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Clinicopathological features and oncological outcomes in breast cancer presenting with nipple discharge

Baran Mollavelioglu · Atılay Özgen · Ecem Hazal Özgen · Ömer Bender · Fatih Levent Balcı · Fazilet Erözgen · Selman Emiroglu · Mustafa Tukenmez · Ravza Yılmaz · Rana Gunoz Comert · Semen Onder · Aysel Bayram · Sidar Bağbudar · Mahmut Muslumanoglu · Neslihan Cabıoğlu

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Abstract

Background Nipple discharge may indicate subareolar or nipple–areola complex (NAC) involvement in nipple discharge-associated breast cancer, which has important implications for surgical planning and prognosis. This study aimed to analyze the clinicopathological features, radiological findings, and oncological outcomes of breast cancer patients presenting with nipple discharge.

Methods Patients who presented with nipple discharge and underwent surgery with a histopathological diagnosis of breast cancer between January 2005 and January 2020 at three tertiary referral centers were retrospectively reviewed. Demographic, clinical, radiological, and pathological data were collected. Demographic, clinical, radiological, and pathological data were retrospectively collected.

Results A total of 205 patients were included. Of those, 71.8% presented with bloody discharge. Most patients had early-stage disease (pTis/T1: 78.8%). Overall, pathological NAC involvement was identified in 26.5% of cases, whereas it was estimated as 34.5% in mastectomy cases, and 60% in patients with MRI-suspicious findings and 48.7% in those with a non-luminal pathology. MRI demonstrated the highest diagnostic accuracy (AUC 0.756, $p<0.001$) for detecting NAC involvement independent predictors of NAC involvement were non-luminal subtype (OR 3.15, 95% CI, $p=0.004$) and retroareolar mass (OR 2.57, 95% CI, $p=0.012$). At a median follow-up of 68 months, locoregional and distant recurrence rates were 2.9% and 9.3%, respectively. No significant differences in disease-free or disease-specific survival were observed between patients undergoing breast-conserving surgery and those treated with mastectomy, or between patients with and without NAC involvement. Lymphovascular invasion and nodal positivity were associated with reduced DFS.

Conclusion Breast cancers associated with nipple discharge are most often diagnosed at an early stage. Careful clinical and radiological evaluation of nipple–areola complex (NAC) involvement is essential in these patients due to the high NAC involvement in clinical and imaging suspicious cases and aggressive tumor biology. When NAC involvement is excluded, breast-conserving surgery and nipple-sparing mastectomy can be considered in appropriately selected patients, with comparable oncological outcomes.

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Keywords Breast cancer · Nipple discharge · Nipple–areola complex · Nipple involvement · Breast-conserving surgery · Mastectomy · MRI · Oncological outcomes

1 Introduction

Nipple discharge refers to any fluid that comes from one or both nipples of the breasts. After breast pain and palpable mass, nipple discharge is the third most common breast-related symptom seen in outpatient clinics with a prevalence of 5–7% [1–5]. Since it is regarded as one of the symptoms of breast cancer, nipple discharge extremely concerns patients, whereas it is rarely associated with cancer [2, 3]. In fact, about 80% of women experience this symptom during their reproductive years [1].

Nipple discharge is categorized as lactational, physiological, and pathological depending on the clinical history and discharge characteristics. Pathological nipple discharge (PND) is usually defined as unilateral, spontaneous, bloody, or serous discharge from a single duct. As there are many causes of PND, it may often lead to diagnostic challenges for the clinician. Even though nipple discharge mainly occurs due to benign causes such as intraductal papilloma and duct ectasia [6], the high degree of anxiety caused by this symptom is closely related to the fear of breast cancer. Therefore, it is of primary importance to distinguish malignancy from benign lesions. In this regard, the initial diagnostic workup consists of physical examination and age-appropriate imaging modalities including mammography and ultrasound (US). Cytological examination of nipple discharge is one of the diagnostic methods that can be utilized; however, it should be kept in mind that its diagnostic accuracy is relatively low [7, 8]. PND accompanied by a palpable mass or radiologic abnormalities is often linked with a high rate of invasive cancer [9, 10]. As an incidence of 5–21% is associated with underlying malignancy [1, 11], all patients presenting with features of PND require thorough evaluation and follow-up and should be referred to a breast surgeon immediately.

In patients evaluated for pathological nipple discharge, the detection of an underlying malignant disease most commonly corresponds to early-stage breast cancer or ductal carcinoma in situ (DCIS), conditions for which surgery remains the mainstay of treatment [12, 13]. The choice of surgical approach should be guided by a comprehensive assessment including physical examination findings with imaging modalities. Given that nipple discharge is the predominant clinical presentation, careful evaluation of potential nipple-areola complex (NAC) involvement is of particular importance [14]. In the absence of clinical or radiological suspicion of NAC involvement and multicentricity, breast-conserving surgery (BCS) should be considered as the preferred surgical option [15].

NAC involvement can be managed either with breast-conserving surgery combined with NAC excision or with mastectomy [14]. For patients without NAC involvement whose breast lesions are not suitable for breast-conserving surgery, nipple-sparing mastectomy (NSM) with implant-based reconstruction is a feasible option [13].

