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Research Article

Impact of Tissue Lipocalin-2 Expression on Pathologic Response and Prognosis Following Neoadjuvant Chemotherapy in Locally Advanced Triple-Negative Breast Cancer

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Abstract

Objectives: This study aimed to evaluate Lipocalin-2 (Lcn-2) expression in patients with locally advanced triple-negative breast cancer (TNBC) and to investigate its association with pathological response following neoadjuvant chemotherapy (NACT), as well as its prognostic relevance in relation to established clinicopathological parameters.

Methods: Fifty-six patients with locally advanced TNBC treated at the Medical Oncology Department of SBÜ Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital were retrospectively analyzed. Lcn-2 expression was assessed immunohistochemically. Associations between Lcn-2 expression and demographic, laboratory, clinical, and histopathological characteristics, as well as response to NACT, were evaluated using appropriate statistical methods.

Results: Lcn-2 expression was detected in 53.6% of patients (n=30). Lcn-2 positivity was significantly associated with a high Ki-67 proliferation index (p=0.032), advanced clinical tumor stage (cT3–T4; p=0.043), and stage III disease (p=0.029). However, no significant association was observed between Lcn-2 expression and pathological complete response following NACT (p=0.666). Additionally, Lcn-2 expression was not correlated with age at diagnosis, menopausal status, comorbidities, lifestyle factors, baseline CA15-3 levels, inflammatory markers, including the neutrophil-to-lymphocyte ratio, histologic subtype, presence of ductal carcinoma in situ, or lymph node involvement.

Conclusion: Lcn-2 expression appears to be associated with features indicative of tumor aggressiveness in locally advanced TNBC. Larger prospective studies are warranted to clarify its prognostic value and potential role as a therapeutic target.

Keywords: Biomarker, Neutrophil Gelatinase-Associated Lipocalin, Pathological Complete Response

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Breast cancer remains the most commonly diagnosed malignancy worldwide.[1] In 2020, it was responsible for approximately 6.9% of all cancer-related deaths globally, ranking as the fifth leading cause of cancer mortality.[2,3]

Triple-negative breast cancer (TNBC) accounts for nearly 15% of all breast cancer cases worldwide and is generally associated with an unfavorable prognosis, with an estimated 200,000 new cases reported each year.[4] TNBC is typically characterized by younger age at diagnosis, larger primary tumor size, higher histological grade, extensive tumor necrosis, and frequent lymph node involvement.[5] Moreover, this subtype is known for its aggressive clinical behavior, with increased risks of distant metastasis, recurrence, and mortality compared with other breast cancer subtypes.[6,7]

In patients with locally advanced breast cancer (LABC), the likelihood of both locoregional and systemic recurrence is substantially higher.[8–10] Neoadjuvant chemotherapy (NACT) has become the standard treatment strategy for patients with locally advanced TNBC. Achieving a pathological complete response (pCR) after NACT is strongly associated with improved disease-free survival and favorable long-term outcomes in this population.[11–13] Nevertheless, identifying reliable biomarkers that can predict which patients will achieve pCR remains a major clinical challenge.

Accumulating evidence suggests that chronic inflammation and the presence of inflammatory cell infiltration play important roles in cancer initiation and progression. Members of the lipocalin protein family are involved in inflammatory responses and detoxification processes within the immune system and have been implicated in tumorigenesis.[14] Lipocalin-2 (Lcn-2), also known as neutrophil gelatinase-associated lipocalin (NGAL), siderocalin, 24p3, or uterocalin, is overexpressed in a variety of pathological conditions, including malignancies.[15,16] Increased Lcn-2 expression has frequently been linked to tumor stage, tumor size, and invasive potential. Experimental and clinical studies indicate that Lcn-2 may contribute to tumor progression through several mechanisms, including enhancement of cellular proliferation, inhibition of apoptosis, and induction of epithelial–mesenchymal transition.[14,17–19]

Previous research has also demonstrated that Lcn-2 gene expression is higher in luminal epithelial cells than in myoepithelial cells in normal breast tissue. Because most breast carcinomas originate from luminal epithelial cells, Lcn-2 may play a significant role in the progression of breast cancer.[19,20] Elevated Lcn-2 levels have been associated with lymph node metastasis, higher histological grade, increased proliferative activity, and poor clinical outcomes in patients with breast cancer.[21] Considering the limited therapeutic options for aggressive subtypes such as TNBC, Lcn-2 has emerged as a potential biomarker and therapeutic target.

