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CLINICAL TRIAL

Pregnancy-associated breast cancer: a multicenter study comparing clinicopathological factors, diagnosis and treatment outcomes with non-pregnant patients

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Abstract

Purpose Pregnancy-associated breast cancer (PABC), defined as breast carcinoma diagnosed during pregnancy or in the first post-partum year, is one of the most common gestation-related malignancies with reported differences in tumor characteristics and outcomes. This multicenter study aims to review cases of PABC in Singapore, including their clinicopathological features, treatment, and clinical outcomes compared to non-PABC patients.

Methods Demographic, histopathologic and clinical outcomes of 93 PABC patients obtained from our database were compared to 1424 non-PABC patients.

Results PABC patients presented at a younger age. They had higher tumor and nodal stages, higher tumor grade, were more likely to be hormone receptor negative and had a higher incidence of multicentric and multifocal tumors. Histological examination after definitive surgery showed no significant difference in tumor size and number of positive lymph nodes suggesting similar neoadjuvant treatment effects. Despite this, PABC patients had worse outcomes with poorer overall survival and disease-free survival, OS ($P < 0.0001$) and DFS ($P < 0.0001$). Termination of pregnancy did not improve survival.

Conclusion Patients with PABC present at a higher stage with more aggressive disease and have poorer outcomes compared to non-PABC patients. Reducing delay in diagnosis and treatment may help improve survival.

Keywords Breast · Cancer · Pregnancy · Gestational

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Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast carcinoma diagnosed during pregnancy or in the first post-partum year [1]. PABC is one of the most common gestation-related malignancies, with an incidence of 1:3000–10,000 pregnancies and has been reported to comprise up to 6.6% of pregnancy-related malignancies [2–5]. It is usually detected by palpation of a breast lump, the presence of nipple discharge, or skin changes [3, 6, 7]. Mean age at diagnosis during pregnancy is 34.8 years [8]. Diagnosis is challenging during pregnancy and the immediate post-partum period due to the hormonally induced changes that may lead to increased firmness and nodularity of the breast [9]. Investigations used in the diagnosis of PABC include ultrasound of the breasts, mammography with abdominal shielding and ultrasound-guided biopsy [10]. Mammography has been reported to have decreased sensitivity during pregnancy, hence ultrasound and histological assessment alone have been recommended [11]. Computed tomographic (CT) scans and bone scans are the preferred methods for exclusion of metastatic disease but are usually avoided in pregnant patients due to their use of ionizing radiation [10].

Treatment for post-partum PABC patients is similar to that of non-pregnancy-associated breast cancer (non-PABC) patients. For pregnant patients however, radiotherapy, endocrine treatment, and targeted therapy such as trastuzumab are deferred until after delivery, while chemotherapy can be started from the second trimester [11–13]. Breast-conserving surgery or mastectomy may be performed during pregnancy after multidisciplinary discussion and close obstetric monitoring. Breast reconstruction is usually delayed until post-partum, in order to avoid prolonged anesthesia exposure and to allow optimal symmetrization of the breasts after delivery [10, 14]. Some authors have demonstrated safety and success utilizing immediate expander insertion and subsequent definitive reconstruction [15, 16]. Sentinel lymph node biopsies during pregnancy have been performed successfully using radioisotope [17]. Blue dye is avoided due to possible risk of anaphylaxis.

Survival rates between pregnant and non-pregnant women have been reported to be similar or worse for PABC [8, 18–21]. An increased risk of local recurrence has been reported in these patients [18, 25–27]. PABC has also been associated with more adverse tumor features, with tumors having a higher grade, higher frequency of hormone receptor-negative status, and higher frequency of Her2 overexpression [23,24].

Few studies regarding the prognosis of breast cancer in pregnancy in Asian patients have been published. This study aims to review cases of pregnancy-associated breast cancer in Singapore, including their clinicopathological features, treatment, and clinical outcomes as compared to non-PABC patients.

Materials and methods

This study was approved by the organizational Centralised Institutional Review Board. Female breast cancer patients aged 45 and under were identified from the breast cancer database of KK Women's and Children's Hospital (KKH), Singapore General Hospital (SGH) and National Cancer Centre Singapore (NCCS) from January 2005 to November 2017. Ninety four patients aged between 25 and 43 with breast cancer diagnosed during pregnancy or within one year post-partum were identified. Of the 93 patients included in the analyses, 52 patients were pregnant during diagnosis and 41 were post-partum. One was excluded due to early loss to follow-up and insufficient clinical data. A control group consisting of 1424 non-PABC patients aged between 16 and 45 were compared to the PABC group. Clinical, histological, and treatment data were obtained and compared between the two groups. Median follow-up was 54.5 months.