Although previous studies have primarily focused on the association between pathological nipple discharge and the risk of underlying breast malignancy, limited evidence is available regarding the clinicopathological characteristics of breast cancers presenting with nipple discharge. In particular, the predictors of pathological nipple–areola complex (NAC) involvement, their implications for surgical decision-making, and the long-term oncological outcomes of different surgical approaches in this specific patient population remain insufficiently investigated.

This study sought to characterize the pathological features and evaluate the surgical and oncological outcomes of breast cancers presenting with nipple discharge in regards to the NAC involvement.

2 Methods

In this retrospective multicenter study, patients who presented with nipple discharge and underwent surgery with a histopathological diagnosis of breast malignancy were analyzed. The study included patients treated between January 2005 and January 2020 at three tertiary referral centers including Istanbul University, Istanbul Faculty of Medicine, Okmeydani Training and Research Hospital, Health Sciences University, and Haseki Training and Research Hospital, Health Sciences University.

Clinical records, radiological imaging reports, cytological results, and pathological data were retrieved from the institutional electronic database and patient charts. Demographic variables (age, menopausal status, family history of breast cancer), clinical presentation (type, laterality, and color of nipple discharge), radiological findings, cytology results, type of surgical procedure, histopathological diagnosis, tumor size, lymph node status, molecular subtype, and adjuvant treatments were systematically recorded.

Patients with benign breast lesions, as well as those diagnosed with distant metastatic disease were excluded from the study.

2.1 imaging and diagnostic evaluation

Radiological evaluation included mammography (MG), US, and magnetic resonance imaging (MRI), performed according to clinical indication and availability. MRI protocols included T1- and T2-weighted sequences with dynamic contrast enhancement for evaluating nipple–areola complex (NAC) invasion. Cytological examination was performed from discharge samples using standard Papanicolaou staining, and results were categorized as benign, atypical, or malignant. Ductoscopy and ductography findings were also reviewed when available. In patients who underwent ductography, radiographic findings such as cut-off signs, filling defects, and ductal dilatation were recorded [14]. During ductoscopy, intraductal lesions were directly visualized, and in cases where intraductal abnormalities were identified, the distance of these lesions from the nipple was measured as reported previously [16, 17].

2.2 Surgical and pathological assessment

Surgical procedures consisted of breast-conserving surgery (BCS) and mastectomy, based on tumor size, location, and patient preference. Sentinel lymph node biopsy or axillary dissection was performed according to clinical and radiological staging.

Pathological nipple–areola complex (NAC) involvement was determined by histopathological examination of the nipple and/or retroareolar tissue when these specimens were available. In patients undergoing breast-conserving surgery, additional NAC excision or retroareolar resection was performed when clinical or radiological findings raised suspicion of NAC involvement. In patients undergoing breast-conserving surgery with preservation of the NAC, the retroareolar margin was routinely marked and submitted separately for pathological evaluation in addition to the standard orientation of the surgical specimen. It was assessed either by intraoperative frozen-section analysis, when indicated, or by final pathological examination. In the absence of pathological assessment of the NAC, patients were considered NAC-negative for statistical analyses if there was no clinical or radiological suspicion of NAC involvement and surgical margins were negative. This approach was adopted to ensure consistency in the classification of NAC involvement across surgical groups.

Patients without documented pathological assessment of the NAC or retroareolar region were excluded from analyses evaluating NAC involvement. Accordingly, statistical analyses of NAC involvement were performed only in patients with available clinical and pathological assessment of the NAC.

Tumors were classified according to the 8th edition of the AJCC staging system, and molecular subtypes were defined using immunohistochemistry for ER, PR, HER2, and Ki-67.

Table 1 Patient demographic and clinical characteristics

Variables	*n*(%)/mean ± SD(range)
Number of patients	205
Age (year)	52.9 ± 13.5(25–86)
Age group	
< 50 years	91(44.4)
≥ 50 years	114(55.6)
Nature of nipple discharge (n = 172)	
Evoked	17(9.9)
Spontaneous	155(90.1)
Number of ducts (n = 115)	
Single duct	103(89.6)
Multiduct	12(10.4)
Localization	
Unilateral	199(97.1)
Bilateral	6(2.9)
Color (n = 156)	
Bloody	112(71.8)
Brown-black	6(3.8)
Yellow	13(8.3)
Clear-serous	13(8.3)
Green-milky	12(7.7)
Retroareolar mass	
No	130(63.4)
Yes	75(36.6)
cT stage	
cTis	24(11.7)
cT1	120(58.5)
cT2	51(24.9)
cT3-4	10(4.9)
cN stage	
cN(-)	173(84.4)
cN(+)	32(15.6)
Systemic therapy	
None	117(57.1)
Neoadjuvant chemotherapy	19(9.3)
Adjuvant chemotherapy	69(33.7)
Breast surgery	
Breast conserving surgery	74(36.1)
MRM	54(26.3)
Simple mastectomy	49(23.9)
SSM	19(9.3)
NSM	9(4.4)
Axillary Surgery	
None	24 (11.7)
SLNB	108 (52.7)
ALND	73 (35.6)
Adjuvant Radiotherapy	
Yes	117(57.1)
No	88(42.9)
pT stage	
pTis/T1	162(79)
pT2/T3/T4	43(21)
pN stage	
pN(-)	155(75.6)
pN(+)	50(24.4)

