Submitted: 29 November, 2022 Accepted: 20 March, 2023 Published: 15 October, 2023 DOI:10.22514/ejgo.2023.069

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Pregnancy-associated breast malignancy mostly presents with an aggressive type of breast cancer

Ilkin Acar[1], Leman Damla Ercan[1], Selman Emiroglu[1], Mustafa Tukenmez[1], Baris Emiroglu[1], Mahmut Muslumanoglu[1], Abdullah Igci[1,2], Vahit Ozmen[1,3], Ahmet Sait Dinccag[1], Neslihan Cabioglu[1,*]

[1]Department of Surgery, Istanbul Faculty of Medicine, Istanbul University, 34390 Istanbul, Turkey
[2]Department of Surgery, American Hospital, 34365 Istanbul, Turkey
[3]Department of Surgery, Istanbul Florence Nightingale Hospital, 34381 Istanbul, Turkey

***Correspondence**
neslicab@yahoo.com;
neslihan.cabioglu@istanbul.edu.tr
(Neslihan Cabioglu)

Abstract

Published reports on the prognosis of pregnancy-associated breast cancer are controversial. This study aims to determine the histopathological features of pregnancy-associated breast carcinoma (PABC) and the outcomes of patients with breast cancer during pregnancy and lactation among Turkish women. The study retrospectively analyzed 29 patients diagnosed with pregnancy-associated breast malignancies who underwent surgery between January 1989 and March 2021. Demographic and pathological data were obtained to evaluate the clinicopathological and prognostic characteristics of the patients. The median age was 36 years (range: 26–42 years). Of the 29 patients with breast cancer, 13 (44.8%) were diagnosed during pregnancy, and the remaining 16 (55.2%) were diagnosed during lactation. Most patients had clinical tumor stage (cT) cT2–3 (n = 20, 69%) disease, and 15 patients had clinically node (cN)-positive disease (N1 and N2, 51.7%). The majority (n = 19, 65.5%) had invasive ductal carcinoma with high Ki-67 scores (>20%). Patients with lactation-associated breast cancer were more likely to have a family history of breast cancer (44% *vs.* 8%, $p = 0.04$) than those with pregnancy-associated breast cancer. Notably, symptom duration ≥6 months and presenting with cT3–4 or cN(+) disease were associated with poor disease-free and disease-specific survival. However, no difference could be found in outcome among patients with pregnancy- and lactation-associated breast cancer. PABC mostly presents with aggressive tumor molecular subtypes with high Ki-67 scores and more advanced stages associated with poor outcome, possibly due to delayed diagnosis. Therefore, prompt early diagnosis and awareness of this disease might improve survival.

Keywords

Breast cancer; Lactation; Pregnancy; Ki-67; Early diagnosis

1. Introduction

Breast cancer is one of the most common malignancies in women. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or in the first year postpartum. The rate of PABC is 1 in 3000 pregnancies ranging from 0.2 to 3.8% of overall breast cancers [1, 2]. Women over 35 years of age, with a family history, and carrying the breast cancer gene (*BRCA*) mutation have a higher risk of breast cancer during pregnancy.

Despite being one of the most common malignancies during pregnancy after malignant melanoma and cervical cancer, PABC is a relatively rare disease. This rarity hinders the performance of large controlled clinical studies. Furthermore, insufficient data on the tumor biology and variabilities of case series across countries contribute to reported biases.

Some studies report no adverse prognoses between breast cancer and pregnancy, while others report worse prognoses. Younger age at diagnosis and advanced stage at presentation are associated with more aggressive tumor biology and are primarily blamed for the poor outcome [3, 4]. The hormonal status during pregnancy may further compromise disease prognosis [1, 5, 6]. Patients usually present with a palpable mass, and diagnosis is often delayed due to hesitation to undergo diagnostic procedures and limited clinical experience with treatment [7].

Managing PABC presents particular challenges due to the patient population and the effect of pregnancy on the female body. These challenges include diagnostic difficulties resulting from physiological changes in the breast and the need to modify standard treatment protocols to achieve the best maternal and neonatal outcomes. The lack of large controlled clinical trials has resulted in conflicting results on the prognosis of PABC in the literature. Thus, the primary purpose of this study is to determine the clinicopathological characteristics of patients diagnosed during pregnancy and lactation and investigate whether these features have prognostic significance. The

secondary aim is to investigate the clinical course of PABC and its outcome.

2. Materials and methods

This study retrospectively analyzed 6236 patients who underwent surgery for breast cancer diagnosis between January 1989 and March 2021 at the Breast Clinic of the Department of Surgery, Istanbul University Faculty of Medicine. Of these, 29 cases with a diagnosis of PABC were identified. After obtaining approval from the institutional ethical committee, a retrospective study was conducted using the data of these patients. Patient demographic data, clinical stage, tumor characteristics, surgery type, histopathologic features, nodal status, and hormone receptors were recorded. Patients were separated into two groups: those with PABC and those with lactation-associated breast cancer.

2.1 Treatment

The treatment approaches for each patient diagnosed with PABC were discussed in weekly multidisciplinary breast oncology meetings held by the surgery, radiology, pathology, medical, and radiation oncology departments. The multidisciplinary therapy, including surgery and chemotherapy before delivery, was tailored according to the gestational week of the mother.

