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Research Article

Assessment of Disease Activity Using Fecal Occult Blood Test in Patients with Inflammatory Bowel Disease

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Abstract

Objectives: Assessment of disease activity is essential for treatment and follow-up in inflammatory bowel disease (IBD). Colonoscopy is the gold standard but it is invasive and costly for frequent monitoring. Therefore, simple and non-invasive biomarkers are needed. To evaluate fecal occult blood (FOB) testing in assessing disease activity in patients with ulcerative colitis (UC) and Crohn's disease (CD).

Methods: A total of 115 patients (56 UC, 59 CD) were included. Clinical activity was assessed using the Modified Mayo Score for UC and the Harvey–Bradshaw Index for CD. FOB testing was performed in all patients and endoscopic activity was evaluated in 59 patients. Associations between FOB test and disease activity were analyzed.

Results: Clinically active disease was present in 30.4% of UC and 25.4% of CD patients. FOB positivity was significantly associated with clinical activity in UC (p=0.009), but not in CD (p=0.109). In UC, FOB showed 88.2% sensitivity and 48.7% specificity for detecting clinical activity and was also associated with endoscopic activity (p=0.031). No significant association was observed in CD.

Conclusion: FOB testing may represent a simple, inexpensive, and non-invasive tool for assessing disease activity in UC, but appears limited in CD.

Keywords: Inflammatory Bowel Disease, Fecal Occult Blood Test, Colitis, Ulcerative, Crohn Disease

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In genetically predisposed individuals, inflammatory bowel disease (IBD) arises from a disordered immune response against the microbiota induced by environmental factors.[1] IBD is a chronic inflammatory disease of the gastrointestinal tract that can undergo phases of activation and remission, resulting in a high rate of morbidity and death. Ulcerative colitis (UC) and crohn's disease (CD) are the two primary categories.

The choice of treatment for IBD depends in part on the activation and location of the illness. Disease activity was assessed using clinical activity indices as well as laboratory, endoscopic, and histological tests. Laboratory tests such as CRP, ESR, and fecal calprotectin (FC) are commonly performed. Nevertheless, FC is not an affordable test available at every facility around the nationwide. Active mucosal inflammation is often present in asymptomatic individuals, and clinical indicators are

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not necessarily correlated with actual inflammation with IBD. Even with adequate medication, the majority of IBD patients experience illness exacerbations as a result of symptoms including diarrhea and bloody stools, and it can be challenging to anticipate these exacerbations in advance of symptom onset. If recurrences can be detected in the asymptomatic stage, the treatment of relapse may be commenced early, and patients can be given an easier remission phase.

Colonoscopy is widely recognized as the gold standard for assessing mucosal inflammation and disease activity in patients with IBD. However, the colonoscopic examination is sometimes challenging to perform because of expense and patient discomfort.[2]

Currently, all IBD patients in clinical and laboratory remission undergo endoscopic mucosal repair as the goal of their applied therapy. However, colonoscopy should be used in patient with IBD in clinical and laboratory remission in order to achieve the aim of endoscopic mucosal repair in daily practice. Colonoscopic examination can sometimes be a burden because of the above-mentioned disadvantages. In this setting, endoscopic mucosal healing is increasingly determined by biomarkers rather than by colonoscopy. Previous research has demonstrated that fecal indicators are predictive of prognosis, particularly clinical recurrence, and represent endoscopic mucosal inflammation and mucosal healing in the FC and fecal occult blood (FOB) tests. Consequently, fecal markers can be used to track individuals in clinical remission to assess mucosal repair and disease recurrence without the need for colonoscopy.[3,4]

The FOB test is currently used in the general population for colorectal cancer screening. In the protocol conducted by the Ministry of Health for screening CRC in our country, it is recommended to perform a two-year FOB test and a colonoscopy every 10 years (https://hsgm.saglik.gov.tr/tr/kanser-tarama-standartlari/listesi/kolorektal-kanser-tarama-program%C4%B1-ulusal-standartlar%C4%B1.html).

The FOB test measures the amount of blood in stool samples automatic equipment, simply and quickly.[5] Given the limitations of invasive endoscopic procedures and the need for simple, cost-effective, and non-invasive biomarkers in the follow-up of inflammatory bowel disease, fecal markers have gained increasing attention. Although fecal calprotectin is widely used, its limited availability and high cost restrict its routine use in daily practice. Fecal occult blood testing is an inexpensive, easily accessible, and rapid stool-based test; however, data regarding its role in assessing disease activity in inflammatory bowel disease, particularly in Crohn's disease, remain limited. Therefore, this study aimed to evaluate the utility of fecal occult blood testing in assessing both clinical and endoscopic disease activity in patients with ulcerative colitis and Crohn's disease.

Methods

Study Population

This study included 115 patients included with clinical, endoscopic, radiological, and histopathological confirmed IBD diagnosis in the Department of Gastroenterology at Dokuz Eylul University Hospital.

Exclusion criteria for patients;

- History of colorectal surgery history due to IBD
- History of colorectal cancer
- History of alcohol and substance abuse
- Pregnancy

The study was approved by the Institutional Non-Interventional Research Local Ethics Committee on 15 February 2018 (Approval No: 2018 / 05-36) and in accordance with the precepts established by the Declaration of Helsinki, and informed consent was obtained from all the participants.

*D*emographic and Laboratory Data

Age, sex, type, and duration of the disease, the area of the disease in the intestine, and drugs used for the treatment of IBD, smoking, routine hemogram (hemoglobin, hematocrit, and platelet values), and CRP values, which are inflammatory markers, were obtained from the records in the database of the Hospital Information Management System (HBYS) (Probel version V1).

Clinical Activity Index Data

Patients were evaluated for remission and activation by using specific clinical activity indices. Modified Mayo Scoring was used to evaluate the clinical activity of UC, and Harvey Bradshaw Index (HBI) was used to evaluate the clinical activity of CD.

Mayo score, including stool frequency, rectal bleeding, endoscopic findings, and 4 criteria including global assessment by the clinician (0, normal; 1, mild; 2, medium; 3, heavy). Each criterion is scored between 0 and 3. In this study, we used the Modified Mayo Clinic score, which did not include endoscopic evaluation. Accordingly, patients who received 2 points or less were in remission. HBI; It includes five criteria; general well-being, abdominal pain, daily fluid defecation count, abdominal mass, and complications. Accordingly, patients who received 4 points or less were considered to be in remission.

Endoscopic Activity Index Data

Endoscopic activity was examined in 59 (51.3%) of the patients (27/59 CH, 32/59 UC, 18/59 flexible sigmoidoscopy,

41/59 colonoscopy). The Mayo endoscopic sub-score was used for endoscopic activity scores in patients with UC. For CD, the presence of an ulcer was considered as an active disease, and no endoscopic scoring was performed.

Fecal Occult Blood Testing

Stool samples of patients were taken, and FOB was examined within 20 h. An HM-Jack stool secret blood autoanalyzer was used (Extel Hemo-Auto). In this test, the change in agglutination caused by the hemoglobin in latex particles coated with antibodies against human hemoglobin was determined in terms of turbidity, and the amount of blood in stool was quantified. Results were evaluated as either positive or negative. (Normal values: 0-12 ng/ml, results above 12 ng/ml were considered positive).

We compared the results of the FOB test in clinically and endoscopically active and remission IBD patients, thus demonstrating the role of the FOB test in determining the clinical and endoscopic activity of the disease.

Statistical Analyses

All analyses were performed using SPSS 17 statistical package program. The normal distribution suitability of the numerical variables was tested using the Shapiro-Wilk Test. Numerical variables were described using the mean and standard deviation, and categorical variables were described using frequency and percentage values. The correlation between categorical variables, Chi-square test, and the relationship between numerical variables were investigated by Spearman correlation analysis. Two independent means were compared using the Mann-Whitney U test. Again, the independent mean was compared using the post-hoc Dunn's test after the Kruskal-Wallis test. Statistical significance was defined as a value of $p < 0.05$.

Results

The study groups were categorized as UC (n = 56) and CD (n = 59). A total of 115 patients, 44 of whom were female (38.3%) and 71 of whom were male (61.7%), were included in the study. The UC and CD subgroups were similar in terms of age and sex distributions (p=0.20, p=0.079). There was no significant difference between the mean hemoglobin, hematocrit levels, platelet values, and CRP levels of the patients (p=0.20, p=0.20, p=0.194, and p=0.301, respectively). No significant differences were observed between the two groups in terms of smoking and disease duration (p=0.206 and p=0.524 respectively). While 12.5% proctitis, 64.3% left colitis, and 23.2% pancolitis involvement were observed in the UC group; 25.4% ileal, 28.8% colonic, and 45.8% ileocolonic involvement were observed in the CD group. In the UC group, 5-ASA use was more frequent, whereas immunomodulatory therapy was more frequent in the CD group ($p < 0.001$).

Based on the Modified Mayo Score, 17/56 (30.4%) UC patients had clinically active disease; based on the HBI, 15/59 (25.4%) CD patients had clinically active disease. There was no significant difference in clinical activation status between the two groups (p=0.555). At the same time, no significant difference was found between the CD and UC groups in terms of FOB test positivity (p=0.981) (Table 1).

In the UC group, clinical activity was not associated with age, sex, platelet count, CRP level, smoking status, disease duration, disease location, or treatment (all $p > 0.05$); however, hemoglobin and hematocrit levels differed between active and remission groups ($p = 0.020$ and $p = 0.026$, respectively), with lower values in active disease (Table 2).

In the CD group, clinical activity was not associated with age, hemoglobin, hematocrit, platelet count, smoking status, disease duration, disease location, or treatment (all $p>0.05$); CRP levels were higher in active disease than remission (16.6± 19.1 vs 7.4± 11.2 mg/L; p=0.017) (Table 2).

In the UC group, FOB positivity was not associated with age, sex, hemoglobin, hematocrit, platelet count, CRP level, or smoking status (all $p>0.05$), but was associated with the activation score ($p = 0.001$). The activation score was 2.4± 2.2 in FOB-positive patients and 0.5 ± 1.0 in FOB-negative patients (Table 3).

In the CD group, FOB positivity was not associated with age, sex, hemoglobin, hematocrit, platelet count, or activation score (all $p>0.05$), but was associated with CRP level and smoking status ($p = 0.038$ and $p = 0.049$, respectively). CRP levels were higher in FOB-positive CD patients than FOB-negative patients (11.7± 15.3 vs 6.4± 11.3 mg/L; $p = 0.038$). Smoking history was more frequent among FOB-positive patients (p=0.049) (Table 3).