The present study aimed to investigate the association between immunohistochemically determined Lcn-2 expression and pathological response to neoadjuvant chemotherapy in patients with locally advanced TNBC. Pathological response was evaluated using the Residual Cancer Burden (RCB) scoring system based on surgical specimens obtained after NACT. In addition, we examined the relationship between Lcn-2 expression and various clinicopathological characteristics, as well as other established predictive and prognostic factors in this patient cohort.

Materials and Methods

This study included 56 voluntary patients diagnosed with locally advanced triple-negative breast cancer (TNBC) who were followed up and treated with neoadjuvant chemotherapy (NACT) at the Medical Oncology Clinic of the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital. The TNBC group consisted of patients who were negative for both hormone receptors and HER2. HER2 negativity was confirmed by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). Patients with absent HER2 protein expression or with scores of +1 or +2 on IHC were evaluated as HER2-negative. Cases with HER2 scores of +1 or +2 by IHC were further assessed using FISH, and HER2 negativity was confirmed. Locally advanced breast cancer (LABC) was defined based on the literature as including stage IIB (T2N1, T3N0) and stage IIIA–IIIB–IIIC breast cancers.

Data on patients' date of diagnosis, blood test results at diagnosis, histopathological features of biopsy samples, Ki-67 index, TNM staging, echocardiographic evaluation before NACT, and date of surgery after NACT were obtained from the hospital's electronic medical records.

Archival diagnostic pathology specimens were retrieved for all patients. The paraffin-embedded tissue blocks from these cases were processed using a Leica Bond Max immunohistochemistry system, including incubation and deparaffinization steps. Sections of 3 μm thickness were prepared, followed by heat-induced epitope retrieval using EDTA for 20 minutes. Tissue sections were incubated for 30 minutes with anti-Lipocalin-2/NGAL antibody (catalog no.: rabbit monoclonal [EPR19912], Abcam, Cambridge Biomedical Campus, CB2 0AX, UK) at a 1:2000 dilution. For secondary detection, a Leica HRP-conjugated polymer detection kit (DS9800, Newcastle, United Kingdom) was used. The protocol included 10 minutes with hydrogen peroxide, 8 minutes with post-polymer, 8 minutes with polymer, 8 minutes with DAB chromogen, and 10 minutes with hema-

toxylin. Slides were washed at each step, dehydrated, and mounted using Entellan. Colon tissue was used as a positive control.

Stained sections were evaluated under a light microscope based on staining intensity (0–3; 0=negative, 1=weak, 2=moderate, 3=strong) and staining extent (0–4; 0=negative, 1=0–25%, 2=26–50%, 3=51–75%, 4=76–100%), as described in the literature. Representative immunohistochemical staining patterns of Lipocalin-2 (Lcn-2) observed in tumor tissues from patients included in the study are presented in Figures 1–4. Figure 1 demonstrates the absence of Lcn-2 staining in triple-negative breast cancer tissue (×40 magnification). Weak Lcn-2 staining is illustrated in Figure 2 (×100 magnification), whereas Figure 3 shows moderate staining intensity (×100 magnification). Strong Lcn-2 expression is demonstrated in Figure 4 (×400 magnification). Colon adenocarcinoma tissue was used as a positive control for Lipocalin-2 staining, as shown in Figure 5. A composite expression score was calculated by multiplying intensity and extent scores; scores of 0–1 were classified as negative, and scores of 2–12 as positive. Comparisons were made between the Lcn-2-negative and Lcn-2-positive expression groups in terms of patients' age at diagnosis, comorbidities, menopausal status, CA15-3 levels, neutrophil counts and neutrophil-to-lymphocyte ratio (NLR), Ki-67 index, presence of accompanying ductal carcinoma in situ (DCIS), T and N classification at diagnosis, stage, tumor size, and chemotherapeutic response evaluated in post-NACT surgical specimens.