Neoadjuvant chemotherapy based on an anthracycline regime (AC = anthracycline + cyclophosphamide) without taxanes was started at the 14th gestational week for patients diagnosed in the second trimester. Taxane-based chemotherapy was delivered in the postpartum period for patients diagnosed during pregnancy. Radiotherapy to the chest wall and axilla was delivered to all patients following the completion of chemotherapy. The oncological and surgical management of patients diagnosed in the late third trimester after the 34th gestational week was also postponed to the postpartum period.

2.2 Statistical analyses

A Microsoft Excel® database (Microsoft Corp., Redmond, WA, USA) was used to extract the data for statistical analysis. The Chi-square or Fisher's exact test was used to calculate categorical values, with a p-value of < 0.05 considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows® version 22.0 (IBM Corp., Armonk, NY, USA). The survival endpoints were breast cancer disease-free survival (DFS) and disease-specific survival (DSS).

DFS was calculated from the date of surgery to any locoregional recurrence, distant metastases, contralateral breast cancer, or death from any cause. Patients with Stage IV disease were excluded from the DFS analysis. DSS was calculated from the date of surgery to death from breast cancer. If none of these events occurred, survival was censored at the last outpatient visit. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. The independent prognostic impact of pregnancy on survival was evaluated using multivariate Cox proportional hazard regression models, expressed as the hazard ratio (HR) with 95% confidence intervals (CIs). Each model was adjusted for the variables that were statistically significant in the univariate analysis.

3. Results

3.1 Patient and tumor characteristics

The study included 29 patients diagnosed with PABC, with 13 (44.8%) diagnosed during pregnancy and 16 (55.2%) diagnosed during lactation. The demographic features of the patients are presented in Table 1. The median age was 36 years (range: 26–42 years). Six (46.2%) patients were diagnosed in the first trimester, four (30.8%) patients in the second trimester, and three (23.1%) patients in the third trimester.

Two of six (33%) patients diagnosed during the first trimester chose therapeutic abortion. Eight of 29 (28%) patients had a family history of breast cancer, with one patient in the pregnancy group and seven patients in the lactation group having such a history. Patients in the lactation group were more likely to have a family history of breast cancer (p = 0.044). Two out of seven (29%) patients in the lactation group with a family history of breast cancer were found to have the *BRCA1/2* mutation, with one patient having the *BRCA1* mutation and the other patient having the *BRCA2* mutation.

The hormone receptor status of patients showed mostly estrogen receptor (ER) positivity (n = 17, 58.6%) and progesterone receptor positivity (n = 15, 51.7%). In addition, seven patients had HER2-positivity (25%). A large proportion of the tumors (82.6%) had high Ki-67 positivity (≥20%), with nine patients (56.3%) having levels ≥35%. The molecular subtype analysis identified luminal cancers in 17 (60.7%) patients and non-luminal HER2-positive and triple-negative breast cancers in 11 (39.3%) patients.

The most prevalent histological type was invasive ductal carcinoma (n = 19), followed by mixed-type carcinoma (n = 4). Other histological types included metaplastic carcinoma (n = 1), ductal carcinoma in situ (n = 1), invasive lobular carcinoma (n = 1), and other types of carcinomas (n = 3) (Table 1).

Out of these cases, seven patients were diagnosed with multifocal/multicentric disease. Multifocality/multicentricity was significantly more frequent in the pregnancy group than in the lactation group (n = 6, 46.2% *vs.* n = 1, 6.7%; p = 0.029). No statistically significant differences in tumor characteristics were observed between the pregnancy and lactation groups (Table 1).

Most patients had T stages II and III, accounting for 69% of the sample. The clinical stages were distributed as follows: 10.3% were in Stage I, 65.5% were in Stage II, 17.2% were in Stage III, and 6.9% were in Stage IV. The clinical axillary status was N0 in 14 (48.3%) patients, N1 in seven (24.1%) patients, and the remaining seven (24.1%) patients presented with N2 or N3. Notably, patients with PABC had a high nodal involvement (cN1–3, 51.7%), but there was no significant difference between the pregnancy and lactation groups. Two patients with Stage IV underwent surgery with curative intent and had no local or locoregional relapse. However, one of them died due to liver and brain metastasis in the 11th month

TABLE 1. Clinical and tumor characteristics of patients.