According to the Modified Mayo score in the UC group, 17 patients (30.3%) were clinically active and 15 of these patients had a positive FOB test. There was a statistically significant difference between FOB test positivity and clinical activation ($p = 0.009$) (Table 4). The sensitivity, specificity, positive predictive value, and negative predictive value of the FOB test for UC were 88.23%, 48.71%, 42.85%, and 90.47%, respectively.

In the CD group, 15 patients (25.4%) were clinically active according to HBI and the FOB test was positive in 12 of these patients. There was no significant relationship between FOB test positivity and clinical activation (p=0.109) (Table 4). The sensitivity, specificity, positive predictive value, and negative predictive value of the FOB test for CD were 80.00%, 43.18%, 32.43%, and 86.36%, respectively.

The current endoscopy of a total of 59/115 patients (UC,

Table 1. Demographic characteristics of the participants

	UC (n=56)	CD (n=59)	Total (n=115)	p
Age (Mean ± SD)	47.4± 3.1	48.5±13.9	47.9±13.5	0.200
Gender [n (%)]				0.079
Woman	26 (46.4)	18 (30.5)	44 (38.3)	
Man	30 (53.6)	41 (69.5)	71 (61.7)	
Hemoglobin, gr/dL	13.4±0.1	15.2±1.7	14.3±0.9	0.200
Hematocrit, %	40.3±0.5	51.9±7.9	46.2±4.2	0.200
Platelet value, 10^3/uL	281250±13110	292593±15514	287069±14343	0.194
CRP, mg/L	9.2±2.3	9.7±1.8	9.4±2.0	0.301
Smoking [n (%)]				0.206
Yes	13 (23.2)	20 (33.9)	33 (28.7)	
No	43 (76.8)	39 (66.1)	82 (71.3)	
Disease duration [n (%)]				0.524
≤ 5 years	28 (50.0)	26 (44.1)	54 (47.0)	
> 5 years	28 (50.0)	33 (55.9)	61 (53.0)	
Disease location (UC)				
Proctitis	7 (12.5)	-	-	
Left Colitis	36 (64.3)	-	-	
Pancolitis	13 (23.2)	-	-	
Disease location (CD)				
Ileal	-	15 (25.4)	-	
Colonic	-	17 (28.8)	-	
Ileocolonic	-	27 (45.8)	-	
Treatment [n (%)]				<0.001
5-ASA	36 (64.3)	10 (16.9)	46 (40.0)	
Systemic Steroids	1 (1.8)	3 (5.1)	4 (3.5)	
Immunomodulatory	3 (5.4)	27 (45.8)	30 (26.1)	
5-ASA + Immunomodulatory	16 (28.5)	19 (32.2)	35 (30.4)	
FOB Test [n (%)]				0.981
Pozitif	35 (62.5)	37 (62.7)	72 (62.6)	
Negatif	21 (37.5)	22 (37.3)	43 (37.4)	
Clinical activation [n (%)]				0.555
Remission	39 (69.6)	44 (74.6)	83 (72.2)	
Active	17 (30.4)	15 (25.4)	32 (27.8)	

32/56; CD, 27/59) were examined. In the UC group, 21/32 patients had endoscopically active disease; FOB was positive in 18/21. There was a significant correlation between FOB test positivity and endoscopic activation (p = 0.031) (Table 4). The sensitivity, specificity, positive predictive value, and negative predictive value of the FOB test in demonstrating endoscopic activation in patients with UC were 85.7%, 63.6%, 81.8%, and 70.0%, respectively. In the CD group, 22/27 patients had endoscopically active disease; FOB was positive in 16/22. In this group, no significant correlation was found between FOB test positivity and endoscopic activation (p=0.295) (Table 4). The sensitivity, specificity, positive predictive value, and negative predictive value of the FOB test in demonstrating endoscopic activation in patients with CD were 72.7%, 60.0%, 88.8%, and 33.3%, respectively.

Associations between FOB positivity and clinical and endoscopic disease activity differed between UC and CD (Table 4–6).

Table 2. Relationship between disease activation with clinical features in UC and CD subgroups

	UC - Remission	UC - Active	p (UC)	CD - Remission	CD - Active	p (CD)
Age (Mean ± SD)	47.6±13.0	47.0±13.8	0.782	50.5±13.6	42.7±13.5	0.59
Gender [n (%)]			0.950			0.355
Woman	18 (69.2)	8 (30.7)		12 (66.7)	6 (33.3)	
Man	21 (70.0)	9 (30.0)		32 (78.0)	9 (22.0)	
Hemoglobin, gr/dL	13.7±1.3	12.7±1.4	0.02	13.5 ± 1.5	13.2±1.8	0.695
Hematocrit, %	41.2±3.6	38.4±4.0	0.026	40.3 ± 4.7	40.9±9.0	0.896
Platelet, 10^3/uL	270000±840074	305000± 123984	0.417	279000 ± 85413	331000±184334	0.595
CRP, mg/L	5.5±6.0	17.0±28.9	0.202	7.4 ± 11.2	16.6±19.1	**0.017**
Smoking [n (%)]			0.468			0.226
Yes	8 (61.5)	5 (38.5)		13 (65.0)	7 (35.0)	
No	31 (72.1)	12 (27.9)		31 (79.5)	8 (20.5)	
Disease duration			0.771			0.713
≤ 5 years	20 (71.4)	8 (28.6)		20 (76.9)	6 (23.1)	
> 5 years	19 (67.9)	9 (32.1)		24 (72.7)	9 (27.3)	
Treatment [n (%)]			0.324			0.385
5-ASA	26 (76.5)	8 (23.5)		8 (80.0)	2 (20.0)	
Systemic steroids	1 (100.0)	0 (0.0)		1 (33.3)	2 (66.7)	
Immunomodulatory	1 (33.3)	2 (66.7)		20 (74.1)	7 (25.9)	
5-ASA+Immunomod	10 (62.5)	6 (37.5)				

Discussion

IBD is characterized by numerous episodes of clinical remission and acute exacerbations, necessitating ongoing medication and monitoring of the disease status. More specifically, a later acute exacerbation can be predicted by identifying the disease activity during asymptomatic intervals.[6] Selecting the most effective course of therapy for patients with IBD requires the identification of inflammatory activity. Therefore, investigators have actively focused on identifying ideal disease markers. Optimal markers should be specific to the disease, correctly reflect disease activity, be easily applicable in clinical practice, and be able to identify patients at risk of relapse.

Table 3. Relationship between FOB test positivity with clinical features in UC and CD subgroups

	UC-positive	UC-negative	p (UC)	CD-positive	CD-negative	p (CD)
Age (Mean ± SD)	45.4±12.9	50.8±13.1	0.157	47.0±13.8	51.0±13.9	0.319
Gender [n (%)]			0.333			0.317
Woman	18 (69.2)	8 (30.7)		13 (72.2)	5 (27.7)	
Man	17 (56.6)	13 (43.3)		24 (58.5)	17 (41.5)	
Hemoglobin, gr/dL	13.1±1.5	13.9±1.1	0.115	13.3±1.6	13.9±2.2	0.206
Hematocrit, %	39.5±4.1	41.7±3.2	0.117	40.2±4.4	42.4±4.2	0.221
Platelet value, 10^3/uL	284000±101604	275000±94111	0.571	390000±128066	264000±98993	0.085
CRP, mg/L	9.7±19.6	8.3±12.9	0.202	11.7±15.3	6.4±11.3	0.038
Activation score	2.4±2.2	0.5±1.0	0.001	3.0±2.4	2.4±1.8	0.421
Smoking [n (%)]			0.935			0.049
Yes	8 (61.5)	5 (38.5)		16 (80.0)	4 (20.0)	
No	27 (62.7)	16 (37.2)				

Table 4. Relationship between clinical and endoscopic activation status and FOB test in UC and CD subgroups

BD Type	FOB Test	Clinical activation: Remission	Clinical activation: Active	Total	p
UC	Positive	20 (51.3%)	15 (88.2%)	35 (62.5%)	0.009
	Negative	19 (48.7%)	2 (11.8%)	21 (37.5%)	
	Total	39 (100.0%)	17 (100.0%)	56 (100.0%)	
CD	Positive	25 (56.8%)	12 (80.0%)	37 (62.7%)	0.109
	Negative	19 (43.2%)	3 (20.0%)	22 (37.3%)	
	Total	44 (100.0%)	15 (100.0%)	59 (100.0%)	
Total	Positive	45 (54.2%)	27 (84.4%)	72 (62.6%)	0.003
	Negative	38 (45.8%)	5 (15.6%)	43 (37.4%)	
	Total	83 (100.0%)	32 (100.0%)	115 (100.0%)	
IBD type	FOB Test	Endoscopic activation: Remission	Endoscopic activation: Active	Total	p
UC	Positive	4 (36.4%)	18 (85.7%)	22 (68.8%)	0.031
	Negative	7 (63.6%)	3 (14.3%)	10 (31.2%)	
	Total	11 (100.0%)	21 (100.0%)	32 (100.0%)	
CD	Positive	2 (40.0%)	16 (72.7%)	18 (66.7%)	0.295
	Negative	3 (60.0%)	6 (27.3%)	9 (33.3%)	
	Total	5 (100.0%)	22 (100.0%)	27 (100.0%)	
Total	Positive	6 (37.5%)	34 (79.1%)	40 (67.8%)	0.041
	Negative	10 (62.5%)	9 (20.9%)	19 (32.2%)	
	Total	16 (100.0%)	43 (100.0%)	59 (100.0%)	

Colonoscopy is currently the gold standard procedure for assessing the state of the mucosa in patients with IBD. However, colonoscopy is painful for patients and has the potential to worsen their condition. Additionally, even in remission, research has found that colonoscopy alone might exacerbate the condition.[7] Thus, it is challenging to perform regular colonoscopies, which are necessary for sufficient monitoring of the IBD status, because of the expense and discomfort to patients. To address this clinical issue, research has been conducted on non-invasive markers. Numerous non-invasive techniques have been developed in recent years to assess intestinal inflammation, but a simple test that is widely recognized and has a high success rate has not been discovered.[8,9] Despite being utilized as traditional indicators of inflammation, ESR and CRP values have limited therapeutic use because they are indicative of systemic inflammation rather than mucosal inflammation.[10,11] Compared to individuals with CD, people with UC have a lower correlation between CRP level and disease activity.[12] Similarly, in our study, although there was a significant relationship between CRP levels and disease activity in patients with CD, no statistical significance was found in patients with UC.