Table 1 (continued)

Variables	*n*(%)/mean ± SD(range)
Tumor size	
< 2 cm	164(80)
≥ 2 cm	41(20)
Lymphovascular invasion (LVI)	
Negative	153(74.6)
Positive	52(25.4)
Estrogen receptor (ER) (n = 174)	
Positive	129(74.1)
Negative	45(25.9)
Progesterone receptor (PR) (n = 163)	
Positive	109(66.9)
Negative	54(33.1)
HER2 (n = 137)	
Negative	101(73.7)
Positive	36(26.3)
Molecular subtype (n = 172)	
Luminal	131(76.2)
Non-luminal	41(23.8)
Cytology (n = 88)	
Negative	47(53.4)
Positive	41(46.6)
Tumor type	
DCIS	45(22)
DCIS+microinvasion	11(5.4)
IDC	107(52.2)
ILC	10(4.9)
IDC + ILC	15(7.3)
Other	17(8.3)
NAC involvement (n = 189)	
Negative	139(73.5)
Positive	50(26.5)

SD: standard deviation, MRM: Modified radical mastectomy, SSM: Skin sparing mastectomy, NSM: nipple-areola sparing mastectomy, DCIS: Ductal carcinoma in situ, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma

2.3 Statistical analysis

All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY). Categorical variables were compared using the Pearson chi-square or Fisher's exact test, while continuous variables were analyzed with the independent samples t-test or Mann–Whitney U test, depending on data distribution. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of NAC involvement. Diagnostic performance of mammography, ultrasonography, and magnetic resonance imaging for predicting pathological NAC involvement was evaluated by calculating sensitivity, specificity, and overall diagnostic accuracy. Receiver operating characteristic (ROC) curve analysis was performed, and the area under the curve (AUC) was calculated for each imaging modality. Agreement between imaging findings and pathological NAC involvement was assessed using Cohen's kappa coefficient. Survival analyses were performed using the Kaplan–Meier method to assess disease free survival (DFS) and overall survival (OS) rates, and differences were assessed with the log-rank test. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

A total of 205 patients with breast malignancy associated with nipple discharge were analyzed. The mean age was 52.9 ± 13.5 years (range, 25–86), and 114 patients (55.6%) were ≥ 50 years. The majority presented with spontaneous nipple discharge (90.1%), while evoked discharge was observed in 9.9%. Discharge was predominantly unilateral (97.1%), and bloody discharge was the most common type (71.8%). Clinically, most patients had cT1 tumors (58.5%), with cN positivity in 15.6%.

3.2 Surgical treatment and pathological findings

The majority ($n = 131$, 63.9%) underwent mastectomy, whereas 74 patients (36.1%) had breast-conserving surgery. Regarding axillary management, 24 patients (11.7%) did not undergo any axillary surgical procedure; sentinel lymph node biopsy (SLNB) was performed in 108 patients (52.7%), and axillary lymph node dissection (ALND) in 73 patients (35.6%). Pathological staging revealed pTis/T1 in 78.8% and pT2-3–4 in 21.2% of cases. Lymph node metastasis was detected in 24.4%, and lymphovascular invasion in 25.4%. Tumor biology according to the immunohistochemistry staining showed luminal subtypes in 76.2% of patients, while non-luminal tumors accounted for 23.8%. Overall, NAC involvement was observed in 26.5% of cases (34.5% in the mastectomy group vs. 13.7% in the BCS group (Table 1).

Among the 74 patients who underwent breast-conserving surgery, additional nipple–areola complex (NAC) excision or retroareolar resection was performed in 20 patients due to clinical or radiological suspicion of NAC involvement. Pathological NAC involvement was confirmed in 10 of these patients. For the purposes of statistical analysis, the remaining 54 patients treated with breast-conserving surgery were considered to have no pathological NAC involvement, based on negative surgical margins and the absence of clinical or radiological suspicion.

16 of the 205 patients were excluded from the statistical analysis of nipple–areola complex (NAC) involvement because their pathology reports did not include specific histopathological evaluation of the retroareolar region or the NAC. Statistical analyses related to nipple–areola complex (NAC) involvement were therefore performed based on the remaining 189 patients with available and clearly documented clinical and pathological evaluation of the NAC.

3.3 Imaging findings associated with NAC involvement

All patients underwent preoperative imaging with at least one modality. Ultrasonographic imaging was available in 190 of the 205 patients, mammography in 176 patients, and breast MRI in 95 patients.

Mammography (MG) revealed abnormalities in 30.2% of NAC-involved cases, but demonstrated limited diagnostic performance overall, with low sensitivity (30.2%), moderate specificity (81.8%), and poor discriminative capacity (area under the curve (AUC) 0.560, $p = 0.098$). Thus, MG alone was not reliable in predicting NAC involvement.

Ultrasonography (US) detected NAC-related abnormalities more frequently. It showed a sensitivity of 53.2% and specificity of 85.7%, with an AUC of 0.695 ($p < 0.001$), indicating moderate diagnostic accuracy. US was particularly useful for identifying subareolar extension and ductal dilatation, but still failed to detect nearly half of NAC-involved tumors.

Among the 95 patients who underwent MRI, findings suspicious for nipple–areola complex (NAC) invasion were identified in 31 cases. Of these 31 patients, 20 underwent mastectomy, and pathological NAC involvement was confirmed in 12 patients (60%).