The histopathological assessment of the surgical specimens after NACT was based on the Residual Cancer Burden (RCB) index to evaluate treatment efficacy and tumor response. The RCB index classifies residual disease as follows: RCB-0 (no residual disease; pathological complete response, pCR), RCB-1 (minimal residual disease), RCB-2 (moderate residual disease; partial response), and RCB-3 (extensive residual disease; non-response or minimal response/chemoresistance). Additionally, pathological complete response (pCR) was defined as the absence of invasive tumor in both the breast and axilla after NACT.

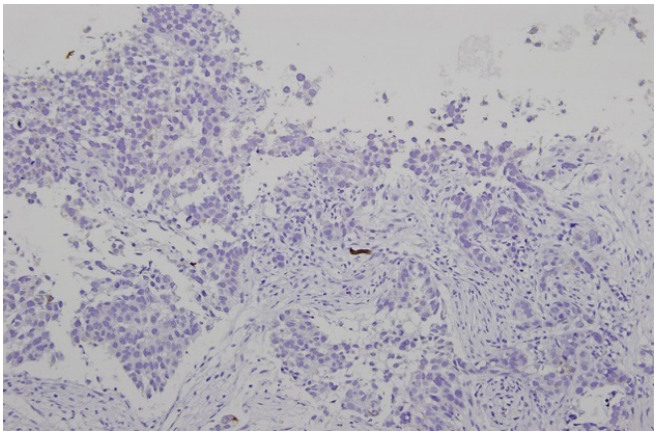

Figure 1. Absence of lipocalin-2 expression in tumor cells (×40).

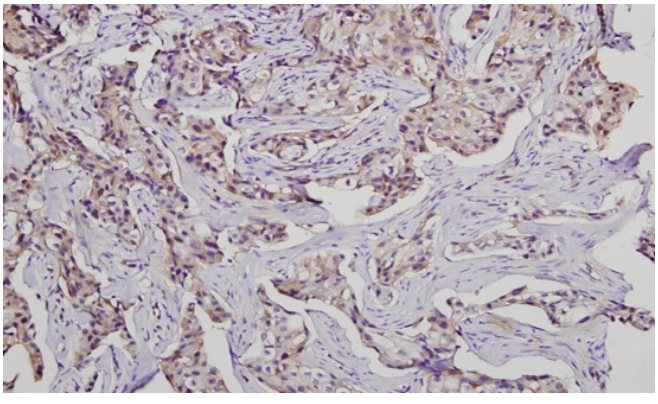

Figure 2. Weak (intensity 1) lipocalin-2 staining in tumorcells (×100).

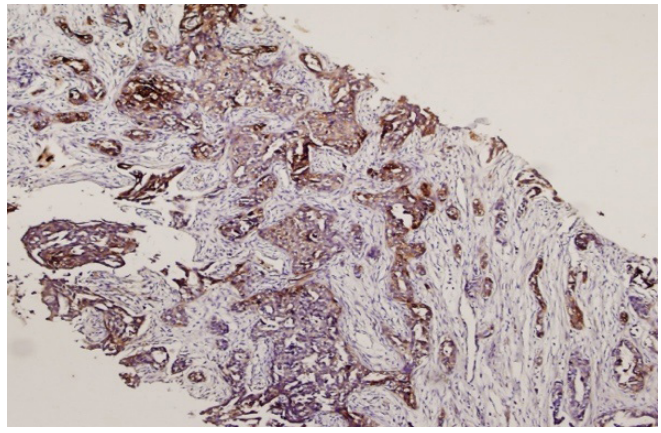

Figure 3. Moderate (intensity 2) lipocalin-2 staining in tumor cells (×100).