Patients in both the PABC and non-PABC groups who were diagnosed within the institution underwent routine breast imaging. Patients who were pregnant were not subjected to mammography. Staging scans were routinely done for the control group but only ultrasounds of the liver were done for pregnant patients. Staging CT scans and bone scans were deferred until post-partum. Histological confirmation using core needle biopsy was used to establish the diagnosis of cancer. A multidisciplinary team treatment approach consisting of the breast surgeon, medical oncologist, radiologist and radiation oncologist, was employed in the treatment of all patients, including the obstetric service for patients who were pregnant on diagnosis. Patients were either treated with neoadjuvant chemotherapy or definitive surgery prior to adjuvant therapy. Patients who were diagnosed during pregnancy and required chemotherapy during gestation, started treatment from the second trimester. Chemotherapy was stopped at 35 weeks of gestation to allow for recovery prior to imminent delivery. Chemotherapy was resumed after delivery. Radiation treatment was only administered to post-partum patients. Patients with Her2 enriched tumors received targeted therapy and patients with hormone receptor positive tumors were given endocrine treatment. For patients diagnosed during pregnancy, radiotherapy, targeted treatment and endocrine therapy were only administered after delivery.

Primary and secondary outcomes were overall survival (OS) and disease-free survival (DFS). Both outcomes were treated as time to event data. OS was defined as the duration between initial diagnosis of PABC or first clinic date to the last contact date or date of death, whichever was later. An

event occurred in case any death occurred otherwise patient was censored. DFS was defined as the duration between initial diagnosis date of PABC or first clinic visit due to pregnancy till the date of disease progression or death, whichever is earlier. An event occurred if there was any symptom of disease progression, otherwise was censored.

All demographic, clinical, histological and treatment related data were summarized based on whether patient had PABC or not (non-PABC). Continuous and categorical variables were summarized as mean [standard deviation (SD)] or median [interquartile range (IQR)], whichever appropriate, and frequency (percentages), respectively. Differences between PABC and non-PABC were tested using two sample *T*-test or Mann Whitney *U*-test, whichever appropriate, and Chi-Square test, respectively. For OS and DFS, survival curves were plotted using Kaplan Meier (KM) plot and differences in survival curves was analyzed using log-rank test. To find out associated risk factors for OS and DFS, separate univariate and multivariable Cox proportional regression models were fit. Final multivariable model was selected using forward, backward and stepwise variable selection method. Quantitative association from Cox regression were expressed as hazard ratio (HR) with 95% confidence interval (95%CI). *P* value < 0.05 was considered as statistical significance. All tests were two-sided. All analyses were carried out using SAS9.4.

Results

PABC patients presented at a younger age compared to non-PABC patients with a mean (SD) age of 34.7 (4.0) years old, compared to 37.8 (4.1) years old for the non-PABC group (< 0.0001). No significant differences were noted in terms of family history of cancer. PABC patients had both significantly higher tumor ($P = 0.0083$) and nodal ($P = 0.0416$) stages on presentation compared to the control group. Higher histological grade was observed among PABC patients ($P = 0.0007$) There was a greater tendency toward estrogen receptor (ER) negative ($P = 0.0242$) and progesterone receptor (PR) negative ($P = 0.0176$) status among PABC patients. Multicentric tumors ($P = 0.0434$) or multifocal tumors ($P < 0.0001$) occurred more frequently in the PABC group. There was no difference in the incidence of family history of breast cancer between the two groups. Only 13 patients underwent genetic testing (three tested positive for BRCA mutation). Tables 1, 2 and 3 describe the demographic, clinical characteristics and treatment outcomes between patients with PABC and those that are not pregnancy related.

Of the 93 patients with PABC, 52 were pregnant, with 22 being in their first trimester, 13 in their second trimester, and 17 in their third trimester. Twenty of these patients underwent termination of pregnancy, 29 had normal delivery, and one had elective caesarean section. Two cases had unknown outcomes. Thirteen patients had chemotherapy during pregnancy, receiving doxorubicin, cyclophosphamide, and taxanes. Four (30.8%) of them delivered prematurely

Table 1 Demographic characteristics between non-PABC and PABC patients

Variable	Non-PABC patients $N = 1424$	PABC patients $N = 93$	Total $N = 1517$	P value (Fisher's/*T*-test)
Age (years)				< 0.0001
Mean (SD)	37.8 (4.1)	34.7 (4.0)	37.6 (4.1)	
Min, Max	25, 43	25, 43	25, 43	
Race				< 0.0001
Chinese	939 (65.9)	45 (48.4)	984 (64.9)	
Malay	178 (12.5)	7 (7.5)	185 (12.2)	
Indian	59 (4.1)	25 (26.9)	84 (5.5)	
Others	248 (17.4)	16 (17.2)	264 (17.4)	
Family History				0.3523
N#	1272	93	1365	
No	1013 (79.6)	70 (75.3)	1083 (79.3)	
Yes	259 (20.4)	23 (24.7)	282 (20.7)	
Lump on presentation				< 0.0001
N#	920	88	1008	
No	0	5 (5.7)	5 (0.5)	
Yes	920 (100)	83 (94.3)	1003 (99.5)	