Of the remaining 11 patients with BCS, 5 (45.5%) underwent complete NAC excision or additional retroareolar excision. Pathological NAC involvement was identified in 4 patients (80%) within this subgroup. In the

remaining six patients, although MRI demonstrated findings suspicious for NAC involvement, the decision to preserve the NAC was made after integrating the overall clinical, radiological, and intraoperative findings. The retroareolar surgical margin was carefully evaluated in all cases and was confirmed to be free of tumor on pathological examination.

MRI provided the highest diagnostic accuracy among the modalities. MRI demonstrated sensitivity of 72.7%, specificity of 78.6%, and an overall accuracy of 77.2%, with AUC 0.756 ($p<0.001$) and substantial diagnostic agreement (kappa = 0.450). MRI was particularly valuable in detecting occult NAC invasion not visualized on MG or US, and contributed significantly to preoperative surgical planning (Table 2).

3.4 Predictors of NAC involvement

Univariate analysis showed that age ≥ 50 years (OR: 2.46, 95% CI, $p=0.010$), non-luminal subtype (OR: 3.26, 95% CI, $p=0.002$), retroareolar mass on physical examination (OR:3.08, 95% CI, $p<0.001$), and higher pathological T stage (pT2-3–4) (OR: 2.83, 95% CI, $p=0.047$) were significantly associated with NAC involvement. Among the six patients with cT4 tumor, NAC involvement was observed in three patients (50%) on histopathological examination. The remaining three patients were classified as cT4 because of localized skin involvement remote from the nipple–areola complex and showed no pathological NAC involvement. Patients who underwent mastectomy had a higher rate of NAC involvement compared with those treated with breast-conserving surgery (34.5% vs. 13.7%, OR: 3.32, 95% CI, $p=0.002$) (Table 3). In multivariate analysis, retroareolar mass on physical examination (OR: 2.57, 95% CI: 1.24–5.34, $p=0.012$), and non-luminal subtype (OR: 3.15, 95% CI: 1.45–7.09, $p=0.004$) remained as independent predictors (Table 4).

3.5 Cytology and ductal procedures

Among patients who underwent additional diagnostic procedures, cytology was performed in 88 patients; 41 (46.6%) were positive and 47 (53.4%) were negative. In univariate analysis, positive nipple discharge cytology was associated with a higher rate of pathological NAC- involvement compared with negative cytology (31.6% vs. 14.6%); however, this association did not reach statistical significance (OR 2.69, 95% CI 0.89–8.12; $p=0.073$).

Ductoscopy was performed in 34 patients, demonstrating abnormal findings in 76.5% of in situ lesions and 58.8% of invasive lesions. Ductography was performed in 12 patients and revealed abnormal findings in all cases.

3.6 Adjuvant treatments, recurrence and survival outcomes

Overall, 117 patients (57.1%) did not receive systemic treatment including chemotherapy with/without targeted therapies, while 19 patients (9.3%) underwent neoadjuvant systemic theatment and 69 patients (33.7%) received adjuvant systemic treatment. Adjuvant radiotherapy was administered to 117 patients (57.1%), whereas 88 patients (42.9%) did not receive postoperative radiotherapy. Radiotherapy was routinely delivered after breast-conserving surgery and selectively after mastectomy according to pathological stage, nodal status, surgical margin status, and multidisciplinary treatment recommendations. All hormone receptor–positive patients received appropriate adjuvant endocrine therapy according to current treatment guidelines. All HER2-positive patients

Table 2 Diagnostic performance of US, MG, and MRI in detecting pathological nipple involvement

Imaging findings	AUC	Sensitivity(%)	Specificity(%)	Accuracy(%)	Kappa	*P*
US	0.695	53.2(25/47)	85.7(114/133)	77.2(139/180)	0.397	**<0.001**
MG	0.560	30.2(13/43)	81.8(99/121)	68.3(112/164)	0.128	0.098
MRI	0.756	72.7(16/22)	78.6(55/70)	77.2(71/92)	0.450	**<0.001**

AUC: Area Under the Curve, US: Ultrasonography, MG: mammography, MRI: magnetic resonance imaging

Table 3 Univariate analysis results of variables associated with nipple involvement