Kochan et al.[12] demonstrated that laboratory measurements helped to illustrate clinical activity, but they did not find any appreciable improvement in endoscopic follow-up or mucosal healing. Therefore, fecal markers are therefore more accurate and promising[13]

Table 5. Relationship between clinical activation and endoscopically activation in UC and CD groups

IBD type	Clinical activation status	Endoscopic: Remission	Endoscopic: Active	Total	p
UC	Remission	9 (81.8%)	8 (38.1%)	17 (53.1%)	0.132
	Active	2 (18.2%)	13 (61.9%)	15 (46.9%)	
	Total	11 (100.0%)	21 (100.0%)	32 (100.0%)	
CD	Remission	5 (100.0%)	13 (59.1%)	18 (66.7%)	0.136
	Active	0 (0.0%)	9 (40.9%)	9 (33.3%)	
	Total	5 (100.0%)	22 (100.0%)		

Table 6. Evaluation of all results in UC and CD Groups

IBD type	FOB test	Clinical remission	Clinical active	p (Clinical)	Endoscopic remission	Endoscopic active	p (Endoscopic)
UC	Positive	20 (51.3%)	15 (88.2%)	0.009	4 (36.4%)	18 (85.7%)	0.031
	Negative	19 (48.7%)	2 (11.8%)		7 (63.6%)	3 (14.3%)	
	Total	39 (100.0%)	17 (100.0%)		11 (100.0%)	21 (100.0%)	
CD	Positive	25 (56.8%)	12 (80.0%)	0.109	2 (40.0%)	16 (72.7%)	0.295
	Negative	19 (43.2%)	3 (20.0%)		3 (60.0%)	6 (27.3%)	
	Total	44 (100.0%)	15 (100.0%)		5 (100.0%)	22 (100.0%)	
Total	Positive	45 (54.2%)	27 (84.4%)	0.003	6 (37.5%)	34 (79.1%)	0.041
	Negative	38 (45.8%)	5 (15.6%)		10 (62.5%)	9 (20.9%)	
	Total	83 (100.0%)	32 (100.0%)		16 (100.0%)	43 (100.0%)	

In this study, we aimed to investigate the relationship between the clinical, laboratory (CRP), and endoscopic activities of the FOB test and to investigate the clinical benefit of the FOB test, which is a non-invasive, easy-to-use, easy-to-reach and cheap stool examination. In our study, while a significant relationship was found between disease activation and FOB test results clinically and endoscopically in patients with UC, there was no significant relationship between CD and FOB test results. When we compared the clinical and endoscopic activations of the patients, there was no statistically significant difference between them.

The FOB test has been mentioned as an additional biomarker in a few recent investigations.[8] The FOB test in UC patients may be a non-invasive and useful biomarker for assessing clinical and endoscopic activity, according to a literature review by Ryu et al.[14] Currently, FC shows great promise as a noninvasive indicator of mucosal inflammation, and several studies have linked it to mucosal violence.[15] In the course of monitoring and treating the condition, FC was discovered in a study by Satwik et al.[16] to potentially serve as an alternate marker for colonoscopy potentially. In another UC patient trial, the FOB test was shown to indicate treatment effectiveness in patients with active endoscopic activation and mucosal improvement following therapy, even though FC was better than the FOB test in representing disease activation. However, FC is often only useful in tertiary facilities, taking a long time to obtain findings, and most significantly, is a costly testing approach. Furthermore, it has been shown that stool samples taken on the same day from the same patient may provide significantly different FC findings.[17]

According to Nakarai et al.[15], the FC and FOB tests demonstrated important characteristics in the clinical relapse prediction of UC patients. The FOB test is the most economical option. In a related investigation, the FOB test had 92% sensitivity and 71% specificity in predicting mucosal repair in UC patient.[18] Individuals in UC remission who have a negative FOB test have a recurrence risk that is six times lower than that of those who have a positive result.[19]

According to Takashima et al.[3], individuals with UC may predict mucosal healing with both the FC (82% sensitivity, 62% specificity) and FOB tests (95% sensitivity, 62% specificity). Similarly, our study showed that the FOB test could predict endoscopic activation with 85% sensitivity and 63% specificity in the patients group with UC. Ma et al.[4] conducted a study that revealed that individuals with IBD, particularly those diagnosed with UC, showed similar responses to the FOB and FC tests in defining mucosal healing. Chang et al.[17] demonstrated that FC and FOB tests successfully predict changes in the mucosa along the course of the disease and strongly correlate with endoscopic activity in patients with UC. As the FOB test is inexpensive and has a high positive predictive value, it is recommended for tracking disease activity following mucosal healing following induction treatment. They maintained that positive FOB test results during stable patient follow-up would facilitate additional research and decision-making.

Different studies including UC patients found that the FOB test had a sensitivity of 63% specificity of 81% for demonstrating clinical activation, and 73% specificity of 81% for endoscopic activation. According to these findings, endoscopic activation rather than clinical activation may be predicted by a positive FOB test result.[14] Similarly, in our study, a significant correlation was found between the degree of clinical and endoscopic activity calculated using the Modified Mayo Scoring in the UC group and the positivity of the FOB test. These results are compatible with those of studies in this field. In the CD group, according to the Harvey Bradshaw Index, there was no significant relationship between the clinical activity evaluation and FOB test positivity.

Our study shows that these parameters may be useful in reflecting the clinical disease activity and mucosal healing

in patients with IBD. Therefore, the FOB test can provide an "easily accessible" method for assessing mucosal status to assess the effectiveness of treatment aimed at establishing disease remission in patients with IBD. In this case, patients will be able to monitor IBD more readily and regularly because of the FOB test's quick findings and affordable costs to physicians.[9,12] Repeated analysis of several samples is believed to lower the possibility of mistakes and may be helpful in monitoring disease activity. The FOB test high false-positive values demand caution in misinterpreting the results.[14]

The limitations of this study are that some demographic data were retrospectively accessed from the patient records. The FOB test could not be compared with other fecal biomarkers such as FC. Although the clinical activity index was evaluated in all patients, the most valuable method providing information about mucosal inflammation and healing was applied to 59 patients, not to all patients. Since the FOB test examined in our hospital is not a numerical result, the statistics were made according to the positive and negative results. A cost analysis of the FOB test was not conducted.

Conclusion

In this study, the FOB test was used to determine disease activity as an alternative to a more expensive fecal indicator such as FC.

The FOB test was compatible with endoscopic activity indices rather than the clinical activity indices used to determine disease activity.

In this study, unlike in previous publications, the FOB test was examined in both UC and CD and contributed to the literature.

Disease activity in IBD can be determined using the FOB test, which is an inexpensive, simple, and easy method.

Disclosures

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Ethics Committee Approval: The study was approved by the Dokuz Eylul University Non-Interventional Research Local Ethics Committee on 15 February 2018 (Approval No: 2018 / 05-36) and in accordance with the precepts established by the Declaration of Helsinki, and informed consent was obtained from all the participants.

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Research Article

Perceived Stress Enhances Eating Disorders by Affecting Leptin, Ghrelin and Adiponectin Levels

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Abstract

Objectives: The aim of this study is to assess the relationship between stress and eating disorders in young adults, which may be the initial symptom or result of many diseases today.

Methods: SCOFF and PSS tests were applied to 313 women in order to assess eating disorders (ED) and stress disorder (SD). According to the results of the questionnaire tests, the participants were divided into subgroups according to their ED status and body mass index (BMI). Subgroups were compared to investigate the relationship between ED and SD. The effect of SD on adipocytokine levels was compared among the 4 subgroups.

Results: The ED rate was 46.6%, and the SD rate was 34.5%. The SD rate was observed to be higher in the ED(+) group when compared with the ED(-) group (54.1% vs. 17.4%, p<0.001). In all three groups (BMI<18.5 and ED(+), BMI>25 and ED(+), and 18.5≤BMI≤25 and ED(+)), SD risk was observed to be higher than in the 18.5≤BMI≤25 and ED(-) group (OR 8.56, 7.34, and 3.59; p=0.001, p=0.002, and p=0.012, respectively). Leptin levels were lower, and ghrelin and adiponectin levels were higher in the SD(+) subgroup compared with the SD(-) subgroup in the group with ED(+) and BMI<18.5. Leptin levels were higher, and ghrelin and adiponectin levels were lower in the SD(+) subgroup compared with the SD(-) subgroup in the group with ED(+) and BMI>25.

Conclusion: Perceived stress significantly influences leptin, ghrelin, and adiponectin levels and is associated with eating disorders in young adults.

Keywords: Adiponectin, Eating Disorders, Ghrelin, Leptin, Stress Disorder

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Stress is a term that is frequently used in various social, academic, and employment settings. It is well known that everyone needs a certain amount of motivating pressure to do their best. However, when pressure exceeds a person's ability to cope, it causes stress. Moreover, stress can create a cycle of distress and reduce the ability to cope, even in ordinary situations. Many stress factors are encountered frequently today. In today's competitive teaching and study environment, students are faced with more stress than ever before. The source of stress can be education, exams, peers, teachers, or parents.[1] College students frequently encounter stressful situations that can cause negative academic, emotional, and health consequences.[2] They are also subjected to a number of stressful causes, such as gradual overload, constant pressure to succeed, competition with colleagues, and, in some countries, financial burden and concerns about the future.[3] As all these can lead to psychopathology, the health of college students, especially healthcare students, has been the subject of increasing focus in recent years.[4,5] Voltmer et al.[6] reported a decrease in health quality and an increase in risk patterns, indicating the need for prevention and health promotion focusing on individual behaviour.

Eating disorders (ED) are important health problems that may occur as a result of the interaction of genetic, endocrinological, hypothalamic, and environmental factors such as stress. Stress factors can affect a person's eating habits. The change in eating habits paves the way for conditions called nutritional disorders. Nutritional disorders include Anorexia Nervosa (AN), Bulimia Nervosa (BN), binge ED, reactive binge eating disorders, evening eating syndrome, and nonspecific nutritional disorders.[7] Nutritional disorders cause insufficient and/or disproportionate intake of carbohydrate, protein, and fat, as well as insufficient intake of vitamins, minerals, and trace elements in the body. Lack of prodromic symptoms and diagnostic criteria in the early stages of ED often causes delayed diagnosis. In the later stages of malnutrition, it can lead to more serious diseases such as severe depression, epilepsy, hair loss, muscle loss, bone loss, dental caries, growth retardation, anemia, and gastrointestinal and cardiac problems. Intervention for malnutrition with early diagnosis can eliminate the risk of future negative consequences.[8]

The aim of this study was to determine the prevalence of eating disorders among college students at Celal Bayar University Faculty of Medicine and Faculty of Nursing and to investigate the relationship between eating disorders and perceived stress in order to contribute to the development of appropriate preventive strategies for improving public health. Also, this study aimed to evaluate the effects of stress disorder on metabolic parameters such as leptin, ghrelin, and adiponectin.