Characteristics	Categories	All n (%)	Pregnancy (n = 13, 44.8%) n (%)	Lactation (n = 16, 55.2%) n (%)	*p*
Age (median)	All	36 (26–42)	34 (28–41)	36.5 (26–42)	0.379
Family history-breast cancer					
	Positive	8 (27.6)	1 (7.7)	7 (43.8)	0.044*
	Negative	21 (72.4)	12 (92.3)	9 (56.3)	
Symptom duration (months) (median/mean)					
	All	3.5 (1–18)	3 (1–18)	4 (1–12)	0.963
	<6 mon	17 (58.6)	8 (61.5)	9 (56.3)	0.999
	≥6 mon	12 (41.4)	5 (38.5)	7 (43.8)	
Trimester period (n = 13)					
	1st Period	6 (46.2)	6 (46.2)	-	
	2nd Period	4 (30.8)	4 (30.8)	-	
	3rd Period	3 (23.1)	3 (23.1)	-	
Type of Tumor					
	Ductal carcinoma in situ (DCIS)	1 (3.4)	0 (0)	1 (6.3)	0.341
	Invasive ductal carcinoma (IDC)	19 (65.5)	9 (69.2)	10 (62.5)	
	Invasive lobular carcinoma (ILC)	1 (3.4)	1 (7.7)	0 (0)	
	IDC + ILC	4 (13.8)	2 (15.4)	2 (12.5)	
	Metaplastic	1 (3.4)	1 (7.7)	0 (0)	
	Others	3 (10.3)	0 (0)	3 (18.8)	
cT					
	Tis-I	4 (13.8)	3 (23.1)	1 (6.3)	0.451
	II–III	20 (69)	8 (61.5)	12 (75)	
	IV	5 (17.2)	2 (15.4)	3 (18.8)	
c Stage					
	0–I	3 (10.3)	2 (15.4)	1 (6.3)	0.740
	II	19 (65.5)	9 (69.2)	10 (62.5)	
	III	5 (17.2)	1 (7.7)	4 (25)	
	IV	2 (6.9)	1 (7.7)	1 (6.3)	
cN					
	Negative	14 (48.3)	7 (53.8)	7 (43.8)	0.867
	Positive	15 (51.7)	6 (46.2)	9 (56.2)	
NAC receiving status					
	Received	15 (51.7)	6 (46.2)	9 (56.2)	0.867
	Not received	14 (48.3)	7 (53.8)	7 (43.8)	
Pathological complete response after NAC					
	Breast	1 (7.1)	1 (20)	0 (0)	0.357
	Axilla	4 (28.6)	2 (40)	2 (22.2)	0.580
	Breast & axilla	1 (7.1)	1 (20)	0 (0)	0.357
Surgery Type					
	Breast conversing surgery	6 (20.7)	4 (30.8)	2 (12.5)	0.364
	Mastectomy	23 (79.3)	9 (69.2)	14 (87.5)	
Grade (n = 26)					
	I–II	10 (38.5)	6 (46.2)	4 (30.8)	0.688
	III	16 (61.5)	7 (53.8)	9 (69.2)	

TABLE 1. Continued.

Characteristics	Categories	All n (%)	Pregnancy (n = 13, 44.8%) n (%)	Lactation (n = 16, 55.2%) n (%)	*p*
LVI					
	Positive	10 (34.5)	5 (38.5)	5 (31.3)	0.714
	Negative	19 (65.5)	8 (61.5)	11 (68.8)	
Tumor Foci					
	Unifocal	22 (75.9)	7 (53.8)	15 (93.8)	0.026*
	Multifocal/multicentric	7 (24.1)	6 (46.2)	1 (6.2)	
ER					
	Positive	17 (58.6)	8 (61.5)	9 (56.3)	0.999
	Negative	12 (41.4)	5 (38.5)	7 (43.7)	
PR					
	Positive	15 (51.7)	8 (61.5)	7 (43.8)	0.562
	Negative	14 (48.3)	5 (38.5)	9 (56.3)	
HER-2 (n = 28)					
	Positive	7 (25)	4 (30.8)	3 (20)	0.670
	Negative	21 (75)	9 (69.2)	12 (80)	
Ki-67 (n = 23) (median)	All	40 (10–90)	60 (15–80)	25 (10–90)	0.351
Molecular subtype (n = 28)					
	Luminal A	2 (7.1)	2 (15.4)	0 (0)	0.384
	Luminal B/HER2(−)	12 (42.9)	5 (38.5)	7 (46.7)	
	Luminal B/HER2(+)	3 (10.7)	1 (7.7)	2 (13.3)	
	Non-luminal B/HER2(+)	4 (14.3)	3 (23.1)	1 (6.7)	
	Triple-negative	7 (25)	2 (15.4)	5 (33.3)	

*cT: Clinical tumor stage; NAC: Neoadjuvan chemotherapy; c Stage: Clinical Stage; LVI: lymphovascular invasion; ER: estrogen receptor; PR: progesterone receptor; *: statistically significant.*

after surgery, and the other patient died due to lung and bone metastasis in the 68th month after surgery.

Of the three patients with clinical Stage I, one patient had DCIS and received tamoxifen after surgery. The remaining two patients underwent upfront surgery followed by adjuvant chemotherapy and hormone therapy.

3.2 Treatment and outcome

Most patients underwent mastectomy (n = 23, 79.3%). Among them, seven (24.1%) had multicentric breast tumors, and six had cT3 or cT4 disease. Of the remaining patients, one had a *BRCA* gene mutation, and the other nine underwent mastectomy due to an inappropriate tumor-to-breast size ratio.

More than half of the patients had clinically node-positive disease (n = 15, 51.9%). Of the 29 patients, 12 had sentinel lymph node biopsy (SLNB) alone, while nine underwent axillary lymph node dissection (ALND), and eight had ALND alone. During pregnancy, six patients underwent SLNB using a radio-tracer technique by low-dose Tc-99 injection.