Variables (N = 189)		NAC involvement (+)	Univariate	
	N	n(%)	OR (95% CI)	P
Age group				
< 50 years	82	14(17.1)	Reference	
≥ 50 years	107	36(33.6)	2.46(1.22–4.97)	**0.010**[a]
Nature of nipple discharge				
Evoked	16	5(31.3)	Reference	
Spontaneous	141	38(27)	0.81(0.27–2.49)	0.715[a]
Number of ducts, n(%)				
Single duct	95	27(28.4)	Reference	
Multiduct	11	4(36.4)	1.44(0.39–5.32)	0.727[b]
Localization, n(%)				0.344[b]
Unilateral	183	50(27.3)	N/A	
Bilateral	6	0(0)	N/A	
Color				
Bloody	102	29(28.4)	Reference	
Other	39	11(28.2)	0.99(0.44–2.24)	0.979[a]
Retroareolar mass				
No	117	21(17.9)	Reference	
Yes	72	29(40.3)	3.08(1.5–6.01)	**< 0.001**[a]
cT stage, n(%)				
cTis	21	4(19)	Reference	
cT1	112	30(26.8)	1.56(0.48–4.99)	0.590[b]
cT2	47	12(25.5)	1.46(0.41–5.19)	0.759[b]
cT3-4	9	4(44.4)	3.4(0.62–18.75)	0.195[b]
cN stage, n(%)				
cN(-)	159	41(25.8)	Reference	
cN(+)	30	9(30)	1.23(0.52–2.91)	0.631[a]
Breast surgery				
Breast cancer surgery	73	10(13.7)	Reference	
MRM	47	17(36.2)	3.57(1.46–8.73)	**0.004**[a]
Simple mastectomy	43	18(41.9)	4.54(1.84–11.17)	**< 0.001**[a]
SSM	17	5(29.4)	2.63(0.76–9.06)	**0.004**[b]
NSM	10	0(0)	N/A	
pT stage, n(%)				
pTis/T1	149	34(22.8)	Reference	
pT2/3/4	40	16(40)	2.26(1.08–4.72)	**0.029**[a]
pN stage, n(%)				
pN(-)	144	36(25)	Reference	
pN(+)	45	14(31.1)	1.36(0.65–2.83)	0.417[a]
Tumor size				
< 2 cm	151	36(23.8)	Reference	
≥ 2 cm	38	14(36.8)	1.86(0.87–3.98)	0.104[a]
Lymphovascular invasion (LVI)				
Negative	140	33(23.6)	Reference	
Positive	49	17(34.7)	1.72(0.85–3.49)	0.129[a]
Estrogen receptor (ER)				
Positive	122	28(23)	Reference	
Negative	43	20(46.5)	2.92(1.40–6.08)	**0.003**[a]
Progesterone receptor (PR)				
Positive	105	22(21)	Reference	
Negative	51	25(49)	3.63(1.76–7.47)	**< 0.001**[a]
HER2				
Negative	97	23(23.7)	Reference	
Positive	35	14(40)	2.15(0.94–4.88)	0.066[a]

Table 3 (continued)

Variables (N=189)		NAC involvement (+)	Univariate	
	N	n(%)	OR (95% CI)	P
Molecular subtype				
Luminal	124	28(22.6)	Reference	
Non-luminal	39	19(48.7)	3.26(1.53–6.94)	**0.002**[a]
Cytology				
Negative	41	6(14.6)	Reference	
Positive	38	12(31.6)	2.69(0.89–8.12)	0.073[a]
Tumor Type				
DCIS	39	7(17.9)	Reference	
Invasive	150	43(28.7)	1.84(0.75–4.48)	0.176[a]

OR, Odds ratio; CI, Confidence interval, MRM: Modified radical mastectomy, SSM: Skin sparing mastectomy, NSM: nipple-areola sparing mastectomy, DCIS: Ductal carcinoma in situ

[a]Pearson chi-square test

[b]Fisher's exact test

Table 4 Multivariate analysis results of variables associated with nipple areola complex- involvement

Variables	B	SE	OR (95% CI)	*P**
Age (≥50y)	0.66	0.39	1.93(0.89–4.16)	0.095
High pT stage (pT2-3–4)	0.65	0.41	1.92(0.86–4.29)	0.113
Non-luminal molecular subtype	1.17	0.41	3.15(1.45–7.09)	**0.004**
Retroareolar mass	0.94	0.37	2.57(1.24–5.34)	**0.012**

OR, Odds ratio; CI, Confidence interval; B, Unstandardized beta coefficient; SE, standard error

*Analyses were performed using a binary logistic regression model with the enter method

Table 5 Oncological outcomes and survival analysis

Variables	Statistics
Local-regional recurrence, n(%)	6(2.9)
Systemic recurrence, n(%)	19(9.3)
Disease-specific death, n(%)	14(6.8)
Median follow-up (IQR)	68(24–103)
5-year disease-free survival probability[a], %	88
5-year overall survival probability[a], %	94.3

[a]Survival probability was estimated using the Kaplan–Meier method

received anti-HER2 treatment. Systemic therapy and radiotherapy decisions were made on an individualized basis by the multidisciplinary tumor board.

At a median follow-up of 68 months (IQR: 24–103), local-regional recurrence occurred in 6 patients (2.9%) and systemic recurrence in 19 patients (9.3%). A total of 14 disease-specific deaths (6.8%) were observed. The 5-year DFS probability was 88%, and the 5-year OS probability was 94.3% (Table 5).

The presence or absence of NAC-involvement did not significantly affect recurrence or survival outcomes. Univariate Cox regression analysis demonstrated that lymphovascular invasion (HR: 2.98, $p=0.008$) and pathological nodal positivity (HR: 2.23, $p=0.045$) were significantly associated with reduced DFS (Table 6).