Methods

Patients and Study Design

A total of 313 volunteer students and research assistants aged between 18 and 30 years from the Faculties of Medicine and Nursing of Celal Bayar University were enrolled in this study between 2014 and 2016. Patients with conditions that may lead to malabsorption, including ulcerative colitis, Crohn's disease, celiac disease, cystic fibrosis, chronic pancreatitis, and chronic liver or kidney disease, were excluded. In addition, individuals with a history of gastrointestinal surgery, including gallbladder, esophagus, stomach, small intestine, large intestine, liver, or pancreatic resection, were not included in the study.

The study protocol was approved by the Ethics Committee of Celal Bayar University (Approval No: 232; Approval Date: June 04, 2014). All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to blood sampling.

All 313 individuals completed the SCOFF questionnaire and the Perceived Stress Scale (PSS) to evaluate eating disorders and perceived stress levels, respectively.[9,10] The questionnaires were translated into Turkish by the authors, and a preliminary validity assessment was conducted prior to the study.[11,12] Following the questionnaire assessments, anthropometric measurements, including height and weight, were recorded. Age, medical history, and the presence of any comorbid diseases were also documented.

Participants included in the study had no comorbid diseases and were not receiving hormonal therapy. According to the literature, a body mass index (BMI) between 18.5 and 25 kg/m^2 was accepted as the normal range.

Based on the SCOFF questionnaire results, participants were categorized according to eating disorder (ED) status (SCOFF ≥2 positive vs. SCOFF <2). In addition, participants were grouped according to BMI categories (BMI >25 kg/m^2, BMI <18.5 kg/m^2, or 18.5≤BMI≤25 kg/m^2). Comparisons were performed to evaluate the relationship between these parameters and stress levels according to PSS score levels among the subgroups.

For biochemical analyses, blood samples were obtained from a total of 120 volunteers distributed among the following subgroups: ED(+) and BMI <18.5 (n=25), ED(+) and BMI >25 (n=25), 18.5≤BMI≤25 and ED(+) (n=30), and 18.5≤BMI≤25 and ED(-) (n=40).

Serum Analysis

Blood samples were collected from volunteers into vacuum tubes without anticoagulants for biochemical analyses.

Samples were centrifuged at 300×g for 10 minutes, and serum fractions were separated. The obtained serum samples were stored at −80°C until batch analysis.

The following biochemical parameters were measured: fasting glucose, fasting insulin, cortisol, lipid profile, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), phosphorus (P), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), free thyroxine (free T4), anti-gliadin IgA, anti-gliadin IgG, tissue transglutaminase IgA, and hemogram levels. Insulin resistance was evaluated using the homeostatic model assessment for insulin resistance.

In accordance with the study by Fontbonne et al.[13], insulin resistance was defined as HOMA-IR values above 1.80 for women and 2.12 for men.

All biochemical parameters were analyzed at the Celal Bayar University Biochemistry Laboratory. Adiponectin, leptin, and ghrelin plasma levels were measured using enzyme-linked immunosorbent assay (ELISA) methods.

Adiponectin levels were determined using commercial ELISA kits (Assaypro Human Adiponectin ELISA Kit, Missouri, USA). The mean intra-assay coefficient of variation (CV) of the kit was 3.0%, while the inter-assay CV was 8.3%.

Leptin levels were measured using ELISA kits (DRG Instruments GmbH, Marburg, Germany). The analytical sensitivity of the assay was 1.0 ng/mL. The intra-assay CV values were 5.95% at 3.15 ng/mL and 6.91% at 24.62 ng/mL. The inter-assay CV values were 11.55% at 2.71 ng/mL and 8.66% at 26.15 ng/mL.

Ghrelin levels were measured using commercial ELISA kits (Human Ghrelin Total, EMD Millipore Corporation, Missouri, USA). The analytical sensitivity of the assay was 50 pg/mL. The intra-assay CV values were 1.26% at 384 pg/mL and 0.90% at 904 pg/mL. The inter-assay CV values were 7.81% at 384 pg/mL and 6.28%.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 15.0 (IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were evaluated using descriptive statistics and normality assessments. Continuous variables were expressed as mean±standard deviation (SD), while categorical variables were presented as frequency (n) and percentage (%). Comparisons between categorical variables were performed using the chi-square test. For comparisons between two independent groups, Student's t-test was applied for normally distributed variables. When the data did not meet the assumptions of normal distribution, the Spearman correlation test was used. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was applied where appropriate. All statistical tests were two-tailed, and a p value of <0.05 was considered statistically significant.

Results

The average age of the study population was 24.62 years (range, 18–30 years). According to the results of the SCOFF Test (Sick, Control, One Stone, Fat, Food) and the Perceived Stress Scale (PSS) questionnaire test, the rate of SD was 34.5% (n=108), and the rate of ED was 46.6% (n=146).

While 54.1% (n=79) of individuals in the ED group (n=146) had SD, the SD rate in the non-ED population was 17.4% (n=29) (p<0.001) (Table I). It was observed that individuals with BMI<18.5 or BMI>25 had more SD than individuals with normal BMI (64.3% vs. 35.7%, 61% vs. 39%, and 24.3% vs. 75.7%; p<0.001, p<0.001, and p<0.001, respectively) (Table 2).

Four subgroups were defined as BMI<18.5 and ED(+) (n=42), BMI>25 and ED(+) (n=23), 18.5≤BMI≤25 and ED(+) (n=63), and 18.5≤BMI≤25 and ED(-) (n=167) according to BMI levels and ED status. Subgroup analysis was performed for SD among the four subgroups. The 18.5≤BMI≤25 and ED(-) subgroup was determined as the control group. A comparison was made between these subgroups to assess the relationship between stress levels. It was observed that the stress rates were significantly higher in the three groups with eating disorders when compared with the control group (BMI<18.5, p=0.001 for the ED(+) group; BMI>25, p=0.002 for the ED(+) group; and 18.5≤BMI≤25, p=0.012 for the ED(+) group). It was determined that the risk of SD was higher in the BMI<18.5 and ED(+) group, BMI>25 and

Table 1. The relationship between eating disorders and stress disorder

Groups	SD (+)	SD (-)	p
ED (+)	79 (%54.1)	67 (%45.9)	<0.001
ED (-)	29 (%17.4)	138 (%82.6)	

BMI: Body mass index; ED: Eating disorders; SD: Stress disorder.

Table 2. SD rates according to BMI

	SD (-)	SD (+)	p
BMI<18.5	35,7%	64,3%	<0.001
18.5≤BMI≤25	75,7%	24,3%	<0.001
BMI>25	39%	61%	<0.001

BMI: Body mass index; SD: stress disorder.

ED(+) group, and 18.5≤BMI≤25 and ED(+) group than in the 18.5≤BMI≤25 and ED(-) subgroup (OR 8.56, 7.34, and 3.59, respectively). In addition, there was a significantly higher risk of stress in the BMI<18.5 or BMI>25 and ED(+) subgroups than in the 18.5≤BMI≤25 and ED(+) subgroup (p=0.014 and p=0.021) (Table 3).

Blood analysis was performed on a total of 120 volunteers among the people participating in the survey study. These volunteers were divided into four subgroups according to their BMI and ED status: BMI<18.5 and ED(+) (n=25), BMI>25 and ED(+) (n=25), 18.5≤BMI≤25 and ED(+) (n=30), and 18.5≤BMI≤25 and ED(-) (n=40). Fasting glucose, fasting insulin, HOMA-IR score, cortisol, lipid profile, Na, K, Cl, Ca, P, hemogram, AST, ALT, ALP, GGT, BUN, creatinine, TSH, free T3, free T4, anti-gliadin IgA, anti-gliadin IgG, tissue transglutaminase IgA, ACTH, cortisol, and HOMA values were compared between the four subgroups of 120 participants. There was no statistically significant difference in biochemical values between the groups. It was observed that SD(+) was higher in subgroups that had ED(+), similar to the general population participating in the survey study (p=0.002, p=0.019, p=0.002) (Table 4).

Adipocytokine levels were studied in these four subgroups, and the differences between parameters are shown in Table 5. Leptin levels were lower, and ghrelin and adiponectin levels were higher in the SD(+) subgroup when compared with the SD(-) subgroup in the group with ED(+) and BMI<18.5 (p<0.001, p=0.011, and p=0.001, respectively). Leptin levels were higher, and ghrelin and adiponectin levels were lower in the SD(+) subgroup compared with the SD(-) subgroup in the group with ED(+) and BMI>25 (p<0.001, p<0.001, and p<0.001, respectively). In the subgroup with normal BMI, no such relationship could be established in terms of SD (p>0.05) (Table 5).

Table 3. Distribution of study groups and stress rates

Subgroups	SD (+)	SD (-)	OR (Lower-upper)	p
BMI<18.5 and ED (+)	64.3%	25.7%	8.56 (4.05-18.09)	0.001
BMI>25 and ED (+)	61%	39%	7.34 (3.53-15.63)	0.002
18.5≤BMI≤25 and ED (+)	42.9%	57.1%	3.59 (1.88-6.77)	0.012
18.5≤BMI≤25 and ED (-)	17.4%	82.6%		

BMI: Body mass index; OR: Odds ratio; SD: Stress disorder.

Table 4. Distribution of volunteer participants who donated blood for serum adipocytokine among groups and SD rates

Subgroups	SD (+)	SD (-)	p
BMI<18.5 and ED (+) (n=25)	64.0%	36%	0.002
BMI>25 and ED (+) (n=25)	60.0%	40%	0.019
18.5≤BMI≤25 and ED (+) (n=30)	43.3%	56.7%	0.002
18.5≤BMI≤25 and ED (-) (n=40)	17.5%	82.5%	

BMI: Body mass index; SD: Stress disorder.

Discussion

Eating disorders are important health problems that can occur as a result of the interaction of genetic, endocrinological, hypothalamic, and environmental factors. The rate of ED investigated with the SCOFF test varies between 11.8% and 48.8% among the young population.[14] The rate of ED in the population included in our study was found to be 46.6%. In the analysis using PSS among college students, the rate of SD in women was found to be 48%.[15] In a study conducted with other stress scales, it was observed that the rate of students under intense stress among medical students was up to 52%.[16] In another study conducted among female students, this rate was reported to be 43%.[17] The rate of SD in the population included in our study was found to be 34.5%.