More than half of the cases (51.7%) in our series received neoadjuvant chemotherapy (NAC). Of all the patients who received NAC, only one patient (7.1%) achieved a complete pathological response in the breast and axilla, while four (28.6%) patients had a complete pathological response in the axilla.

Six of the 15 patients who received NAC (46.2%) were diagnosed during pregnancy. Five of the six patients who received AC as the NAC regimen during pregnancy received taxane-based chemotherapy in the postpartum period. The other patient was diagnosed with cT2N0/ypT1N0 luminal B HER-2 negative breast cancer and received only six cycles of AC as an NAC regimen followed by hormonotherapy. All nine patients (56.2%) received taxane-based chemotherapy during lactation.

Six patients were diagnosed during the first trimester. Two of the six patients (33.3%) had a therapeutic abortion. Two (33.3%) of six patients received upfront surgery at the 7th and 10th gestational week, followed by adjuvant chemotherapy starting at the 15th gestational week. The other two patients (33.3%) had AC-based NAC during pregnancy and taxane-based chemotherapy after surgery during the postpartum period.

The median follow-up time was 36 months (range: 6–240 months), during which no local or regional recurrence was detected in either group (Table 2). The only factor that affected overall survival in the Kaplan-Meier survey analysis was the clinical tumor stage (cT I–II *vs.* cT III–IV; $p = 0.009$).

The 5-year DFS was 70.3%, and the 5-year DSS rates were 69.6% (Table 2). Significant factors associated with poor 5-year DFS in the univariate analysis were symptom

TABLE 2. Outcome in pregnancy-associated breast cancer.

Outcome	All n (%)	Pregnancy n (%)	Lactation n (%)	*p*
Locoregional recurrence	0 (0)	0 (0)	0 (0)	-
Distant organ metastasis (n = 27)	7 (25.9)	2 (16.7)/12	5 (33.3)/15	0.408
Stage IV (n = 29)	2 (6.9)	1 (7.7)/13	1 (6.3)/16	0.999
Distant organ metastasis				
Bone	3 (42.9)	1 (50)	2 (40)	
Lung	1 (14.2)	0 (0)	1 (20)	0.792
Multiple organs	3 (42.9)	1 (50.0)	2 (40.0)	
Time to metastasis				
6–12 mon	4 (57.1)	1 (50.0)	3 (60.0)	
13–24 mon	2 (28.6)	1 (50.0)	1 (20.0)	0.646
25–36 mon	1 (14.3)	0 (0)	1 (20.0)	
Death	6 (23.1)	3 (23.1)	3 (18.8)	0.999
Median follow-up	36 (11–240)	27 (11–240)	37 (12–114)	0.660
5 year-Disease Free Survival (DFS, %)	70.3	81.8	62.3	0.391
5 year-Disease Specific Survival (DSS, %)	69.6	69.9	66.7	0.689

No local or regional recurrence was detected in either group. $p < 0.05$ is statistically significant. DSS: Disease-specific survival.

duration of 6 months or longer, clinical axillary positivity, more advanced tumor stage (cT3–4), and locally advanced stages (IIB–III) and receiving NAC, as shown in Figs. 1,2 and Table 3. Notably, factors affecting DFS in the Kaplan-Meier survival analysis were the clinical tumor stage (cT1–2 *vs.* cT3–4; $p = 0.022$) and timing of diagnosis (pregnancy *vs.* lactation; $p = 0.045$) (Fig. 2). Multivariate Cox regression analysis was also performed to identify factors associated with DFS (Table 4). The identified factors were symptom duration of 6 months or longer (HR = 15.3; 95% CI: 1.6–142.7; $p = 0.017$), clinical axillary positivity (HR = 11.1; 95% CI: 1.1–107.4; $p = 0.038$), and presence of cT3–4 (HR = 6.8; 95% CI: 1.3–35.46; $p = 0.034$). Factors affecting DSS were symptom duration of 6 months or longer (HR = 12.4; 95% CI: 1.1–138.8; $p = 0.041$) and the presence of cT3–4 (HR = 10.2; 95% CI: 1.2–87.6; $p = 0.034$) (Table 4).

4. Discussion

PABC is a rare disease in our institution and worldwide, but it is one of the most common types of cancer during pregnancy with a frequency of 1 in 3000 pregnancies [1, 2]. Patients often report a painless mass after a significant amount of time has passed since its appearance, which can result in delayed diagnosis in many cases [5]. Changes in the breast or new lumps that develop during pregnancy or lactation periods can be considered normal by the patient and the medical practitioner, which may contribute to delays in diagnosis.

A review by Woo *et al.* [8], noted that older studies reported delays in diagnosis lasting as long as 6 months or more, but more recently published studies show an average delay of 1 to 2 months. However, a recent study has shown that delays in treatment including time to chemotherapy or surgery were not frequently observed [9]. In our study, 12 patients had delayed diagnoses of more than 6 months, and eight had progressed disease with nodal involvement. It is possible that, due to the more conservative nature of our population, women may take longer to consult with a breast surgeon after symptoms appear. Our study also found that the factors affecting DFS were symptom duration (6 months or more), axillary lymph node involvement, and the presence of locally advanced breast cancer. These factors are consistent with the literature, which indicates that delays in diagnosis increase the risk of axillary lymph node involvement, a sign of advanced-stage disease. Additionally, in our study, eight (28%) patients had a family history of breast cancer, and 29% of these patients in the lactation group had BRCA1/2 mutations. When comparing the pregnancy and lactation groups, a family history of breast cancer was significantly more common in the lactation group ($p = 0.044$).