4 Discussion

Most women experience nipple discharge at some point in their lives. However, the incidence of breast cancer among patients presenting with nipple discharge is relatively low [18]. The initial step in evaluating such patients is to determine the characteristics of the discharge. Unilateral, spontaneous, and bloody nipple discharge

Table 6 Univariate Cox regression analysis results of variables associated with disease-free and disease-specific survival

Variables		Univariate DFS		Univariate DSS	
		HR(95% CI)	*P*	HR(95% CI)	*P*
Age group	<50 years	Reference		Reference	
	≥50 years	1.22(0.55–2.70)	0.620	1.36(0.47–3.94)	0.576
NAC involvement	Negative	Reference		Reference	
	Positive	1.15(0.47–2.82)	0.759	2.03(0.62–6.65)	0.243
cT stage	cTis	Reference		Reference	
	cT1	0.91(0.12–6.92)	0.929	0.45(0.06–3.68)	0.459
	cT2	0.82(0.10–7.06)	0.857	0.30(0.03–3.36)	0.329
	cT3-4	7.69(0.83–71.15)	0.072	5.27(0.51–54.06)	0.162
cN stage	cN(-)	Reference		Reference	
	cN(+)	2.34(0.96–5.70)	0.061	2.63(0.80–8.66)	0.112
pT stage	pTis/T1	Reference		Reference	
	pT2/3/4	1.65(0.70–3.85)	0.251	2.00(0.65–6.13)	0.225
pN stage	cN(-)	Reference		Reference	
	cN(+)	2.23(1.02–4.90)	**0.045**	1.78(0.62–5.13)	0.286
LVI	Negative	Reference		Reference	
	Positive	2.98(1.34–6.66)	**0.008**	1.98(0.64–6.11)	0.236
ER	Positive	Reference		Reference	
	Negative	1.40(0.57–3.45)	0.459	1.55(0.47–5.18)	0.475
PR	Positive	Reference		Reference	
	Negative	1.83(0.78–4.32)	0.166	1.66(0.51–5.47)	0.401
HER2	Negative	Reference		Reference	
	Positive	1.53(0.54–4.35)	0.427	0.47(0.06–3.78)	0.479
Molecular subtype	Luminal	Reference		Reference	
	Non-luminal	1.12(0.79–1.59)	0.504	1.27(0.76–2.11)	0.59

HR, Hazard Ratio, CI, Confidence interval, LVI, lymphovascular invasion

is considered pathological and warrants further investigation for underlying malignancy. This highlights the importance of distinguishing pathological nipple discharge from benign presentations, as early recognition of suspicious discharge characteristics may facilitate timely diagnosis and appropriate surgical planning.

In this study, we evaluated the clinicopathological characteristics and outcomes of breast cancer patients presenting with nipple discharge. In accordance with previous reports, nipple discharge in this cohort was most often unilateral, spontaneous, and bloody. Among patients diagnosed with breast malignancy, 71.8% presented with bloody nipple discharge. Although bloody discharge is more commonly associated with malignant and high-risk lesions, it is noteworthy that benign entities such as intraductal papilloma may also frequently present with this symptom [19].

One of the most critical aspects to be assessed in patients with nipple discharge is involvement of the nipple–areola complex (NAC). Physical examination and imaging are the main tools for its evaluation. The diagnostic performance of imaging modalities differs substantially in detecting NAC involvement. Mammography is often the first imaging method of choice. However, mammography is known to have low sensitivity in detecting nipple involvement [20]. In our cohort, MMG showed very low sensitivity (30.2%). Ultrasonography (US) showed higher sensitivity (53.2%), particularly in detecting ductal dilatation and subareolar lesions. The combined use of MMG and US, as suggested by previous reports, may improve diagnostic yield [21]. Magnetic resonance imaging (MRI), however, demonstrated the highest diagnostic accuracy in our cohort, consistent with previous studies emphasizing its superiority in delineating retroareolar tumor spread and subclinical NAC invasion [22]. MRI's high-resolution capability enables detection of early changes in the nipple base, which is crucial for preoperative surgical decision-making. Based on our findings, MRI should be considered the imaging modality of choice when NAC involvement is clinically or radiologically suspected, or when nipple preservation is being contemplated. It should also be acknowledged that MRI was not performed routinely in all patients but was obtained according to clinical indication, particularly in cases with suspicious clinical or conventional imaging findings or when nipple

Table 7 Series of patients with breast cancer associated with nipple discharge

Variables	Cabioglu et al., (2004) [15]	Chang et al., (2017) [13]	Hou et al., (2025) [32]	Amburn et al., (2025) [25]	Mollavelioglu et al., (2025)[b]
Time period	1990–2002	2009–2014	2014–2023	2000–2023	2005–2020
Number of cases	48	60	226	93	205
DCİS/ İnvasive	29(60.4%)/ 19(39.6%)	29(48.3%)/ 23(38.3%)	NA	38 (40.9%)/55 (59.1%)	24 (11.7%)/181 (88.3%)
Tis+T1/ T2-3–4	43(89.6%)/ 5(10.4%)	47(78.3%)/ 13(21.7%)	158 (69.9%)/ 68 (30.1%)	61 (65.6%)/ 32 (34.4%)	144 (70.2%)/ 61 (29.8%)
N0/ N+	NA	53(88.3%)/ 7 (11.7%)	188 (83.2%)/ 38 (16.8%)	NA	173 (84.4%)/ 32 (15.6%)
BCS/ Mastectomy	24(50.0%)/ 24(50.0%)	21(35.0%)/ 39(65.0%)	0 (0%)/ 226 (100%)	0 (0%)/ 93 (100%)	74 (36.1%)/131 (63.9%)
Luminal/ Non-luminal	13(72.2%)/ 6(27.8%)	54(90.0%)/ 6(10.0%)	174 (76.9%)/52 (23.1%)	73 (78.5%)/20 (21.5%)	131 (76.1%)/41 (23.9%)
NAC involvement	6 (12.5%)	10 (16.7%)	NA	34 (36.6%)	50 (26.5%)[c]
Adjuvant RT	13 (27.1%)	25 (41.7%)	NA	NA	117 (57.1%)
Chemotherapy	7 (14.6%)	13 (21.7%)	NA	NA	88 (42.9%)
Local recurrence	3 (6.3%)	0 (0%)	11 (4.9%)[a]	NA	6 (2.9%)
Distant recurrence	1 (2.1%)	0 (0%)	8 (3.5%)[a]	NA	19 (9.3%)
Follow-up time (months)	45	27	77	NA	68