N# represents number of available patients. Categorical and continuous variables were tested using Fisher's exact test and two sample *T*—tests, respectively

(31–33 weeks age of gestation), and three (23.1%) had low birth weight (37–38 weeks age of gestation, birth weight 2316–2500 g). Of the 17 patients who did not receive chemotherapy during pregnancy, three (17.6%) had premature delivery (32–34 weeks) and one (5.9%) had low birth weight (2482 g). None had birth defects.

No differences were observed in mean tumor size ($P = 0.5895$) and number of positive axillary lymph nodes ($P = 0.1233$) between PABC and non-PABC patients after pre-operative chemotherapy.

Local recurrence among PABC patients was significantly higher ($P = 0.0268$) at 10.9% compared to the control group (5.0%). Distant recurrence was significantly higher for PABC at 17.4% compared to just 0.9% for non-PABC ($P < 0.0001$). Nodal recurrence was more frequently observed in the PABC group at 12.0% PABC compared to 1.9% for non-PABC ($P < 0.0001$). There was no difference in developing contralateral breast cancer in both groups ($P = 0.4574$). Ten out of the 52 pregnant patients (19.2%) and 11 out of the 41 post-partum PABC patients (26.8%) eventually died from breast cancer.

Kaplan–Meier analysis showed PABC patients had worse survival probability (Fig. 1, $P < 0.0001$), recurrence-free probability (Fig. 2, $P = 0.0003$), local recurrence-free probability (Fig. 3, $P = 0.0031$), nodal recurrence-free probability (Fig. 4, $P < 0.0001$), and distant recurrence-free probability (Fig. 5, $P < 0.0001$), when compared to non-PABC patients. There was no significant difference in development of contralateral breast cancer between the two groups (Fig. 6, $P = 0.1537$).

Within the PABC group, there was no significant difference in OS (Fig. 7, $P = 0.2218$) and DFS (Fig. 8, $P = 0.3420$) between patients who were pregnant upon diagnosis compared to those who were post-partum. Patients who had termination of pregnancy had no significant OS (Fig. 9, $P = 0.1359$) or DFS (Fig. 10, $P = 0.7887$) advantage compared to those who continued with their pregnancy. Race (Indian and Malay) had a negative effect on OS although this was not statistically significant (Fig. 11, $P = 0.3910$).

Univariate Cox regression analysis showed that PABC, higher tumor grade, hormone receptor-negative disease, higher tumor and nodal stage, higher TNM stage, multifocality, and Indian or Malay race were associated with a worse OS and DFS. Multivariable analysis found that having PABC and higher overall TNM stage were independently associated with worse OS and DFS. The need for neoadjuvant chemotherapy was associated with worse OS, while treatment with targeted anti-Her2 therapy was associated with better DFS. In addition, higher tumor grade and higher TNM stage, negative Her2 status were associated with worse OS. Negative ER status, higher TNM stage, and multicentricity, were associated with reduced DFS (Tables 4 and 5).

Table 2 Tumor and clinical characteristics between non-PABC and PABC patients

Variable	Non-PABC Patients $N = 1424$	PABC Patients $N = 93$	Total $N = 1517$	P value (Fisher's/*T*-test)
Histology				0.3965
DCIS	70 (4.9)	1 (1.1)	71 (4.7)	
IDC	1182 (83.0)	84 (90.3)	1266 (83.5)	
ILC	48 (3.4)	3 (3.2)	51 (3.4)	
Mucinous	58 (4.1)	2 (2.2)	60 (4.0)	
Others	66 (4.6)	3 (3.2)	69 (4.5)	
ER				0.0242
N#	1424	90	1514	
Negative	420 (29.5)	37 (41.1)	457 (30.2)	
Positive	1004 (70.5)	53 (58.9)	1057 (69.8)	
PR				0.0176
N#	1424	92	1516	
Negative	487 (34.2)	43 (46.7)	530 (35.0)	
Positive	937 (65.8)	49 (53.3)	986 (65.0)	
Her2				1.0000
N#	1424	91	1515	
Negative	1060 (74.4)	68 (74.7)	1128 (74.5)	
Positive	364 (25.6)	23 (25.3)	387 (25.5)	
Tumor Grade				0.0007
N#	1383	90	1473	
Grade 1	190 (13.7)	2 (2.2)	192 (13.0)	
Grade 2	489 (35.4)	30 (33.3)	519 (35.2)	
Grade 3	704 (50.9)	58 (64.4)	762 (51.7)	
Focality				< 0.0001
N#	1113	93	1206	
Unifocal	976 (87.7)	6 (6.5)	982 (81.4)	
Multifocal	137 (12.3)	87 (93.5)	224 (18.6)	
Centricity				0.0434
N#	1207	93	1300	
Unicentric	1176 (97.4)	87 (93.5)	1263 (97.2)	
Multicentric	31 (2.6)	6 (6.5)	37 (2.8)	
T stage				0.0083
N#	1401	93	1494	
Ti	75 (5.4)	1 (1.1)	76 (5.1)	
T1	626 (44.7)	29 (31.2)	655 (43.8)	
T2	566 (40.4)	50 (53.8)	616 (41.2)	
T3	102 (7.3)	11 (11.8)	113 (7.6)	
T4	32 (2.3)	2 (2.2)	34 (2.3)	
N stage				0.0416
N#	1401	92	1493	
N0	812 (58.0)	43 (46.7)	855 (57.3)	
N1	344 (24.6)	24 (26.1)	368 (24.6)	
N2	148 (10.6)	12 (13.0)	160 (10.7)	
N3	97 (6.9)	13 (14.1)	110 (7.4)	