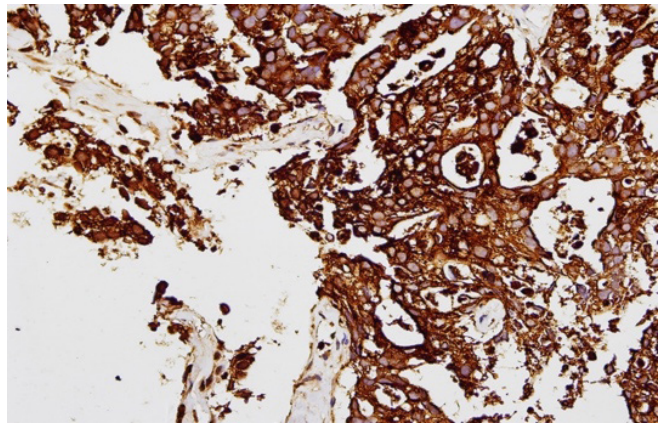

Figure 4. Strong (intensity 3) lipocalin-2 staining in tumor cells (×400).

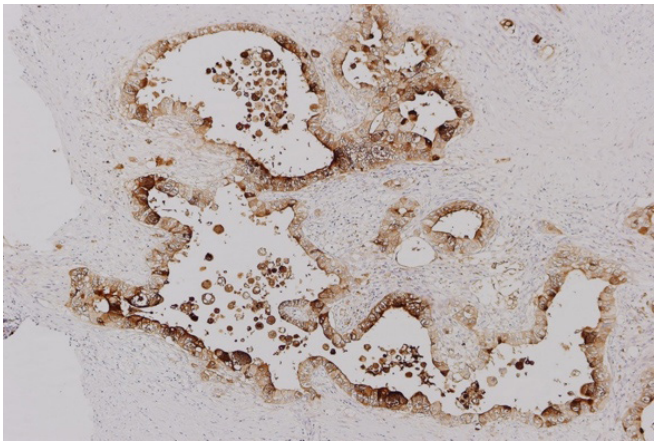

Figure 5. Lipocalin-2 staining in colon adenocarcinoma used as control tissue.

This study was approved by the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (Approval No: 2021-09/1361, Date: 09.09.2021). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

All statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, and continuous variables were summarized as means and standard deviations. The Shapiro–Wilk test was used to determine the normality of distribution for continuous variables. For variables with non-normal distribution, comparisons between two groups were made using the Mann–Whitney U test, while normally distributed variables were compared using the independent samples t-test. The Kaplan–Meier method was used to evaluate associations between variables and disease-free survival. A p-value of ≤0.05 was considered statistically significant.

AI-assisted technology (ChatGPT, OpenAI, GPT-5.3) was used solely for language editing and improving the clarity of the manuscript. The authors take full responsibility for the accuracy, integrity, and originality of the content.

Results

The mean age at diagnosis among patients was 50±12.5 years (range: 29–75). Demographic, comorbid, clinical, and histopathological characteristics of the patients are summarized in Table 1. A total of 12 patients (21.4%) had hypertension (HT), and 14 (25%) had diabetes mellitus (DM). Half of the patients (50%, n=28) were premenopausal.