If PABC is diagnosed in the first trimester, a woman should have the option to terminate the pregnancy, although it does not improve maternal prognosis or overall outcome [10]. In our study, after a thorough discussion of options, two patients diagnosed in the first trimester chose to have a therapeutic abortion. Patients with PABC were younger and tend to have more aggressive tumor characteristics and more advanced clinical stage than those non-pregnant patients, and had worse prognosis [11–13]. These characteristics include lack of ER expression as non-luminal tumor types, *i.e.*, triple negative breast cancer (TNBC), higher tumor grade, increased luminal B type (Ki-67 $\geq$20.0%), and higher tumor and nodal stages. In concordance with previous studies, we also have shown increased aggressive tumor profile including luminal B and TNBC, increased rate of axillary nodal positivity and more advanced clinical tumor stage along with increased rate of mastectomy in the present cohort.

Previous studies that investigated whether pregnancy or

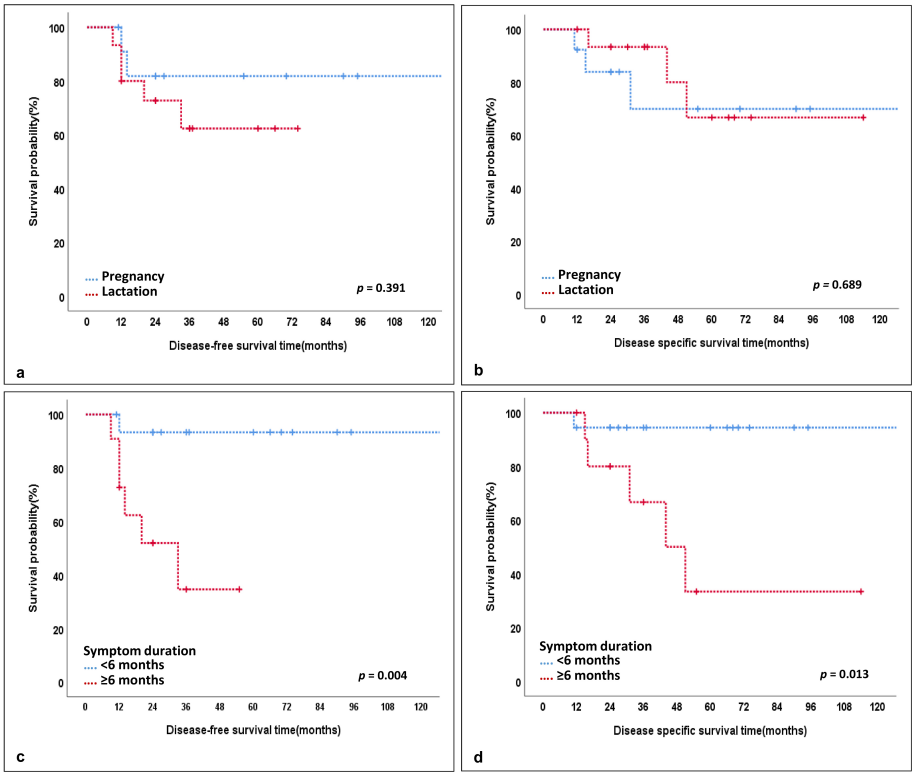

FIGURE 1. Survival outcomes according to the special condition of the disease and symptom duration time. a–b. Disease-free and disease-specific survival according to the special condition of the disease (pregnancy *vs.* lactation; $p = 0.045$). c–d. Disease-free (DFS) and disease-specific survival (DSS) according to the symptom duration time (<6 months *vs.* ≥6 months).