N# represents number of available patients. Categorical and continuous variables were tested using Fisher's exact test and two sample *T*—tests,

Table 2 (continued)

respectively

Table 3 Treatment outcomes between non-PABC and PABC patients

Variable	Non-PABC Patients $N=1424$	PABC Patients $N=93$	Total $N=1517$	P value (Fisher's/*T*-test)
Tumor Size (cm)				0.5895
N#	1424	92	1516	
Mean (SD)	2.6 (2.09)	2.8 (2.37)	2.11 (1.9)	
Median (IQR)	2.1 (1.9)	2.3 (2.3)	2.1 (1.9)	
No. of positive nodes				0.1233
N#	1377	88	1465	
Mean (SD)	2.3 (5.28)	3.3 (5.82)	2.3 (5.32)	
Median (IQR)	0.0 (2.0)	1.0 (3.5)	0.0 (2.0)	
Min, Max	0, 73	0, 26	0, 73	
IBTR				0.8174
N#	1424	92	1516	
No	1341 (94.2)	86 (93.5)	1427 (94.1)	
Yes	83 (5.8)	6 (6.5)	89 (5.9)	
Nodal recurrence				< 0.0001
N#	1424	92	1516	
No	1397 (98.1)	81 (88.0)	1478 (97.5)	
Yes	27 (1.9)	11 (12.0)	38 (2.5)	
Subsequent Contralateral breast cancer				0.5099
N#	1424	92	1516	
No	1388 (97.5)	89 (96.7)	1477 (97.4)	
Yes	36 (2.5)	3 (3.3)	39 (2.6)	
Distant recurrence				< 0.0001
N#	1424	92	1516	
No	1411 (99.1)	76 (82.6)	1487 (98.1)	
Yes	13 (0.9)	16 (17.4)	29 (1.9)	
Local Recurrence				0.0268
N#	1424	92	1516	
No	1353 (95.0)	82 (89.1)	1435 (94.7)	
Yes	71 (5.0)	10 (10.9)	81 (5.3)	

N# represents number of available patients. Categorical and continuous variables were tested using Fisher's exact test and two sample *T*—tests, respectively

Discussion

Studies involving pregnancy-associated breast cancer usually have limited subjects and few have compared pregnant to post-partum PABC patients. There is also a paucity of studies examining PABC patients in Southeast Asia.

While Amant [20] and Murphy et al. [22] reported no differences in survival outcomes between the two groups. Our study showed that PABC patients had a worse OS and DFS compared to non-PABC patients which is in accordance to findings reported by other authors [18, 28, 29]. As there is no significant difference in histology type, this result could be due to PABC patients having larger tumors, a higher incidence of nodal metastasis on diagnosis, higher grade and a greater likelihood to hormone receptor negativity. PABC tumors have a greater tendency to be triple negative but luminal B tumors have also been found to be common among these patients [30, 31]. Increased breast density due to pregnancy and breastfeeding make clinical examination and imaging challenging potentially contributing to a delay in diagnosis for PABC patients [21]. PABC patients in our study had a mean symptom duration of 135 days before being seen by a breast surgeon. Pregnancy at diagnosis is a strong predictor of delaying initial treatment in PABC patients mainly from concerns over fetal well-being and