Fairburn et al.[18] highlighted that the inability to cope with stressful situations properly is an important factor for the emergence and continuation of ED symptoms. Psychological stress was evaluated with a scale by Darby et al.[19], and in this study, it was stated that SD was related to ED symptoms. Sassaroli et al.[20] put forward a hypothesis that stress is related to some cognitive factors that predispose to ED, and as a result of the study, they obtained data supporting this. Indeed, the empirical demonstration of this mechanism has been more reliably supported, showing that important stress is at the source of eating disorders. It has been shown that acquired stress affects eating habits and contributes to obesity in the literature.[21] In another study, it was stated that the risk of a quality-of-life score related to mental health is low in women with altered eating behaviour.[22] There are also studies showing that the desire to lose weight, which did not exist before, is revealed by stress and affects eating behaviour. A decrease in ED symptoms has been shown in participants when the stress factor disappears.[23] In a study comparing patients with obesity with and without ED, it was found that acquired stress scores were higher in those with ED.[24] These findings show that measures should be taken to reduce stress in individuals with ED. In our study, it was investigated whether psychosocial stress is related to ED symptoms. While 54.1% of those in the ED group had SD, the

Tablo 5. Relationship between stress and adipocytokine SD; Stress disorders

Group		Average	SD (+)	SD (-)	p
BMI<18.5	Leptin	3.83±2.56	2.41±1.25	6.36±2.37	<0.001
	Ghrelin	1261.57±481.11	1438.75±506.16	946.56±198.97	0.011
	Adiponectin	25.68±1.78	26.71±1.22	23.86±0.96	0.001
BMI>25	Leptin	24.06±9.13	28.7±8.86	17.11±3.29	<0.001
	Ghrelin	200.50±86.12	144.42±40.18	284.61±64.54	<0.001
	Adiponectin	19.49±1.99	18.26±0.94	21.32±1.72	<0.001
18.5≤BMI≤25 and ED (+)	Leptin	8.89±6.89	11.62± 9.76	6.8±2.0	0.104
	Ghrelin	389.38±163.95	379.88±217.22	396.64±114.90	0.804
	Adiponectin	21.94±1.54	21.90±0.94	21,96±1.90	0.524
18.5≤BMI≤25 and ED (-)	Leptin	8.17±1.82	8,26±1.32	8.16±1.93	0.895
	Ghrelin	454.43±132.00	403.35±134.88	465.26±130,89	0.265
	Adiponectin	21.29±0.79	21.45±0.79	21.26±0.80	0.565

BMI: Body mass index; ED: Eating disorders; SD: Stress disorder.

rate of SD in the non-ED population was found to be 17.4%. As a result, it was seen that the presence of SD was a factor affecting the development of ED. This situation can be explained by the fact that intense anxiety, perfectionism, and low self-esteem, which can be seen in stress disorders, can trigger eating disorders by directing the individual's attention to restriction or an increase in eating. In conclusion, early detection of individuals with stress disorders and medical intervention to this effect are important in terms of preventing eating disorders.

In a study, it was observed that overweight or underweight individuals were in similar psychological conditions, and they were also under more stress than individuals with normal BMI.[25] Looking at the distribution of BMI in stressed individuals in our study, it was observed that BMI was generally lower or higher than normal in stressed individuals. However, it has been found that the BMIs of individuals without stress disorder are mostly normal. Similarly, there are studies in the literature claiming that stress experience triggers eating disorders and affects BMI in a low or high way.[26] Stress disorder may develop in individuals who are thin or fat due to thoughts such as being withdrawn due to their external appearance and feeling inadequate. We think that, by organizing diet and exercise programs for these people, stress disorder can be prevented. Eating behaviour and metabolic parameters are a reflection of acquired stress.

Our study is one of the most comprehensive studies conducted to determine the relationship between leptin, adiponectin, ghrelin, and anthropometric values of ED and SD according to the recent literature. As a result of our study, a direct relationship was found between eating disorders and leptin, ghrelin, and adiponectin among women aged between 18 and 30. When the individuals with a BMI above 25 and those with eating disorders who have positive stress disorder are compared with those who are negative, in those with SD(+), it was observed that leptin levels were significantly high, and ghrelin and adiponectin levels were low. Leptin levels were lower, and ghrelin and adiponectin levels were higher in the SD(+) subgroup compared with the SD(-) subgroup in the group with ED(+) and BMI<18.5. No such relationship was found in those with normal BMI. Psychological stress can affect adipocytokine levels, leading to changes in eating habits and nutritional disorders. In today's societies, it is thought that stress can contribute to obesity by increasing the concentration of leptin. In a study, it was observed that leptin increased in individuals with high stress perception, and this was found to be statistically significant.[27] Declining leptin is an important indicator of energy deficiency, and it is thought to be a mechanism developed by the body against a decrease in energy consumption or production capacity. While leptin was positively correlated with fat mass, it was found to be negatively correlated with ghrelin.[28] Conversely, in low-weight participants, increased ghrelin and decreased leptin levels are present. Low body weight develops due to increased metabolic rate and decreased appetite. Higher ghrelin levels have been found in women with intense stress exposure. Here, it is thought that stress disorder may be caused by the increase in ghrelin by activating the hypothalamo-pituitary-adrenal axis and sympathetic nervous system.[29] There is also a relation between adiponectin levels and psychological stress. It is known that, in premenopausal and postmenopausal women, changes in levels of adiponectin cause changes in eating behaviour and BMI.[30]

Conclusion

In conclusion, as a result of our study, a direct relation was found between eating disorders and leptin, ghrelin, and adiponectin in women aged 18–30 years. However, it was found that stress both contributes to eating disorders and affects adipocytokine levels. This study was conducted with 313 volunteers and only in a limited age group in the female population. It is necessary to expand the study population and conduct further research. The root causes and effects of eating disorders and stress disorder, which are among the most important problems that concern especially the young age group, should be investigated in more extended studies.

Disclosures

Ethics Committee Approval: Ethical approval was obtained from Celal Bayar University Faculty of Medicine Ethics Committee (04.06.2014/232).

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Research Article

Paroxysmal Nocturnal Hemoglobinuria Associated Myelodysplastic Syndrome and Aplastic Anemia: A Single Center Experience

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Abstract

Objectives: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease that could accompany aplastic anemia (AA) and myelodysplastic syndrome (MDS). In this study, we wanted to share our experiences about PNH clone positivity rates and the clinical effects in patients who were being followed up with diagnoses of AA and MDS.
Methods: We investigated 30 people in our study, 22 of whom had MDS and 8 of whom had AA. The PNH scan was carried out using the FLAER method, which is considered the gold standard today.
Results: PNH clone positivity rates were 4.5% in MDS and 62.5% in AA. Two of the patients initiated eculizumab treatment.
Conclusion: It is important to detect a PNH clone because of its effect on the course of other bone marrow diseases, especially AA and MDS.
Keywords: Complement system, Paroxysmal nocturnal hemoglobinuria, Thrombosis

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PNH is a rare disorder with different clinical manifestations.[1] It is caused by a somatic mutation in a hematopoietic stem cell that inactivates the PIG-A gene (phosphotidylinositol glycan anchor biosynthesis, class A). This mutation is concluded with a deficiency of the glycosylphosphatidylinositol (GPI) molecule.[2] GPI-linked proteins, CD55 (decay accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL), are involved in the regulation of the complement system.[3] Deficiency of these proteins results in increased complement sensitivity of PNH cells.[4] The International PNH Interest Group (I-PIG) has proposed a working diagnostic classification with the

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following three categories: classical PNH, PNH accompanying other bone marrow failure conditions (aplastic anemia, myelodysplastic syndrome), and subclinical PNH.[1,5,6]

Myelodysplastic syndrome (MDS) is a group of bone marrow disorders that arise from a defective stem cell. It results in peripheral blood cytopenias.[7,8] In patients with MDS, PNH clone positivity has been reported as 1.1%–8%, and in the MDS-refractory anemia subtype, it has been reported as 17.6%–53.3%. The underlying cause of erythrocyte transfusion dependence in patients with MDS could be PNH clone positivity.[7]

Aplastic anemia is derived from a decrease or absence of hematopoietic precursors in bone marrow and is also characterized by peripheral blood cytopenias.[8,9] PNH clones could be detected in AA; however, most patients express only a small PNH clone size (<10%).[10] It was observed that PNH-associated AA had a better response to immunosuppressive treatment.[10–12] Also, it was shown that 10%–25% of PNH clone-positive AA patients undergo clonal expansion and develop clinical PNH in the future.[12]

In this study, we wanted to share our experiences about PNH clone positivity rates and the clinical effects in our patients who were being followed up with diagnoses of AA and MDS.

Methods

Patients who were admitted to the Department of Hematology of Manisa Celal Bayar University Hospital between May 15, 2015, and January 31, 2018, were included in our work. The PNH test is routinely performed for patients who are followed up in our clinic and diagnosed with MDS and AA. We scanned these patients retrospectively. All patients with aplastic anemia and MDS with hypoplastic or refractory cytopenia or no blast increase were included.

Blood samples were collected from selected patients into two ethylenediaminetetraacetic acid (EDTA) tubes, 2 ml per tube, and were studied within 48 hours. A PNH clone search was performed on a FacsCanto II flow cytometry instrument. Evaluation was performed using CD56, CD24, CD16, and fluorescent aerolizine (FLAER) antibodies that bind to the binding site of GPI, CD45, CD15, and CD64 gating antibodies. CD59 was used to detect type II and type III PNH cells in erythrocytes. For confirmation, CD24 was used in granulocytes, and CD14 was used in monocytes. Complete blood count, LDH, and indirect bilirubin values of the patients included in the study were recorded.

The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics v18.0 software (Armonk, New York: IBM Corp.). In the study, descriptive statistics were performed by determining the mean, median, and ratios of the variables related to the results. A p-value of <0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

Manisa Celal Bayar University Ethics approval was received for this study on 13.05.2015 with number 20478486.220.

Results

A total of 30 people were included in our study, 22 of whom had MDS and 8 of whom had AA. Fifteen of the participants

Table 1. Age-sex-hemogram and biochemical parameters and the first positive clone percentages of patients with PNH clone positivity

Patient	1	2	3	4	5	6
Age	62	65	50	76	55	31
Gender	Female	Female	Female	Female	Female	Female
Diagnosis	PNH, MDS	PNH, AA	AA	AA	AA	AA
PNH clone size, granulocytes (%)	93.75	2.42	0.53	0.13	0.34	0.23
PNH clone size, monocytes (%)	96.9	6.73	1.93	1.55	0.87	0.47
Hb (g/dL)	8.4	6.5	13.3	9.8	11.7	9.6
WBC (/mm^3)	3400	3200	3700	4700	3200	4000
Neu (/mm^3)	2400	2600	1100	1900	1500	2300
Plt (x10^3/ mm^3)	85	16	60	48	155	43
LDH (IU/L)	845	407	237	231	202	190
Indirect Bilirubin (mg/dL)	0.7	0.3	0.36	0.5	0.4	0.4
Time of PNH clone positivity (year)	2016	2016	2017	2017	2015	2016

PNH: Paroxysmal Nocturnal Hemoglobinuria; MDS: Myelodysplastic Syndrome; AA: Aplastic anemia; Wbc: White blood cell; Hb: Hemoglobin; Plt: Platelet; LDH: Lactic dehydrogenase.

were female, and 15 were male. A PNH clone was detected positive in 6 patients, and all of them were female (Table 1). When the PNH clone was diagnosed as positive, none of the patients had PNH-related complications, such as infections, thrombosis, and renal insufficiency.

