

Contrary to the data in the literature, no significant relationship was found between any of the clinical parameters evaluated in this study and the TROP-2 H-score. Given the limited sample size in our study, the prognostic value of TROP-2 needs to be validated in larger series.

Important limitations of our study include a small sample size (particularly for HER2-E), an imbalance in group sizes (only 17 HER2-E and 62 TNBC cases, which may limit the power to detect differences), and a single-institution, retrospective design.

In recent years, the role of TROP-2 in TNBC has attracted considerable interest due to its significant overexpression, rendering it an attractive therapeutic target. The analysis of large case series to ascertain the expression rate and its correlation with clinicopathological parameters in other molecular subtypes (such as HER2-E), as well as in TNBC, holds promise for all breast cancer patients.

Disclosures

1. Institutional review board statement: Ethical approval for this study was obtained from the Ethics

Committee of the Gülhane Training and Research Hospital (Approval No. 2024/58) and all procedures adhered to the Declaration of Helsinki.
2. Assistance with the article: The authors would like to thank Professor Nilgün Seçken for her support.
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4. Conflicts of interest: None.

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