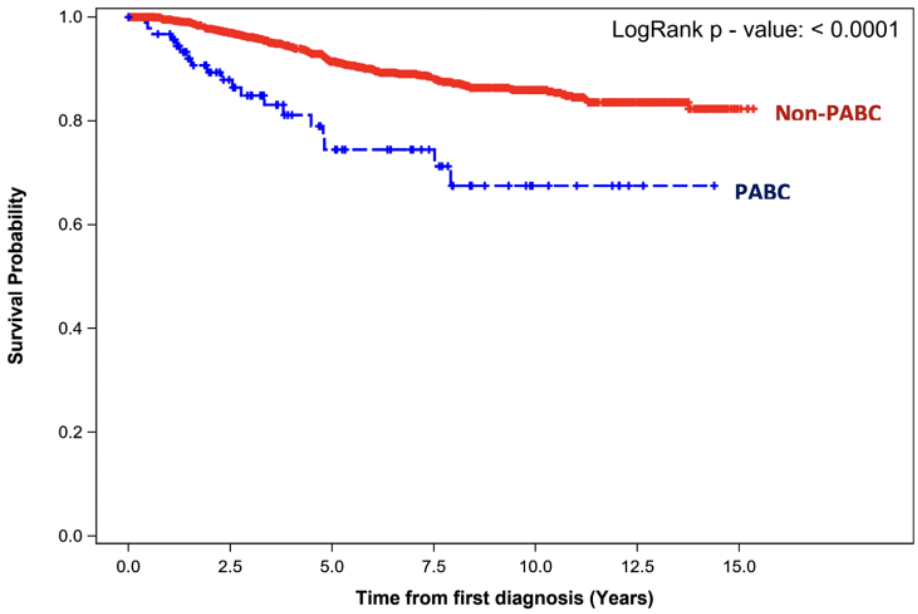

Fig. 1 Overall survival between breast cancer patients with pregnancy-associated breast cancer (PABC) and non-PABC patients

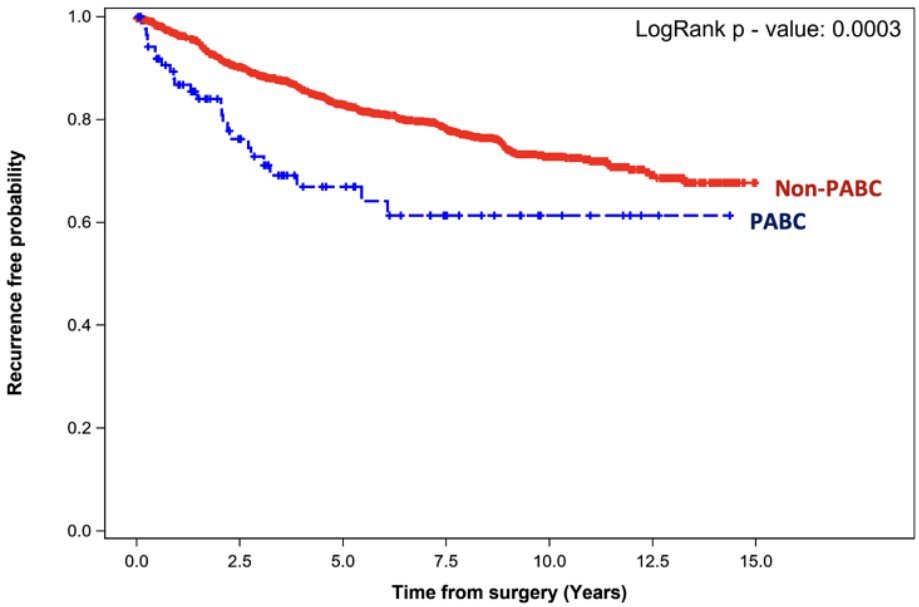

Fig. 2 Disease-free survival between breast cancer patients with pregnancy-associated breast cancer (PABC) and those that are not pregnancy-associated

attribution of symptoms as related to pregnancy changes [32, 33]. PABC patients in this study had a mean duration of 55 days from day of diagnosis to the day of treatment initiation.

With a greater propensity toward higher stage and hormone receptor negativity, PABC patients were more likely receive neoadjuvant chemotherapy. In our study, the lack of significant difference in tumor size and nodal positivity after definitive surgery between PABC and non-PABC patients despite PABC patients having significantly higher T and N stage at diagnosis suggests that neoadjuvant therapy yields comparable effects in both groups. However, the eventual poorer disease-free and overall survival outcomes in PABC patients suggests that the other tumor factors or possibly the presence of gestational hormones [21] may also be responsible for the poorer outcomes. The detrimental effects of higher disease stage on diagnosis in PABC patients could potentially be mitigated by earlier referral to a breast cancer specialist and expedited diagnosis and treatment of cancer.

Local, regional and distant recurrence were significantly higher in the PABC group, which further demonstrated the aggressive nature of PABC tumors. Genin et al., have reported contrasting results finding no difference in OS and DFS between the two groups and that PABC patients had a higher risk of local relapse but not distant recurrence [27].