Fourteen of the patients included with the diagnosis of MDS were male, and 8 were female. In 1 (4.5%) of 22 patients diagnosed with MDS, the PNH clone was positive. The PNH clone-positive patient was female, and her clone size was over 10% (Patient 1, Table 1). This patient received transfusion support, methylpredinizolone, and intravenous immunoglobulin (IVIG) therapy before the PNH clone was detected positive. Because of continued transfusion requirement and increased lactic dehydrogenase (LDH) levels, PNH was tested, and high clone levels were detected (Table 1). Anti-C5 monoclonal antibody treatment had initiated.

One of the patients included with the diagnosis of AA was male, and 7 were female. In 5 (62.5%) of 8 patients with aplastic anemia, the PNH clone was positive. All of these 5 patients were female. Patient 2 was treated with methylprednisolone and cyclosporine, and transfusion support was provided before the PNH clone was detected positive. The first PNH clone-detected positive patient was followed up. Anti-C5 monoclonal antibody treatment had initiated due to the patient's non-response to immunosuppressive treatment, transfusion dependence, and clone progression (11.2% in granulocytes and 8.17% in monocytes). The patient's transfusion dependence disappeared. Other patients had minor PNH clones (Patients 3, 4, 5, and 6, Table 1), and they were also followed up for clone progression, and no clone progression had occurred yet. Also, all patients were alive.

Discussion

In many non-PNH situations, such as AA and MDS, testing for PNH can be informative. Patients with AA or MDS with unexplained cytopenia should be tested for PNH at the time of diagnosis for differential diagnosis.[1] Depending on the case selection criteria among MDS patients, the rate of PNH-positive cases varies in the literature, ranging between 1.8% and 41%. GPI-deficient cells are found more commonly in low-grade MDS patients with hypoplastic bone marrow characteristics than in other MDS subtypes.[11]

In our study, we found PNH clone positivity in 4.5% of patients who were diagnosed with MDS. In patients with MDS, the PNH clone positivity rate was reported as 9.8% by Morado et al.[11] and 5% by Mercier et al.[13]. Our rates were similar to those in these studies. Raza et al. found that when all MDS subgroups were included, the detection rate of a PNH clone size above 1% was 1.1% in their prospective multicenter study. Also, there were differences between MDS subtypes: refractory anemia, 1.3%; unclassified, 1.5%; refractory anemia with excess blasts type 1 and type 2, 0.3%; 5q- syndrome, 0%; and refractory cytopenia with multilineage dysplasia, 1%.[14] We found higher rates compared with this study. Consequently, because of the differences in the literature and between MDS subtypes, we need well-designed studies according to the guidelines.

Although the rate of PNH-positive AA cases varies significantly in the literature, ranging from 22% to 89%, it is currently estimated to be about 40% of cases. According to their data, Morado et al.[11] emphasized the importance of testing for PNH in patients diagnosed with AA at any age. In aplastic anemia, we found a clone positivity rate of 62.5%. According to their research, PNH clone positivity rates in patients with AA were described as 45% by Morado et al.[11] and 47% by Mercier et al.[13]. Compared with these studies, we found a higher rate of clone positivity. However, according to the literature, in acquired AA, small-sized PNH clone positivity rates are about 70% at the time of diagnosis.[1] Compared with the literature, our results were similar. We found that a PNH clone size ≥1% was prevalent in 12.5% of patients with AA, which was reported as 18.5% by Raza et al.[14] and 21% by Dunn et al.[15]. Our results were compatible with these studies. As a result, considering these rates, it is worth testing the PNH clone in patients diagnosed with AA.

All of our patients in whom PNH clone positivity was detected were alive. One of our patients received anti-C5 monoclonal treatment because of transfusion dependence, while the other patients were followed up for clone progression. Wang et al. showed that patients who had minor populations of PNH-positive cells had a better response to immunosuppressive treatment than PNH cell-negative patients. Also, none of the PNH-positive patients progressed to acute myeloid leukemia. Furthermore, some patients' pancytopenia remained stable or improved spontaneously without any treatment.[16] Maciejewski et al.[17] studied the relationship between bone marrow failure syndromes, GPI-A protein deficiency, and response rates to immunosuppressive treatment, which were higher in patients who had PNH clones. Considering all these studies and the fact that our patients who had minor clones of PNH are still alive without disease progression, the presence of minor PNH clones increases survival in MDS and AA.

Our study has some limitations. PNH is such a rare disease that its prevalence is estimated to be approximately 16 per million.[18] Our center is small, so the number of patients tested for PNH has been low for this rare disease. In addition, since this study is single-centered, PNH clone positiv-

ity and its effect on MDS and AA were evaluated only in terms of patients in a specific region.

Conclusion

In conclusion, we shared our data about a rare disease that could accompany AA or MDS. Our knowledge of MDS and AA has also improved since we started using the FLAER test. It is important to detect a PNH clone because of its effect on the course of other bone marrow diseases, especially AA and MDS. Since PNH is a rare disease, more studies are needed to determine the frequency of PNH accompanying MDS and AA.

Disclosures

Ethical Committe Approval: Manisa Celal Bayar University Ethics approval was received for this study on 13.05.2015 with number 20478486.220.

Author Contributions: Concept – İA, FA, SED; Design – İA, İB, SED; Supervision – AT, TB, SED; Fundings – İA, AT, SED; Materials – MM, TB, AT; Data collection &/or processing – AT, TB, SED; Analysis and/or interpretation – TB, İA, MM; Literature search – İB, FA, MM; Writing – İA, İB, SED; Critical review – FA, TB, SED.

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Research Article

Perceptions of Interventional Cardiologists in Türkiye Toward Domestic Coronary Devices: A Web-Based Cross-Sectional Survey

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Abstract

Objectives: Türkiye has pursued policies to reduce external dependence on medical technologies; however, physician-level evidence on domestically manufactured coronary devices is limited. We evaluated self-reported utilization, satisfaction, and future-adoption attitudes toward locally manufactured diagnostic catheters, guiding catheters, PTCA balloons, and coronary stents among interventional cardiologists in Türkiye and explored whether these views varied according to selected practice characteristics.

Methods: We conducted a web-based cross-sectional survey between May and June 2020. The questionnaire was distributed through professional e-mail lists and yielded 147 responses. All close-ended items were mandatory, and no missing responses were observed for the variables included in the primary quantitative analyses. Results are reported as n (%). Key proportions are accompanied by 95% Wilson confidence intervals. Exploratory subgroup comparisons used Fisher's exact test after prespecified category collapsing to limit sparse cells.

Results: Respondents came from all seven geographic regions of Türkiye. Of the respondents, 76/147 (51.7%) worked in training and research hospitals, and 61/147 (41.5%) reported a daily PCI volume of 5-10 cases. Low domestic-device use was common across all device classes and was most pronounced for coronary stents, for which 93/147 (63.3%) reported use in ≤20% of cases. Low stent satisfaction (≤20%) was reported by 66/147 (44.9%). For the future-use item, 111/147 physicians (75.5%, 95% CI 68.0-81.8) selected the response "I would use domestic products if quality were sufficient," and 29/147 (19.7%, 95% CI 14.1-26.9) selected "I actively prioritize domestic products." In an exploratory binary analysis, 137/147 respondents (93.2%, 95% CI 87.9-96.3) expressed at least some openness to greater domestic-device use. Perceived import dependency above 75% was reported by 91/147 (61.9%, 95% CI 53.8-69.4). Supportive future attitudes were more frequent among physicians with >10 years in specialist practice than among those with ≤10 years (98.6% vs. 88.3%, p=0.019). No clear association was found with institution type, academic title, or PCI volume.

Conclusion: In this 2020 physician sample, domestically manufactured coronary devices were used infrequently and were rated modestly, especially in the stent category. At the same time, future resistance was not absolute: most respondents indicated willingness to increase use if quality standards were met. The pattern is consistent with a quality-trust gap rather than categorical rejection. The findings remain useful as a pre-acceleration baseline, but they should be interpreted in light of self-reporting, non-response bias, and the time gap between data collection and submission.

Keywords: Interventional cardiology, coronary stents, medical devices, domestic manufacturing, physician survey, Türkiye, health services research

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Many health systems seek to reduce dependence on imported medical devices because supply vulnerability affects continuity of care, affordability, and strategic resilience. The pandemic period made this dependence more visible by exposing bottlenecks in device and equipment supply chains and by renewing interest in local production capacity.[1-6]

Türkiye has long had an import-dominated medical-device market. Official trade guidance has described the sector as heavily dependent on imported products, while more recent country guidance still reports that roughly three-quarters of the market is import-based, despite growth in domestic manufacturing incentives and exports.[7-8] At the same time, the national policy framework has increasingly emphasized local capability, from the Eleventh Development Plan to the current Twelfth Development Plan, alongside regulatory alignment with European medical-device legislation and domestic product-rule frameworks.[8-12]

In interventional cardiology, adoption decisions are made in a high-consequence technical environment. Operators judge devices on deliverability, trackability, radial strength, recoil, visibility, and confidence in real-world performance. These considerations are especially pronounced for coronary stents, where design features and platform characteristics can influence procedural handling and longer-term outcomes.[13-15] Procurement systems also shape uptake because physician preference, institutional purchasing rules, and cost containment intersect in device selection.[3,4,16]

Diffusion of Innovations provides a useful interpretive framework for this problem. Within that framework, technologies with uncertain performance diffuse slowly, whereas technologies perceived as advantageous, reliable, and compatible with clinical workflow are more readily adopted.[17] Physician adoption research in other settings likewise suggests that acceptance depends on perceived utility and trust rather than on novelty alone.[18] Against this background, we surveyed interventional cardiologists in Türkiye during May-June 2020. The aim was to describe self-reported use of domestically manufactured coronary devices, satisfaction with those devices, and attitudes toward future adoption, while treating the 2020 dataset as a baseline snapshot captured before the more recent phase of policy acceleration in domestic medical-technology production.[8-11]

Methods

Study Design and Setting

This study was a cross-sectional, internet-based physician survey reported with reference to the STROBE and CHERRIES frameworks.[19-21] Data collection was performed between 1 May and 30 June 2020. The target population was interventional cardiologists practicing coronary angiography and/or PCI in Türkiye.