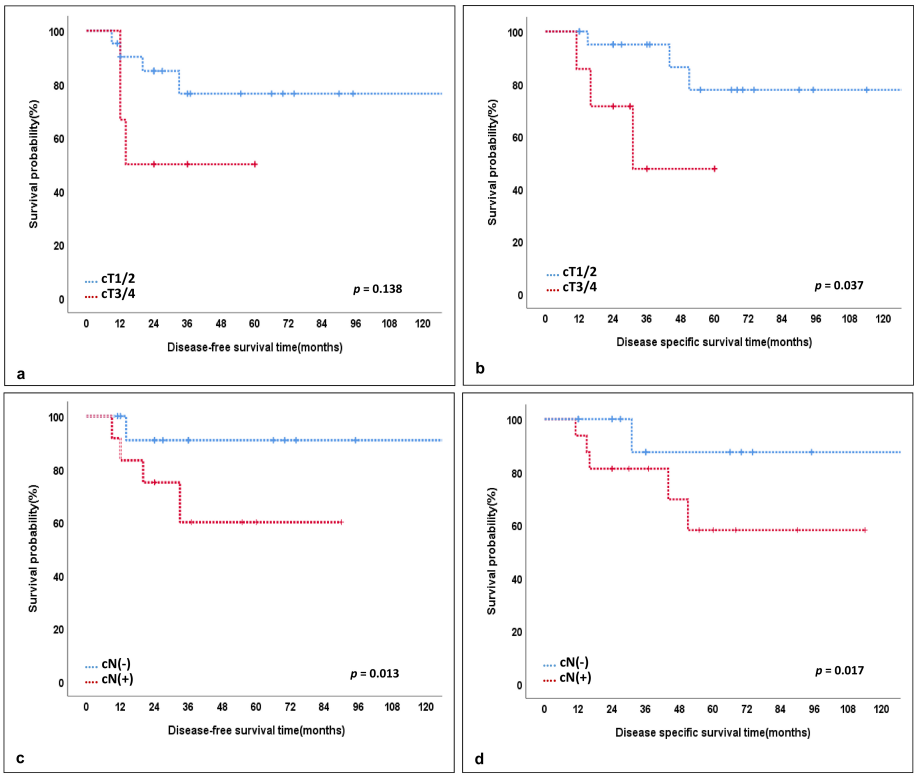

FIGURE 2. Survival outcomes based on clinical tumor stage and axillary nodal status. a. Disease-free survival rate according to the clinical tumor stage. b. Disease-specific survival rate according to the clinical tumor stage. c. Disease-free survival (DFS) rate according to the clinical axillary nodal status. d. Disease-specific survival (DSS) rate according to the clinical axillary nodal status.

TABLE 3. Factors associated with disease-free survival (DFS) and disease-specific survival (DSS).

Characteristics	Categories	Disease-free survival (DFS)		Disease-specific survival (DSS)	
		DFS (%)	*p*-value	DSS (%)	*p*-value
Age					
	≤35	71.6	0.848	74.2	0.488
	>35	71.4		83.9	
Family history (breast cancer)					
	Positive	51.4	0.323	66.7	0.629
	Negative	80.0		77.9	
Diagnosis period					
	Lactation	72.7	0.391	80.0	0.689
	Pregnancy	81.8		83.9	
Symptom duration (mon)					
	≥6 mon	51.9	0.004*	66.7	0.013*
	<6 mon	93.3		94.4	
Type of tumor					
	IDC	66.7	0.839	73.7	0.279
	Others	72.9		77.1	
cT					
	I–II	76.4	0.138	86.4	0.037*
	III–IV	66.7		71.4	
cN					
	Positive	60.0	0.013*	65.9	0.017*
	Negative	90.9		87.5	
c Stage					
	I–IIA	100.0	0.029*	100.0	0.067
	IIB–III	55.6		68.1	
NAC					
	Received	51.9	0.214	74.3	0.045*
	Not received	85.1		91.7	
Surgery type					
	Mastectomy	74.6	0.540	82.9	0.733
	Breast-conserving surgery	83.3		83.3	
Grade					
	I–II	77.8	0.690	85.7	0.920
	III	67.7		75.7	
LVI					
	Positive	77.8	0.721	78.8	0.573
	Negative	81.6		88.2	
Molecular subtype					
	Non-luminal	60.0	0.230	72.7	0.712
	Luminal	74.3		75.0	

IDC: Invasive Ductal Carcinoma.
Log-rank test was used to compare the outcome between patients with different characteristics.
**: p-value < 0.05 is statistically significant.*

TABLE 4. Multivariate Cox regression analyses of disease-free and disease-specific survival.

Factors	Categories	Disease-free survival (DFS)		Disease-specific survival (DSS)	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Symptom duration (mon)					
	≥6 mon	15.3 (1.6–142.7)	0.017*	12.4 (1.1–138.8)	0.041*
	<6 mon	1		1	
cT Stage					
	III–IV	6.8 (1.3–35.46)	0.034*	10.2 (1.2–87.6)	0.034*
	I–II	1		1	
cN Stage					
	Positive	11.1 (1.1–107.4)	0.038*	5.2 (0.4–67.5)	0.212
	Negative	1		1	

*Multivariate Cox regression analyses were performed to identify factors associated with DFS and DSS. The hazard ratios (HRs) are presented with 95% confidence intervals (CIs) and the p-value. *: p-value < 0.05 is statistically significant.*

lactation periods overlapping with breast cancer affect overall prognosis and mortality, have contradictory findings. Increasing clinical evidence have indicated that breast cancer diagnosed at the early postpartum period within one year represents a high-risk form of breast cancer in young women with a poorer survival than those diagnosed during the pregnancy period [14–17]. The aggressive tumor biology, genomic alterations, and immune escape mechanisms have been proposed for the poor prognosis associated with increased risk of metastases during the postpartum period [4, 18–20]. In a meta-analysis, Azim *et al*. [21], compared 3628 patients with PABC to 37,100 patients without it and found that the poor prognosis of PABC was primarily driven by patients with postpartum breast cancer rather than PABC diagnosed during pregnancy. However, some recent studies could not demonstrate any difference in outcome among pregnant, postpartum and non-pregnant women diagnosed with breast cancer when matched by age at diagnosis, year of diagnosis, and tumor stage [9, 22, 23]. In concordance with these reports, patients with PABC during pregnancy or postpartum have shown similar outcome in the current report. However, similar to the study by Kataoka *et al*. [15], patients of the present study in the postpartum period were more likely to have family history of breast cancer compared to those diagnosed during pregnancy.