According to the 8th edition of the AJCC TNM staging system, 35 patients (62.5%) were classified as T2 and 13 patients (23.2%) as T3. Most of the patients (75%, n=42)

Table 1. Demographic, comorbid, clinical, laboratory, and histopathological characteristics of patients with locally advanced triple-negative breast cancer

	Frequency (n)	%
Comorbidity		
None	41	73.2
Present	15	26.8
Hypertension	12	21.4
Diabetes Mellitus	14	25
Coronary Artery Disease	3	5.4
Heart Failure	0	0
Smoking	18	32.1
Alcohol Consumption	2	3.6
ECOG PS		
0	20	35.7
1	36	64.3
Menopausal Status		
Premenopausal	28	50
Postmenopausal	28	50
Stage		
2B	36	64.3
3A	13	23.2
3B	5	8.9
3C	2	3.6
NLR		
< 2.85	35	62.5
≥ 2.85	21	37.5
Grade		
2	4	7.1
3	51	91.1
T		
1	3	5.4
2	35	62.5
3	13	23.2
4	5	8.9
N		
0	3	5.4
1	42	75
2	9	16.1
3	2	3.6
Histopathology		
NOS	40	71.4
İDC	15	26.8

Table 1. Continue

	Frequency (n)	%
DCIS		
Present	19	33.9
Absent	36	64.3
Lcn-2		
Positive	30	53.6
Negative	26	46.4

ECOG PS: Eastern cooperative oncology group performance score; NLR: Neutrophil-to-lymphocyte ratio, NOS: Not otherwise specified; IDC: Invasive ductal carcinoma; DCIS: Duktal carcinoma in-situ, Lcn-2: Lipocalin2.

were found to be N1. The median tumor size was 35.5 mm (range: 5–130 mm). In total, 36 patients (64.3%) were categorized as stage IIB and 13 (23.2%) as stage IIIA. Additionally, 4 patients (7.1%) were diagnosed with inflammatory breast cancer (Table 1).

Histopathologically, 40 patients (71.4%) were classified as invasive carcinoma of no special type (NST/NOS), while 15 patients (26.8%) were identified as invasive ductal carcinoma (IDC). A total of 51 patients (91.1%) were found to have grade 3 tumors (Table 1). Moreover, ductal carcinoma in situ (DCIS) was present in 19 patients (33.9%). The median Ki-67 index was 80% (range: 20–100%).

Patients with Lcn-2 positivity had a significantly higher mean Ki-67 index compared to Lcn-2-negative patients (p=0.032). Lcn-2 positivity was significantly more frequent in patients in the cT3–T4 tumor category (p=0.023). When disease stage was grouped as stage IIB versus stage III, including IIIA, IIIB, and IIIC, Lcn-2 positivity was significantly higher in the stage III group (p=0.017).

No statistically significant association was found between Lcn-2 expression and the presence of DM, HT, smoking or alcohol use, or menopausal status. Similarly, there was no significant relationship between Lcn-2 expression and the presence of DCIS (p=0.992) or histological subtype (NST vs. IDC) (p=0.508).

When nodal status at diagnosis was grouped as N0 (no nodal involvement) versus N1–3 (nodal involvement present), Lcn-2 expression showed no significant difference between the groups (p=0.554). Likewise, no significant association was found between Lcn-2 expression and the presence of inflammatory breast cancer (p=0.615).

Neutrophil and lymphocyte counts at diagnosis were measured, and the neutrophil-to-lymphocyte ratio (NLR) was calculated. The mean neutrophil count was 4,815±1,474 cells/μL (range: 2,320–8,490), and the median lymphocyte count was 1,855 cells/μL (range: 1,000–4,670). The median NLR was 2.32 (range: 0.99–4.92), which was used as the NLR cutoff value in the study. The median CA15-3 level at diagnosis was 20.46 U/mL (range: 4.2–610).

Lcn-2 immunohistochemical staining of pathology specimens revealed Lcn-2 positivity in 30 patients (53.6%). The associations between Lcn-2 expression and patients' demographic, clinical, and histopathological findings, along with the corresponding p-values, are presented in Table 2.

The mean age at diagnosis was 48.6 years in patients with positive Lcn-2 expression and 51.65 years in those with negative Lcn-2 expression. No statistically significant difference was found between the groups in terms of Lcn-2 expression (p=0.368) (Table 3).