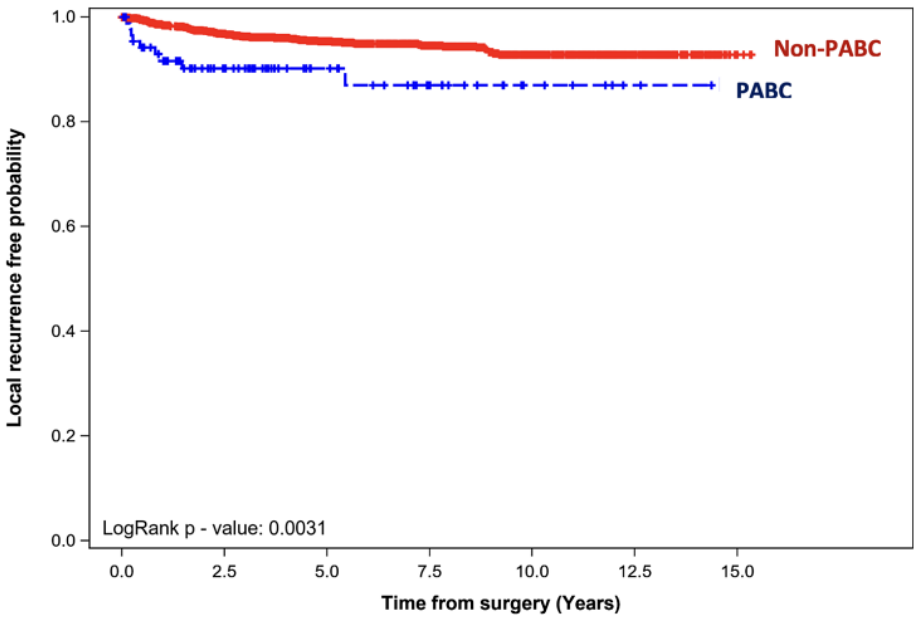

Fig. 3 Local recurrence between patients with pregnancy-associated breast cancer (PABC) and those with breast cancer that are not associated with pregnancy

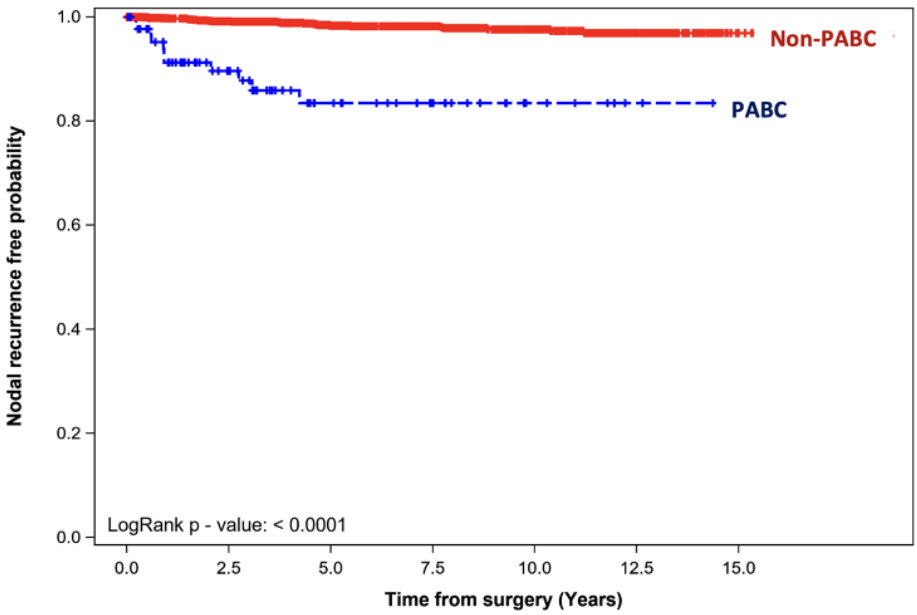

Fig. 4 Regional recurrence between patients with pregnancy-associated breast cancer and non-pregnancy-associated breast cancer patients

Contralateral breast cancer has a cumulative incidence of 5.5% for women less than 45 years old [34]. Although the transient increase in breast cancer following pregnancy was found to peak 6 years after delivery and persists up to 10 years post-partum [21], the tendency for developing contralateral breast cancer in our population was the same for both PABC and non-PABC patients and had also been observed in previous studies [27]. This could be due to the fact that by the time PABC patients develop contralateral breast cancer, the effects of pregnancy are no longer present.