Furthermore, there are widely conflicting results on the prognosis of PABC. Some studies showed a poorer prognosis in PABC [4, 17–20], while others reported similar survival rates to those of non-pregnant control groups [9, 22, 23]. However, the significant factors associated with poor outcome in the current study were symptom duration ≥6 months and presentation with more advanced tumor stages in concordance with previous reports that may be attributed to diagnostic delay [3, 4, 7]. Notably, patients diagnosed with PABC receiving NAC had a lower pathologic complete response (pCR) rate in our study than in other reports [24]. Therefore, novel treatment agents and NAC regimens should be investigated to increase the pCR rates in this specific patient population. Due to the increased incidence of TNBC and PD-L1 expression, immunotherapy might be a promising modality to increase the survival in this patient population [4, 18–20, 25].

Patients with PABC should be treated as closely as possible to the standard recommendations for non-pregnant young women according to the guidelines of the National Comprehensive Cancer Network [26], and Arbeitsgemeinschaft Gynakologische Onkologie-Kommission Breast [27]. However, certain options, such as adjuvant hormonal therapy, monoclonal antibody treatment (including anti-HER2 treatment), and radiotherapy, cannot be administered during pregnancy due to possible complications for the fetus [6, 26, 28]. Breast-conserving surgery (BCS) is an option for pregnant women, like for non-pregnant women. However, BCS is not recommended in the first trimester because the time between surgery and radiotherapy would be too long, which could reduce effectiveness and increase the risk of recurrence. Either mastectomy or BCS can be safely performed for pregnant women after the first trimester [26, 28].

Almost half of the patients diagnosed with clinically node negative PABC underwent SLNB during pregnancy by using low-dose Tc-99 injection as radio-tracer technique. SLNB can be safely performed during pregnancy using low-dose Tc-99 injection, but using blue-dye as SLNB technique during pregnancy is controversial due to the risk of anaphylaxis associated with blue dye [26, 28]. However, some studies did not show any adverse effects of using blue dye for SLNB [29]. After the initial diagnosis, treatment for patients with PABC should be determined by a multidisciplinary team that considers the best care for the mother while also prioritizing the well-being of the fetus.

5. Conclusions

In conclusion, managing breast cancer in pregnant and lactating patients requires the effort of a multidisciplinary team that tailors a treatment approach to each patient, which should be comparable with the treatment for non-pregnant patients in the same age group. Even if our sample size is small, our results suggest that pregnancy and lactation-associated breast cancer mostly presents with aggressive tumor molecular subtypes,

such as non-luminal HER-2 or triple-negative breast cancer, and/or with high Ki-67 scores. It is often diagnosed at a more advanced stage and associated with poor prognosis, probably due to the delayed diagnosis. Therefore, most patients may require neoadjuvant chemotherapy and more aggressive surgeries, such as mastectomies and axillary node dissections. Prompt early detection and awareness of this disease may increase the survival and the quality of life. Advances in systemic therapies may also improve the outcome. Therefore, underlying molecular mechanisms associated with poor prognosis are to be investigated how it should be effectively targeted to improve survival.

AVAILABILITY OF DATA AND MATERIALS

Authors confirm that all data underlying the findings are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

NC, IA and LDE—designed the study. IA, LDE, NC, BE and SE—performed the initial chart review, literature search, data collection and analyses, and manuscript writing. NC, SE, MT, MM, AI, VO and ASD—provided the data acquisition. All authors have read and revised the manuscript critically by making critical comments and typesetting corrections on the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and national research committees, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol has been approved by the Institutional Review Board of Istanbul University, Istanbul Faculty of Medicine, Ethical Committee, Istanbul, Turkey (No: 1107680; 2022/1312). Since the present study was retrospective, formal informed consent was not required.

ACKNOWLEDGMENT

The authors thank Atilla Bozdogan for the statistical analyses.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] de Haan J, Verheecke M, Van Calsteren K, Van Calster B, Shmakov RG, Mhallem Gziri M, *et al*. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. The Lancet Oncology. 2018; 19: 337–346.

[2] Wang B, Yang Y, Jiang Z, Zhao J, Mao Y, Liu J, *et al.* Clinicopathological characteristics, diagnosis, and prognosis of pregnancy-associated breast cancer. Thoracic Cancer. 2019; 10: 1060–1068.

[3] Choi M, Han J, Yang BR, Jang M, Kim M, Kim T, *et al.* Prognostic impact of pregnancy in Korean patients with breast cancer. The Oncologist. 2019; 24: e1268–e1276.

[4] Jerzak KJ, Lipton N, Nofech-Mozes S, Boles D, Slodkowska E, Pond GR, *et al.* Clinical outcomes and prognostic biomarkers among pregnant, postpartum and nulliparous women with breast cancer: a prospective cohort study. Breast Cancer Research and Treatment. 2021; 189: 797–806.

[5] Taylor D, Lazberger J, Ives A, Wylie E, Saunders C. Reducing delay in the diagnosis of pregnancy-associated breast cancer: how imaging can help us. Journal of Medical Imaging and Radiation Oncology. 2011; 55: 33–42.