NA: not applicable

[a]In this study follow-up time is 77 months, but local and distant recurrence was noted during the first 3 years post-surgery

[b]Current report

[c]These percentage was calculated only in patients with clearly reported areolar involvement on pathological examination ($n=189$)

preservation was being considered. Consequently, the reported diagnostic performance of MRI may have been influenced by selection bias. From a clinical perspective, accurate preoperative assessment of NAC involvement is pivotal, as it directly influences the feasibility of breast-conserving and nipple-preserving surgical strategies.

We observed a higher rate (48.7%) of NAC involvement among non-luminal subtypes. This may be attributed to the more aggressive biological nature of non-luminal tumors. Castellano et al. reported that among breast cancer patients presenting with nipple discharge, nipple involvement was more frequently observed in HER2-positive DCIS, which is characterized by a more aggressive phenotype [23]. These findings further support the notion that NAC involvement is influenced not only by tumor location but also by tumor biology. In addition, 76.1% of tumors in our series were of the luminal subtype. Similarly, the series reported in the literature demonstrated a predominance of luminal subtypes, comparable to the distribution observed in our cohort (Table 7).

Advanced T stage was also associated with NAC involvement, although this association did not reach statistical significance — a finding that may be explained by the greater likelihood of NAC invasion with increasing tumor size. Yang et al., in their analysis of 1,190 mastectomy specimens, also found that nipple involvement correlated with higher T stage [24]. Similarly, patients presenting with a retroareolar mass on physical examination were more likely to have NAC involvement.

Pathological NAC involvement varies between 12.5% and 36.6% in large retrospective series regarding nipple discharge-associated breast cancer (Table 7). In our cohort, pathological NAC involvement was observed in 13.7% of patients who underwent BCS and 34.5% of those treated with mastectomy, corresponding to an overall rate of 26.5%, with significantly higher involvement in the mastectomy group. This likely reflects a selection bias, since mastectomy was more frequently performed in patients with higher T stage or stronger clinical/radiological suspicion of nipple involvement. Amburn et al. found pathological nipple involvement in 36.5% of mastectomy patients with nipple discharge. In the same study, they found that among clinicopathological features, only tumor proximity of 1 cm to the areola was associated with pathological NAC involvement [25].

Although our cohort predominantly consisted of early-stage disease, the mastectomy rate was relatively high (63.9%) compared with breast-conserving surgery rates reported for patients without nipple discharge at similar stages. A similar pattern has been reported in other series in the literature (Table 7). Despite the predominance of early-stage disease in breast cancer cases associated with nipple discharge, mastectomy rates were reported as 50% in the study by Cabioglu et al.[15] and 65% in the study by Chang et al.[13] This tendency has been attributed to clinicians' concern regarding potential nipple–areola complex involvement in patients presenting with nipple discharge.

The role of cytological evaluation of nipple discharge remains controversial. Several studies have demonstrated its limited diagnostic value [26]. In our study, pathological cytology results were obtained in 41 of 88 patients (46.6%). In univariate analysis, positive nipple discharge cytology demonstrated a trend toward higher rates of pathological NAC involvement, although this association did not reach statistical significance. This finding likely reflects the limited sensitivity of cytological examination and the relatively small number of patients with evaluable cytology. While cytological positivity has high specificity, its sensitivity remains low and must be interpreted cautiously [27] Accordingly, nipple discharge cytology should not be used as a stand-alone diagnostic tool and must be interpreted in conjunction with imaging and clinical findings.

Ductoscopy may also be beneficial in this patient population. In our series, 34 patients underwent ductoscopy, and 23 (67%) demonstrated abnormal findings. Ductography was performed in 12 patients, all of whom showed abnormal results. However, it should be noted that both ductoscopy and ductography are technically challenging, and their diagnostic accuracy can vary [28, 29]. For this reason, these techniques are best reserved for selected cases in experienced centers rather than routine evaluation. Future studies integrating molecular or cytogenetic testing of nipple discharge samples could enhance diagnostic yield and provide a more personalized diagnostic approach [27, 28]. The majority of patients had Tis or T1 tumors (79%), which is consistent with previous reports [12, 13, 15, 25, 32]. Since most of our patients had early stage breast cancer, the rate of neoadjuvant chemotherapy was relatively low (9.3%), while adjuvant chemotherapy was administered to 33.7%.