While differences in race did not have a significant difference in terms of OS among PABC patients, the general population sample in our study showed that Malay or Indian race was associated with worse OS and DFS on univariate analysis. Studies regarding the effect of race on PABC have been lacking mainly because of the small sample size of most studies. Malay women in Singapore have been reported to demonstrate poorer 5 and10-year OS and DFS rates compared to other races [35]. In studies outside of Asia, it has been reported that PABC patients are more likely to be of non-Caucasian race [32].

Among the PABC patients, there was no significant difference between the OS of patients diagnosed during pregnancy compared to those who were diagnosed post-partum, which is consistent with the results of Muñoz et al. [36]. Our findings were also congruent with the results of Genin

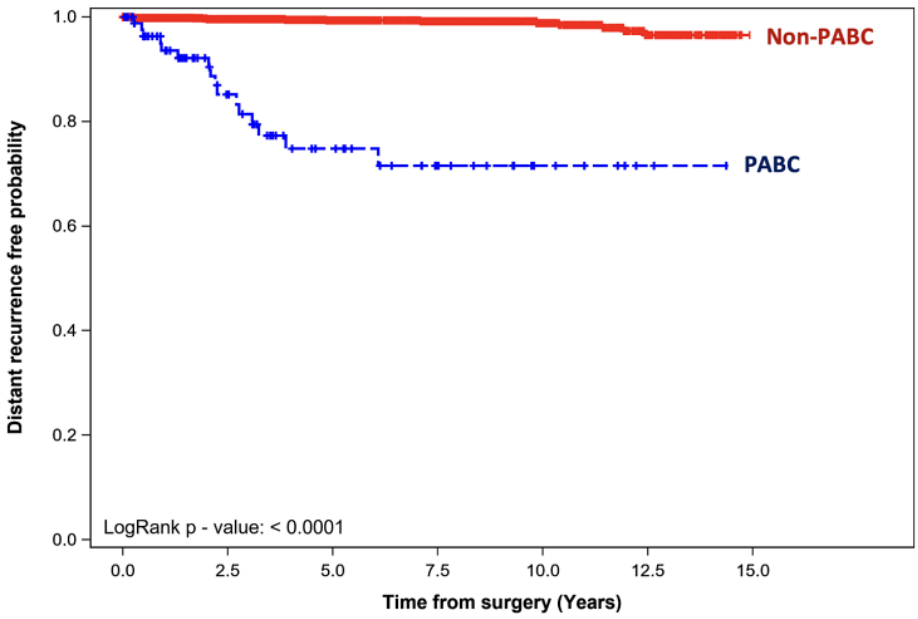

Fig. 5 Comparison between the distant recurrence between patients with pregnancy-associated breast cancer (PABC) and non-PABC patients

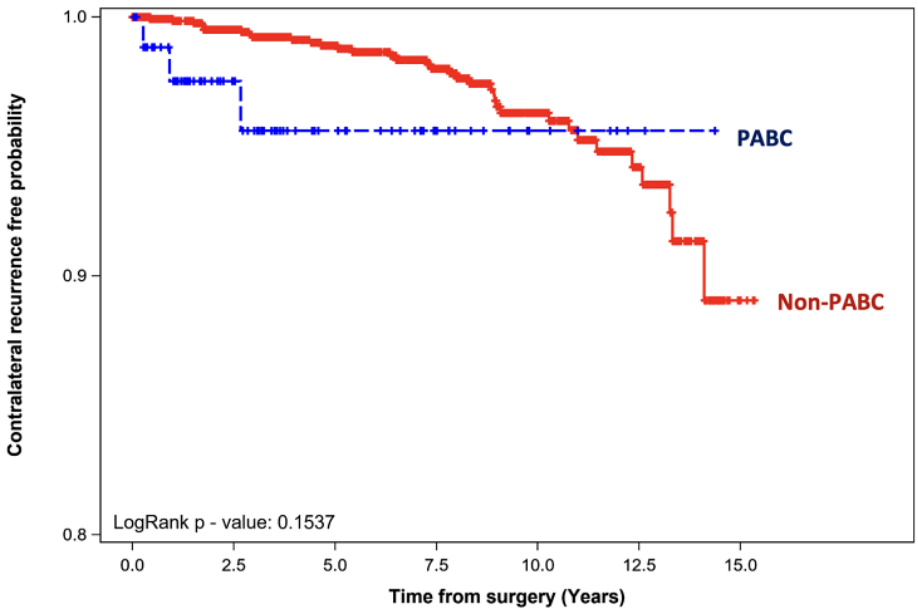

Fig. 6 Contralateral breast cancer between patients with pregnancy-associated breast cancer (PABC) and non-PABC patients

et al., where there was no difference in tumor characteristics between the pregnant PABC patients when compared to ones from post-partum PABC patients [23]. Our results concur with previous studies which state that terminating pregnancy during diagnosis of breast cancer did not confer any significant survival advantage over those who delivered [30, 37].