There was no significant relationship between Lcn-2 expression and mean neutrophil count, lymphocyte count, or neutrophil-to-lymphocyte ratio (NLR) at diagnosis (p=0.339, p=0.511, and p=0.724, respectively). Even when using 2.32 as the NLR cut-off value, the association with Lcn-2 expression remained statistically insignificant (p=0.595).

No statistically significant difference was found in Lcn-2 expression between patients who demonstrated an objective response to neoadjuvant chemotherapy (RCB 0: complete response and RCB 1: partial response) and those who did not

Table 2. Associations between Lcn-2 expression and comorbidities, smoking–alcohol habits and menopausal status, along with corresponding *p*-values

		Lcn-2 Score		
		Negative n (%)	**Positive n (%)**	**p**
Comorbidities				
DM	Present	8 (14.3)	6 (10.7)	0.353
	Absent	18 (32.1)	24 (42.9)	
HT	Present	7 (12.5)	5 (8.9)	0.351
	Absent	19 (33.9)	25 (44.6)	
DM and HT	Present	7 (12.5)	5 (8.9)	0.351
	Absent	19 (33.9)	25 (44.6)	
At Least One Comorbidity (DM. HT. CAD)	Present	18 (32.1)	23 (41.1)	0.531
	Absent	8 (14.3)	7 (12.5)	
Smoking	Present	7 (12.5)	11 (19.6)	0.436
	Absent	19 (33.9)	19 (33.9)	
Alcohol	Present	1 (1.8)	1 (1.8)	0.918
	Absent	25 (44.6)	29 (51.8)	
Menopausal Status	Premenopausal	11 (19.6)	17 (30.4)	0.284
	Postmenopausal	15 (26.8)	13 (23.2)	

DM**:** Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease.

Table 3. Associations between Lcn-2 expression and age at diagnosis, neutrophil and lymphocyte counts, neutrophil-to-lymphocyte ratio (NLR), CA15-3 level and tumor size at diagnosis, along with corresponding p-values

		Lipocalin-2		p
		Negative (n=26)	Positive (n=30)	
Age at Diagnosis (Mean, years)		51.65	48.6	0.368
Neutrophil Count (Mean, cells/μL)		4610.7	4992.3	0.339
Lymphocyte Count (Mean, cells/μL)		2033	2162	0.511
NLR	<2.32 [n (%)]	14 (25)	14 (25)	0.595
	≥2.32 [n (%)]	12 (21.4)	16 (28.6)	
CA15-3 (Mean, U/mL)		33.14	62.29	0.470
Tumor Size (Mean, mm)		40.96	46.93	0.882

NLR: Neutrophil-to-lymphocyte ratio; CA 15-3: Cancer antigen 15-3.

(RCB 2: minimal response and RCB 3: no response) (p=0.666).

In addition, our study compared demographic, laboratory, clinical, and histopathological parameters between patients who achieved a pathological complete response (pCR; RCB 0) and those who did not (RCB 1–3). A pathological complete response was observed in 30.4% of patients (n=17). The pCR rate was significantly higher in the group that received dose-dense anthracycline-based (ddA) neoadjuvant chemotherapy (p=0.047). Likewise, patients with tumors classified as T1–T2 had significantly higher pCR rates compared to those in the T3–T4 group (p=0.013). Moreover, patients with an NLR ≥2.32 had significantly poorer pathological response to NACT (p=0.042). No significant association was found between Lcn-2 expression and pCR (p=0.950) (Table 4). No other demographic, comorbid, laboratory, clinical, or histopathological variables showed a statistically significant association with pCR.

Table 4. Associations between pathological complete response (pCR) and demographic, laboratory, clinical and histopathological variables, with corresponding *p*-values

		pCR		p
		Yes n (%)	No n (%)	
ddA	Used	5 (8.9)	3 (5.4)	0.047
	Not Used	12 (21.4)	36 (64.3)	
T	T1-T2	15 (26.8)	24 (42.9)	0.013
	T3-T4	2 (3.6)	15 (26.8)	
NLR	≥2.32	5 (8.9)	23 (41.1)	0.042
	<2.32	12 (21.4)	16 (28.6)	
Lcn-2	Positive	9 (16.1)	21 (37.5)	0.950
	Negative	8 (14.3)	18 (32.1)	

ddA: "dose dense" anthracycline; T: Tumor stage; NLR: Neutrophil-to-lymphocyte ratio; Lcn-2: Lipocalin-2; pCR: Pathological complete response.