Questionnaire Scope and Variable

The original questionnaire covered cath-laboratory practice more broadly, including institutional characteristics and selected procedural habits. The present report focuses on the domestic-device component of that questionnaire. The analyzed variables included geographic region, institution type, academic title, years in specialist practice, daily PCI volume, self-reported use of domestically manufactured diagnostic catheters, guiding catheters, PTCA balloons, and coronary stents, satisfaction with those device classes, future willingness to increase domestic-device use, and perceived national import dependency. The questionnaire was investigator-developed for this study. A formal psychometric validation study was not performed.

Survey Administration and Data Handling

The survey was distributed through professional e-mail lists, reaching approximately 600 physicians directly. Responses were collected through Google Forms. Close-ended items were mandatory. Two free-text questions were optional and asked about perceived material shortages and suggestions to reduce external dependency; these items were not included in the quantitative analyses. Google Forms was configured to limit duplicate responses through single-account submission. Participation was voluntary and anonymous.

Statistical Analysis

Categorical variables were summarized as n (%). Analyses were planned using an available-case approach at the item level. In practice, no missing responses were observed in any close-ended item included in the primary quantitative analyses, so the denominator was 147 throughout those analyses. Missingness occurred only in the two optional free-text items, which were not entered into the quantitative dataset. Utilization and satisfaction were recorded as ordered percentage bands (≤20%, 20-40%, 40-60%, 60-80%, >80%). For descriptive interpretation, the ≤20% band was treated as a low-use or low-satisfaction category. Key proportions are presented with 95% confidence intervals calculated by the Wilson method.

To address reviewer concerns that purely univariate reporting would underuse the dataset, we performed exploratory bivariate analyses for three prespecified outcomes: supportive future adoption attitude, low coronary-stent use, and low coronary-stent satisfaction. Supportive future adoption was defined as selection of either 'I active-

ly prioritize domestic products' or 'I would use domestic products if quality were sufficient.' For these exploratory analyses, institution type was collapsed into tertiary public/academic centers (university, training and research, and city hospitals) versus state/private hospitals; academic title was collapsed into specialist versus academic rank; years in specialist practice were collapsed into ≤10 versus >10 years; and daily PCI volume was collapsed into <10 versus ≥10 cases/day. Fisher's exact test was used for these 2×2 comparisons. Because these subgroup analyses were exploratory, no multiplicity correction was applied, and the findings are interpreted cautiously. All tests were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Ethics

Institutional academic board approval for the research topic was documented (Decision No. 6; 19 January 2018). Under the local institutional framework in place at the time, a Health Sciences University, Istanbul Bagcılar Training and Research Ethics Committee application was not sought because the survey was anonymous, voluntary, limited to physician opinions, and involved no patients, patient data, or biological material. Electronic informed consent was obtained through the survey introduction statement, and questionnaire completion was accepted as implied consent.

AI Statement

AI tools were not used to generate data, perform statistical analyses, select results, or determine scientific conclusions.

Results

Participant Characteristics

A total of 147 interventional cardiologists responded. Participants represented all seven geographic regions of Türkiye. The largest proportion practiced in the Marmara region (40.8%), and the most common institution type was training and research hospital (51.7%). Specialists accounted for 53.7% of respondents, 36.7% had 5-10 years of specialist experience, and the most common daily PCI volume was 5-10 cases (41.5%) (Table 1). All close-ended items included in the quantitative analysis were complete (Fig. 1).

Table 1. Participant and practice characteristics (N=147)

Characteristic	n (%)
Geographic region	
Marmara	60 (40.8)
Mediterranean	31 (21.1)
Mediterranean	31 (21.1)
Central anatolia	16 (10.9)
Southeastern anatolia	12 (8.2)
Aegean	11 (7.5)
Black Sea	10 (6.8)
Eastern anatolia	7 (4.8)
Institution type	
Training and research hospital	76 (51.7)
University Hospital	34 (23.1)
City Hospital	19 (12.9)
Private Hospital	12 (8.2)
State Hospital	6 (4.1)
Academic title	
Specialist physician	79 (53.7)
Associate professor	49 (33.3)
Professor	19 (12.9)
Years as cardiology specialist	
<=5 years	23 (15.6)
5-10 years	54 (36.7)
10-15 years	35 (23.8)
15-20 years	15 (10.2)
>20 years	20 (13.6)
Daily average PCI volume	
<5 cases	32 (21.8)
5-10 cases	61 (41.5)
10-20 cases	39 (26.5)
20-30 cases	10 (6.8)
>30 cases	5 (3.4)

PCI: Percutaneous coronary intervention. All denominators are N=147.

Domestic-Device Utilization

Low domestic-device utilization was common in all four device categories (Table 2A). The ≤20% use band was selected by 64/147 respondents (43.5%) for diagnostic catheters, 81/147 (55.1%) for guiding catheters, 62/147 (42.2%) for PTCA balloons, and 93/147 (63.3%) for coronary stents. The stent category showed the least penetration of domestic products: only 29/147 respondents (19.7%) reported stent use above the 40% threshold, compared with 51/147 (34.7%) for diagnostic catheters, 33/147 (22.4%) for guiding catheters, and 57/147 (38.8%) for PTCA balloons.

Satisfaction with Domestic Devices

Satisfaction followed a similar pattern (Table 2B). Low satisfaction (≤20%) was reported by 47/147 physicians (32.0%) for diagnostic catheters, 62/147 (42.2%) for guiding catheters, 53/147 (36.1%) for PTCA balloons, and 66/147 (44.9%)

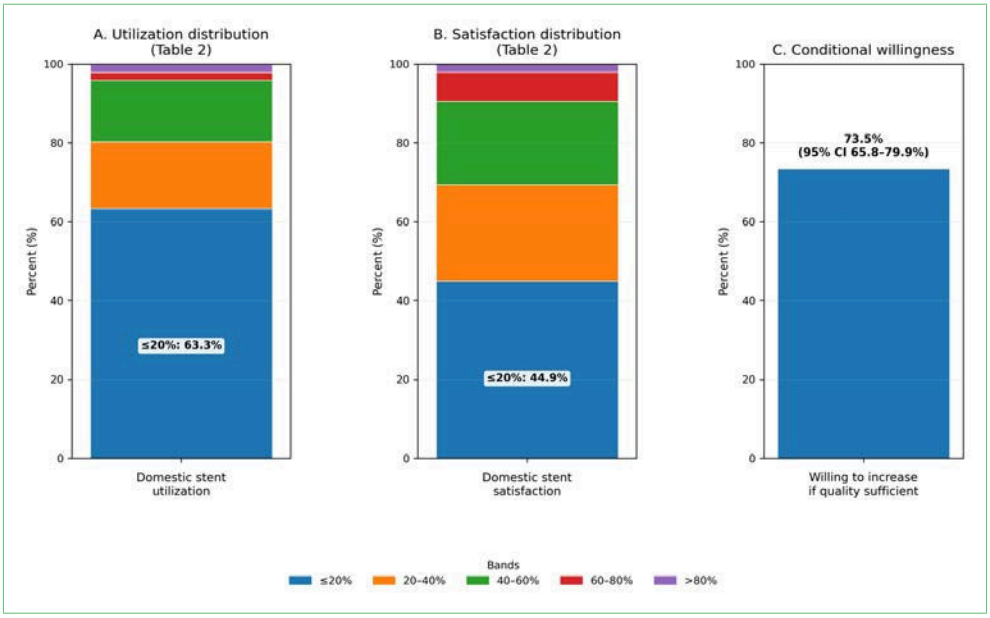


Figure 1. Distribution of domestic-device utilization, satisfaction, and future-use openness. Panel A shows the distribution of self-reported domestic coronary stent utilization across ordinal percentage bands (≤20%, 20-40%, 40-60%, 60-80%, >80%). Panel B shows the corresponding satisfaction distribution for domestically manufactured coronary stents. Panel C shows the proportion of respondents expressing willingness to increase domestic-device use if quality were sufficient. Values are based on 147 respondents.

for coronary stents. Satisfaction above the 40% threshold was reported by 63/147 (42.9%), 42/147 (28.6%), 50/147 (34.0%), and 45/147 (30.6%) respondents, respectively.

Future Adoption Attitudes and Perceived Import Dependency

For the future-use item, the most frequently selected response was "I would use domestic products if quality were sufficient," chosen by 111/147 respondents (75.5%, 95% CI 68.0-81.8). A further 29/147 (19.7%, 95% CI 14.1-26.9) selected "I actively prioritize domestic products." In a binary exploratory summary, 137/147 respondents (93.2%, 95% CI 87.9-96.3) expressed at least some openness to greater domestic-device use. Perceived import dependency remained high: 54/147 respondents (36.7%) estimated dependency at 75-90%, and 37/147 (25.2%) at >90%, for a combined 91/147 (61.9%, 95% CI 53.8-69.4) who perceived dependency above 75% (Table 3).

Table 2. Domestic device utilization and satisfaction by device category (N=147)

Measure	Band	Diagnostic catheter n (%)	Guiding catheter n (%)	PTCA balloon n (%)	Coronary stent n (%)
Utilization	<=20%	64 (43.5)	81 (55.1)	62 (42.2)	93 (63.3)
	20-40%	32 (21.8)	33 (22.4)	28 (19.0)	25 (17.0)
	40-60%	34 (23.1)	29 (19.7)	35 (23.8)	23 (15.6)
	60-80%	9 (6.1)	3 (2.0)	12 (8.2)	3 (2.0)
	>80%	8 (5.4)	1 (0.7)	10 (6.8)	3 (2.0)
Satisfaction	<=20%	47 (32.0)	62 (42.2)	53 (36.1)	66 (44.9)
	20-40%	37 (25.2)	43 (29.3)	44 (29.9)	36 (24.5)
	40-60%	43 (29.3)	31 (21.1)	35 (23.8)	31 (21.1)
	60-80%	10 (6.8)	4 (2.7)	8 (5.4)	11 (7.5)
	>80%	10 (6.8)	7 (4.8)	7 (4.8)	3 (2.0)

Values are n (%). Response bands reproduce the original questionnaire categories and are therefore ordinal descriptive bands rather than exact interval measurements. All denominators are N=147

Table 3. Key adoption attitudes and perceived import dependency (N=147)

Item	n/N (%)	95% CI
Willing to increase domestic device use if quality is sufficient	108/147 (73.5)	65.8-79.9
Perceived import dependency >75%	91/147 (61.9)	53.8-69.4
Perceived import dependency 75-90%	54/147 (36.7)	29.4-44.8
Perceived import dependency 50-75%	47/147 (32.0)	25.0-39.9
Perceived import dependency >90%	37/147 (25.2)	18.8-32.8
Perceived import dependency 20-40%	8/147 (5.4)	2.8-10.4
Perceived import dependency 0-20%	1/147 (0.7)	0.1-3.8

CI: confidence interval (Wilson method).