In our cohort, no significant differences in disease-specific survival (DSS) or disease-free survival (DFS) were observed between patients undergoing BCS and those treated with mastectomy. Hou et al. compared the outcomes of breast cancer patients with nipple discharge who underwent simple mastectomy or nipple-sparing mastectomy (NSM) and similarly found no significant differences in oncological outcomes between the two groups [32].

Our study demonstrated that pathological NAC involvement or pathological nipple discharge did not significantly affect disease-free survival (DFS) or disease-specific survival (DSS). This finding supports the notion that NAC invasion reflects local tumor spread rather than a systemic aggressiveness indicator. The variables associated with worse DSS and DFS were lymphovascular invasion (LVI) and nodal positivity. During a median follow-up of 68 months, only six patients (2.9%) developed locoregional recurrence, and systemic disease occurred in 19 patients (9.3%). These findings suggest that BCS and nipple-preserving approaches may provide favorable oncological outcomes in carefully selected patients, provided that clinical and radiological evaluations exclude NAC involvement.

The main limitations of our study include its retrospective design, and the limited number of patients undergoing ductography or ductoscopy. Another limitation concerns the assessment of NAC involvement in patients treated with breast-conserving surgery. Pathological evaluation of the NAC was performed only in patients with clinical or radiological suspicion, and direct histopathological confirmation was therefore unavailable for a proportion of BCS cases. Patients without NAC excision were considered NAC-negative based on the absence of clinical or radiological suspicion and negative surgical margins. Although this approach reflects routine clinical practice, the possibility of misclassification bias cannot be excluded. Although the total sample size was 205, the low number of recurrence and mortality events limited the power of the prognostic analyses. Despite these limitations, the long follow-up duration and the detailed correlation between clinical, radiological, and pathological NAC involvement improves the clinical relevance of our findings. Nevertheless, this study represents one of the largest cohorts focusing on breast cancer patients with nipple discharge, and the detailed evaluation of NAC involvement provides valuable insights into the clinical relevance of this entity in breast cancer.

5 Conclusion

Breast cancers presenting with nipple discharge are most frequently diagnosed at an early stage; however, this clinical presentation often leads to more extensive surgical approaches due to concerns regarding nipple–areola complex (NAC) involvement. Our findings suggest that nipple discharge alone should not be considered a surrogate marker of NAC invasion or an absolute indication for mastectomy. Careful clinical and radiological evaluation, particularly with the use of magnetic resonance imaging, allows more accurate assessment of NAC involvement and facilitates appropriate surgical planning. In patients without evidence of NAC invasion, breast-conserving surgery and nipple-preserving approaches appear to provide favorable oncological outcomes. Conversely, more extensive surgical procedures, including NAC excision, should be considered in patients with clinical or radiological suspicion of NAC involvement, positive nipple discharge cytology, or aggressive tumor biology, particularly non-luminal subtypes. Given the relatively small number of recurrence events, these findings should be interpreted with appropriate caution and warrant confirmation in larger prospective studies. Despite its retrospective design, this study represents one of the largest cohorts evaluating breast cancer presenting with nipple discharge and supports individualized, evidence-based surgical decision-making in this patient population.

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Data availability The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate This retrospective observational study was approved by the Istanbul Faculty of Medicine Ethics Committee (approval number:11.03.2026–3964253). The study was performed in accordance with the Declaration of Helsinki. Given the retrospective nature of the study and the use of anonymized data extracted from existing medical records, with no additional patient intervention or contact, the need for informed consent was waived by Istanbul Faculty of Medicine Ethics Committee. The need for informed consent was waived by the Istanbul Faculty of Medicine Ethics Committee due to the retrospective nature of the study.

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Authors and Affiliations

Baran Mollavelioglu[1,2,9] · Atılay Özgen[1,2,9] · Ecem Hazal Özgen[3,10] · Ömer Bender[4,11] · Fatih Levent Balcı[5,11] · Fazilet Erözgen[6] · Selman Emiroglu[1,2] · Mustafa Tukenmez[1,2] · Ravza Yılmaz[7] · Rana Gunoz Comert[7] · Semen Onder[8] · Aysel Bayram[8] · Sidar Bağbudar[8] · Mahmut Muslumanoglu[1] · Neslihan Cabıoğlu[1,12]

✉ Neslihan Cabıoğlu
neslicab@yahoo.com; neslihan.cabioglu@istanbul.edu.tr

1 Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

2 Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

3 Faculty of Medicine, BAU Bahçeşehir University, Istanbul, Turkey

4 Vocational School of Health Services, Istanbul Yeni Yüzyıl University, Istanbul, Turkey

5 Department of General Surgery, Istanbul Health and Technology University, Istanbul, Turkey

6 Department of General Surgery, Haseki Training and Research Hospital, Health Sciences University, Istanbul, Turkey

7 Department of Radiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

8 Department of Pathology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

9 Present address: Department of Emergency Medicine, Taksim Training and Research Hospital, Istanbul, Turkey

10 Present address: East Kent Hospitals University, NHS Trust, Canterbury, UK

11 Present address: Okmeydani Training and Research Hospital, Health Sciences University, Istanbul, Turkey

12 Istanbul Faculty of Medicine, Department of General Surgery, Breast Surgery Unit, Istanbul University, Çapa Millet cad. Fatih, 34090 Istanbul, Turkey