[6] Silverstein J, Post AL, Chien AJ, Olin R, Tsai KK, Ngo Z, *et al.* Multidisciplinary management of cancer during pregnancy. JCO Oncology Practice. 2020; 16: 545–557.

[7] Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J, *et al.* Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. Journal of Clinical Oncology. 2013; 31: 2532–2539.

[8] Woo JC. Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. Archives of Surgery. 2003; 138: 91–98; discussion 99.

[9] Crown A, McCartan D, Curry MA, Patil S, Kamer S, Goldfarb S, *et al.* Pregnancy-associated breast cancer: does timing of presentation affect outcome? Breast Cancer Research and Treatment. 2023; 198: 283–294.

[10] Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, *et al.* Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. JAMA Oncology. 2015; 1: 1145–1153.

[11] Tan QT, Alcantara VS, Sultana R, Loh KW, Go AL, Wong FY. Pregnancy-associated breast cancer: a multicenter study comparing clinicopathological factors, diagnosis and treatment outcomes with non-pregnant patients. Breast Cancer Research and Treatment. 2023; 198: 53–66.

[12] Gwak H, Woo SS, Lee E, Park MH, Lee S, Youn HJ, *et al.* Survival of women with pregnancy-associated breast cancer according to clinical characteristics: a propensity score matching study. Medicine. 2022; 101: e30831.

[13] Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. Cancer. 2003; 98: 1055–1060.

[14] Lefrère H, Floris G, Schmidt MK, Neven P, Warner E, Cardonick E, *et al.* Data describing the poor outcome associated with a breast cancer diagnosis in the post-weaning period. Data in Brief. 2021; 38: 107354.

[15] Kataoka A, Ueno T, Yamauchi H, Uehiro N, Takahata C, Takahashi Y, *et al.* Characteristics, treatment trends, and long-term outcomes of Japanese patients with pregnancy-associated breast cancer (PABC). Breast Cancer. 2022; 29: 825–834.

[16] Suelmann BBM, Bakhuis CFJ, van Dooijeweert C, Verloop J, Zweemer R, Linn S, *et al.* Prognosis of pregnancy-associated breast cancer: inferior outcome in patients diagnosed during second and third gestational trimesters and lactation. Breast Cancer Research and Treatment. 2022; 192: 175–189.

[17] Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Research and Treatment. 2016; 160: 347–360.

[18] Asztalos S, Pham TN, Gann PH, Hayes MK, Deaton R, Wiley EL, *et al.* High incidence of triple negative breast cancers following pregnancy and an associated gene expression signature. SpringerPlus. 2015; 4: 710.

[19] Nimbalkar VP, Snijesh VP, Rajarajan S, Alexander A, Kaluve R, Ramesh R, *et al.* Premenopausal women with breast cancer in the early postpartum period show molecular profiles of invasion and are associated with poor prognosis. Breast Cancer Research and Treatment. 2023; 200: 139–149.

[20] Jindal S, Pennock ND, Sun D, Horton W, Ozaki MK, Narasimhan J, *et*

al. Postpartum breast cancer has a distinct molecular profile that predicts poor outcomes. Nature Communications. 2021; 12: 6341.

[21] Azim Jr HA, Botteri E, Renne G, Dell'Orto P, Rotmensz N, Gentilini O, *et al.* The biological features and prognosis of breast cancer diagnosed during pregnancy: a case-control study. Acta Oncologica. 2012; 51: 653–661.

[22] Li Y, Wang Y, Sun Q, Shen S. Clinicopathologic features, treatment, and prognosis of pregnancy-associated breast cancer. Frontiers in Oncology. 2022; 12: 978671.

[23] Johansson ALV, Andersson TM, Hsieh C, Jirström K, Cnattingius S, Fredriksson I, *et al.* Tumor characteristics and prognosis in women with pregnancy-associated breast cancer. International Journal of Cancer. 2018; 142: 1343–1354.

[24] Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, *et al.* Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. Journal of Clinical Oncology. 2008; 26: 778–785.

[25] Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, *et al.* Event-free survival with pembrolizumab in early triple-negative breast cancer. The New England Journal of Medicine. 2022; 386: 556–567.

[26] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast cancer version 4. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Accessed: 23 March 2023).

[27] Ditsch N, Kolberg-Liedtke C, Friedrich M, Jackisch C, Albert U, Banys-Paluchowski M, *et al.* AGO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2021. Breast Care. 2021; 16: 214–227.

[28] Poggio F, Tagliamento M, Pirrone C, Soldato D, Conte B, Molinelli C, *et al.* Update on the management of breast cancer during pregnancy. Cancers. 2020; 12: 3616.

[29] Han SN, Amant F, Cardonick EH, Loibl S, Peccatori FA, Gheysens O, *et al.* Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. Breast Cancer Research and Treatment. 2018; 168: 551–557.

How to cite this article: Ilkin Acar, Leman Damla Ercan, Selman Emiroglu, Mustafa Tukenmez, Baris Emiroglu, Mahmut Muslumanoglu, *et al*. Pregnancy-associated breast malignancy mostly presents with an aggressive type of breast cancer. European Journal of Gynaecological Oncology. 2023; 44(5): 1-10. doi: 10.22514/ejgo.2023.069.