Exploratory Subgroup Analyses

Exploratory bivariate analyses are shown in Table 4. Supportive future adoption attitudes were more frequent among physicians with >10 years in specialist practice than among those with ≤10 years (69/70 [98.6%] vs 68/77 [88.3%], p=0.019). No statistically significant association was observed between supportive future attitude and institution type, academic title, or daily PCI volume. Low coronary-stent use and low coronary-stent satisfaction were not significantly associated with the collapsed institution, title, experience, or PCI-volume groups, although numerically low stent use was more common in state/private hospitals than in tertiary public/academic centers (83.3% vs 60.5%, p=0.070).

Discussion

This survey identified a consistent pattern across four coronary device classes. Current use of domestically manufactured products was low, satisfaction was also limited, and the stent category was viewed least favorably. At the same time, the dominant future-use response was conditional rather than rejectionist: most physicians indicated that they would increase local-device use if quality were sufficient. That combination is best interpreted as a quality-trust gap. Diffusion of Innovations theory predicts that adoption slows when a technology's relative advantage and reliability remain uncertain.[17] Physician adoption studies in other technology domains show a similar dependence on perceived usefulness, compatibility, and trust.[18] In device procurement, cost alone rarely resolves this problem. Purchasing structures can widen or narrow adoption by determining whether physicians can test, compare, and repeatedly use products that meet their clinical expectations.[3,4,16] The stent findings deserve particular attention. Coronary stents are not interchangeable commodities from the operator's perspective. Platform design, strut architecture, visibility, radial strength, longitudinal integrity, and deliverability all affect procedural confidence and downstream performance.[13-15] Against that background, it is unsurprising that the stent category combined the lowest domestic use with the lowest satisfaction. The survey does not identify which technical attributes drove those perceptions, but it does show that the barrier was strongest in the most performance-sensitive device class. The exploratory subgroup analyses add modest analytical depth to an otherwise descriptive survey. The only clear association was that physicians with longer specialist experience more often expressed a supportive future attitude toward greater domestic-device use. This pattern can be read in more than one way. More experienced operators may be less polarized and more willing to incorporate alternative products if quality is documented. Another possibility is that greater exposure to procurement cycles makes senior physicians more familiar with the trade-off between ideal preference and realistic supply constraints. These interpretations remain inferential because the survey was not designed to test mechanisms.

The temporal context is central to interpretation. These data were collected in early 2020, when pandemic-related supply stress was beginning to reshape health-system thinking about industrial resilience.[5,6] Since then, Türkiye's policy language on medical technologies has moved further toward domestic capability, as reflected in successive development plans and current official trade guidance.[8-11] Regulatory alignment with European device rules has also advanced.[7,11,12] Even so, recent official sources still describe the Turkish market as heavily import-dependent, with around 75% of the market composed of imported devices as of the end of 2024.[8] For that reason, the present dataset should not be read as a current market estimate. Its value lies in providing a documented 2020 baseline from before the more recent phase of policy acceleration.

Several limitations should be acknowledged. First, the sample was assembled through professional e-mail distribution rather than a formal national sampling frame. A response rate of roughly 24.5% can be estimated only against the approximately 600 physicians directly reached, and no individual-level information was available for non-responders. A formal non-response bias analysis, therefore, could not be performed, which limits inference about national representativeness.[22-24] Second, all quantitative measures were self-reported and were not externally validated against procurement records or cath-lab inventories. Third, the questionnaire was author-developed and did not undergo formal psychometric validation. Fourth, the data were

collected in 2020, so current attitudes may differ. Fifth, the subgroup analyses required category collapsing because of cell sparsity and should be viewed as exploratory rather than definitive.

The study also has strengths. Respondents were drawn from all seven geographic regions of Türkiye, all close-ended items used in the primary analyses were complete, and four distinct coronary device classes were assessed within the same respondent pool. The questionnaire captured not only current use and satisfaction but also forward-looking attitudes and perceived system-level dependency. That combination allows a more policy-relevant reading than a simple prevalence survey.

In summary, domestically manufactured coronary devices were used sparingly and rated modestly in this 2020 physician sample, especially in the stent category. Yet, the survey does not support a narrative of absolute clinician resistance. The prevailing attitude was conditional openness tied to quality. That finding provides a practical message for industrial and procurement policy: adoption is more likely to move through quality assurance, transparent performance evidence, and operator confidence than through origin labeling alone.

Conclusion

Among interventional cardiologists responding to this 2020 web-based survey, domestically manufactured coronary devices had low reported utilization and modest satisfaction, with coronary stents showing the least favorable profile. Most respondents nevertheless indicated at least conditional openness to greater use if quality standards were met. The results support interpretation in terms of a quality-trust gap and provide a baseline reference for future surveys conducted after the more recent phase of domestic medical-device policy development in Türkiye.

Disclosures

Ethics Committee Approval: Under the local institutional framework in place at the time, a Health Sciences University, Istanbul Bagcılar Training and Research Ethics Committee application was not sought because the survey was anonymous, voluntary, limited to physician opinions, and involved no patients, patient data, or biological material.

Informed Consent: Written consent was obtained from all participants.

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Peer-review: Externally peer-reviewed.

Ethics and Consent: Institutional academic board approval for the research topic was documented (Decision No. 6; 19 January 2018). Under the local institutional framework in place at the time, a separate ethics committee application was not sought because the survey was anonymous, voluntary, limited to physician opinions, and involved no patients, patient data, or biological material. Electronic informed consent was obtained through the survey introduction statement, and questionnaire completion was accepted as implied consent.

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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.

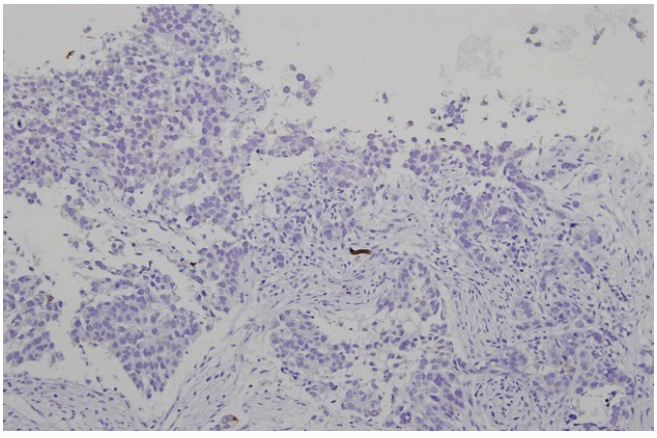


Figure 1. Absence of lipocalin-2 expression in tumor cells (×40).

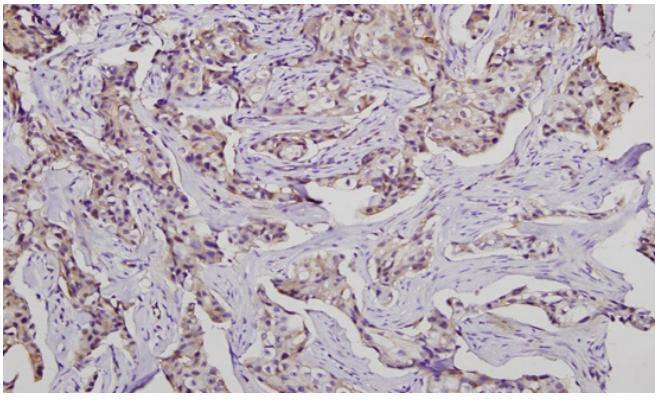


Figure 2. Weak (intensity 1) lipocalin-2 staining in tumorcells (×100).

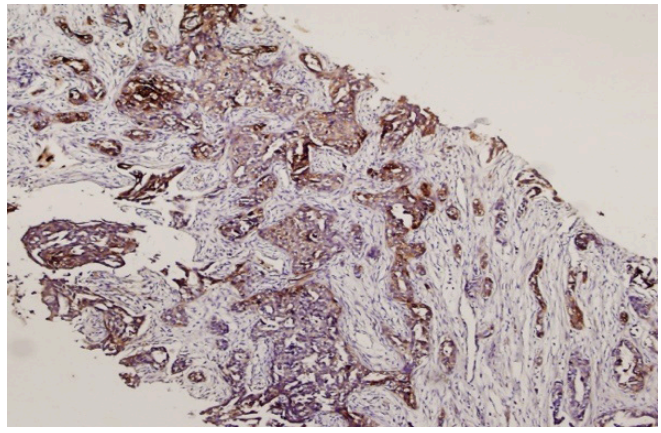


Figure 3. Moderate (intensity 2) lipocalin-2 staining in tumor cells (×100).

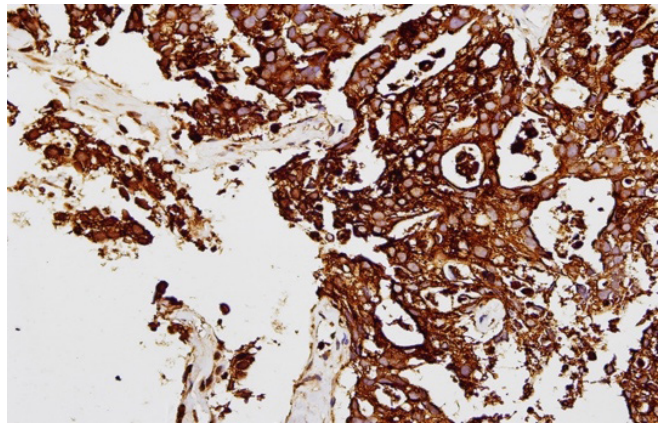


Figure 4. Strong (intensity 3) lipocalin-2 staining in tumor cells (×400).



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		p
		Negative n (%)	Positive n (%)	
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).

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authors' contributions: Concept – MEY, ÖA; Design – MEY, ÖA; Supervision – MEY, ÖA; Fundings – MEY, ÖA, DK, OK; Materials – MEY, ÖA, DK, OK; Data collection and/or processing – MEY, BK, EA, OBK, STB, MB; Analysis and/or interpretation – MEY, ÖA, DK, OK; Literature Review – MEY, BK, EA, OBK, STB, MB; Writing – MEY, ÖA; Critical review – MEY, BK, EA, OBK, STB, MB.

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