Additionally, disease recurrence was observed in 13 patients (23.2%). The median disease-free survival (DFS) was calculated as approximately 60 months (range: 25–94 months). No statistically significant association was found between Lcn-2 expression and DFS (p=0.693). Similarly, no significant relationship was observed between DFS and NLR values when stratified by the cut-off of 2.32 (p=0.202). DFS also showed no statistically significant difference between the T3–4 vs. T1–2 or grade 3 vs. grade 2 tumor groups (p=0.515). However, patients who achieved a pathological complete response (pCR) had significantly longer DFS. While DFS could not be estimated in the pCR group due to the absence of events, it was calculated as 36 months in the non-pCR group (p=0.036).

Discussion

In the present study, Lcn-2 expression was significantly more frequent in larger tumors classified as T3–T4 compared with T1–T2 tumors (p=0.023). However, previous studies have reported inconsistent findings regarding the relationship between tumor size and Lcn-2 expression.[22,23] For example, Kurozumi et al.[22] demonstrated that increasing tumor size was associated with reduced nuclear Lcn-2 expression, whereas no significant association was observed for cytoplasmic staining.

Our results also showed that Lcn-2 expression was significantly higher in patients with stage III breast cancer compared with those with stage IIB disease (p=0.017). This observation is consistent with several previous reports indicating that Lcn-2 expression is associated with more advanced disease stages.[24,25] Similarly, Hu et al.[25] reported increased Lcn-2 expression in patients with advanced breast cancer.

In addition, we identified a significant association between Lcn-2 expression and a high Ki-67 proliferation index (p=0.032). Ki-67 is widely recognized as an important prognostic biomarker in breast cancer, reflecting tumor proliferative activity. Previous investigations have likewise reported a relationship between elevated Ki-67 levels and increased Lcn-2 expression.[23,26]

In our cohort, Lcn-2 positivity was observed in 30 patients (53.6%). Nevertheless, no statistically significant relationship was detected between Lcn-2 expression and age at diagnosis, menopausal status, comorbid conditions such as diabetes mellitus or hypertension, or lifestyle-related factors, including smoking and alcohol consumption.

Although breast cancer is most commonly diagnosed in postmenopausal women, it can develop across a wide age

range.[27] Approximately three-quarters of breast cancer cases occur after the age of 50, whereas fewer than 5% are diagnosed in women younger than 35 years.[28,29] In a study conducted by Rao et al.[30] involving 50 TNBC patients, the mean age at diagnosis was reported as 46.8 years. In agreement with these findings, the mean age at diagnosis in our study population was 50 years (range: 29–75).

Consistent with several previous reports, our analysis did not demonstrate a significant association between Lcn-2 expression and patient age (p=0.368) or menopausal status (p=0.284). Although certain studies have suggested that higher Lcn-2 expression may be more common in younger patients with breast cancer, many investigations have failed to confirm a clear relationship between age and Lcn-2 expression.[21,24] Likewise, Tsakogiannis et al., [31] in a study of 73 patients with breast cancer, reported no significant correlation between Lcn-2 expression and menopausal status.

Similarly, we found no significant associations between Lcn-2 expression and diabetes mellitus (p=0.353) or smoking status (p=0.436), findings that are consistent with previously published reports.[31] In addition, no relationship was observed between Lcn-2 expression and hypertension (p=0.351) or alcohol consumption (p=0.918).

The majority of triple-negative breast cancers are classified histologically as invasive carcinoma of no special type (NST/NOS).[32] Our results were consistent with this observation, as the distribution of histological subtypes in our cohort was similar to that reported in previous studies. For instance, Thike et al.[5] reported that 606 out of 653 TNBC cases (92%) were classified as invasive carcinoma, NOS. Likewise, Rao et al.[30] reported that 31 of 50 TNBC cases (84%) belonged to the NOS category.

In the present study, no significant difference in Lcn-2 expression was detected between invasive ductal carcinoma (IDC) and NOS subtypes (p=0.508). Bauer et al.[21] evaluating multiple breast cancer subtypes, reported Lcn-2 expression in 94% of IDC/NOS tumors. In contrast, Villodre et al.[24] observed significantly increased Lcn-2 expression in IDC/NOS tumors and reported particularly high expression levels in inflammatory breast cancer, which were associated with a poorer prognosis. However, in our cohort, no statistically significant relationship was found between Lcn-2 expression and inflammatory breast cancer (p=0.615).

We also found no significant association between Lcn-2 expression and tumor grade (grade 2 vs. grade 3; p=0.335). While some studies have reported increased Lcn-2 expression in higher-grade tumors,[21,25,26] others, including the large cohort study by Wenners et al.[33] (n=650) and the work by Cramer et al.,[34] did not observe such an association.

Similarly, Lcn-2 expression was not associated with nodal involvement (N0 vs. N1–3; p=0.554) in our study. Although several reports have suggested potential associations between Lcn-2 and lymphovascular invasion or lymph node metastasis,[21–23] Wenners et al.[33] did not find such relationships. The absence of a significant association in our study may partly be explained by the relatively small sample size.

Furthermore, we did not observe any significant relationships between Lcn-2 expression and serum CA15-3 levels, neutrophil count, lymphocyte count, or the neutrophil-to-lymphocyte ratio (NLR). Likewise, no association was found between Lcn-2 expression and the presence of ductal carcinoma in situ (DCIS) (p=0.992). To the best of our knowledge, the relationship between Lcn-2 expression and DCIS has not previously been examined in the literature.

No significant correlations were identified between Lcn-2 expression and NLR (p=0.595), CA15-3 levels (p=0.470), neutrophil count (p=0.339), or lymphocyte count (p=0.511). Although previous studies have not directly investigated these relationships, Qiu et al.[35] demonstrated that an elevated baseline NLR (cut-off: 2.85) was associated with poorer prognosis in a cohort of 406 TNBC patients.

Pathological response following neoadjuvant chemotherapy represents a key prognostic indicator in TNBC, an aggressive breast cancer subtype characterized by high rates of recurrence and metastasis.[30] While several studies have suggested that Lcn-2 overexpression may be associated with poor prognosis in TNBC,[24,25] our findings did not demonstrate a significant association between Lcn-2 expression and pathological response to NACT (p=0.666). In contrast, Yau et al.[36] in a large pooled analysis of 5,161 patients with breast cancer, reported that higher Residual Cancer Burden (RCB) scores were strongly associated with worse long-term outcomes. The lack of a significant association in our study may be related to the relatively limited sample size.

Conclusion

In conclusion, our findings did not demonstrate a significant relationship between Lcn-2 expression and response to neoadjuvant chemotherapy in patients with locally advanced TNBC. Nevertheless, Lcn-2 expression was associated with several clinicopathological features that are generally considered indicators of poor prognosis. These results suggest that Lcn-2 may still have potential clinical relevance in TNBC.

Previous studies have proposed Lcn-2 as a potential independent prognostic biomarker due to its associations with several clinical and pathological parameters, including age at diagnosis, tumor type, tumor size, histological grade,

disease stage, hormone receptor status, Ki-67 proliferation index, lymphovascular invasion, lymph node involvement, and metastatic spread. However, larger prospective studies are required to confirm these relationships and to better clarify the potential clinical utility of Lcn-2 in breast cancer.

Disclosures

Ethics Committee Approval: This study was approved by the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (Approval No: 2021-09/1361, Date: 09.09.2021).

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