The fetal complications encountered in our study included prematurity and intrauterine growth retardation (IUGR). It has been observed that pregnant patients who received chemotherapy had a significantly higher risk of preterm delivery [38]. Low birth weight, however, was not significantly different from that of the general population. In a population-based study by Schechter et al., they found that pregnancies complicated by breast cancer have a fivefold greater risk of preterm delivery, twofold greater likelihood of preterm premature rupture of membranes, but no difference in risk of IUGR, congenital anomalies, or intrauterine fetal death when compared to women without breast cancer [5]. However, they were unable to directly correlate these findings with receipt of chemotherapy and they did not include data on pregnancies that were terminated. Ring et al. did not report fetal abnormalities from patients who received chemotherapy during the second or third trimester of pregnancy [13]. Likewise, no congenital defects were recorded in our study.

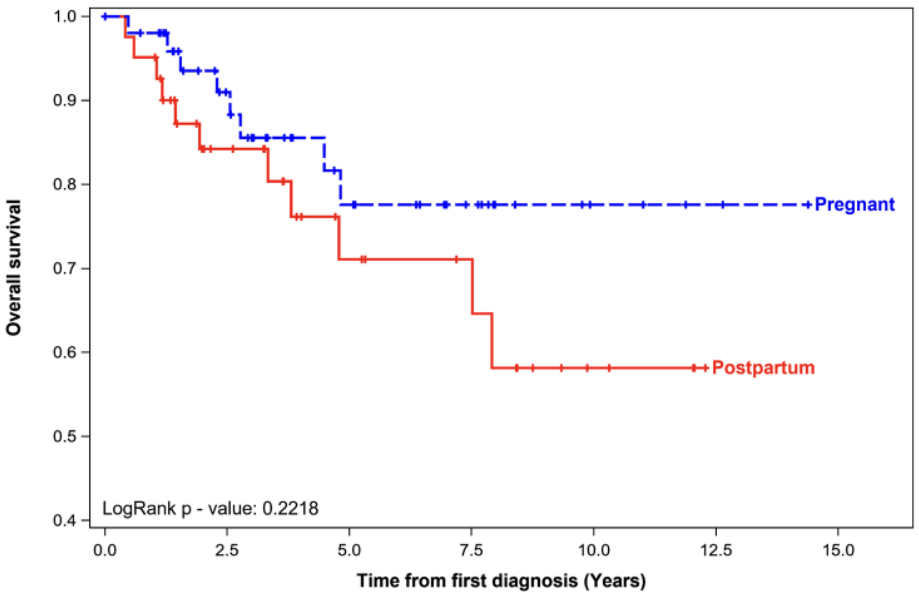

Fig. 7 Difference in overall survival among pregnancy-associated breast cancer patients who were pregnant at diagnosis compared to those who were post-partum

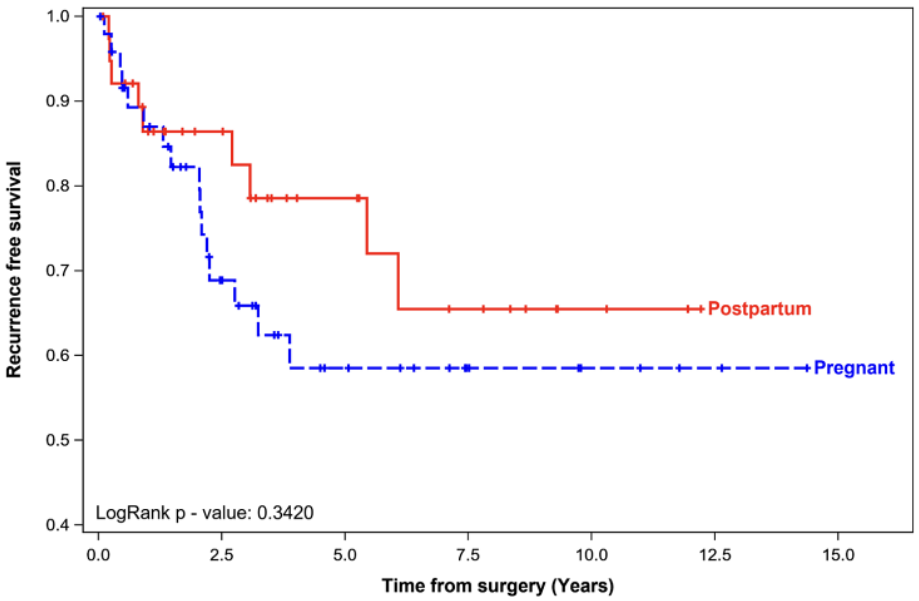

Fig. 8 Difference in disease-free survival among pregnancy-associated breast cancer patients who were pregnant at diagnosis compared to those who were post-partum

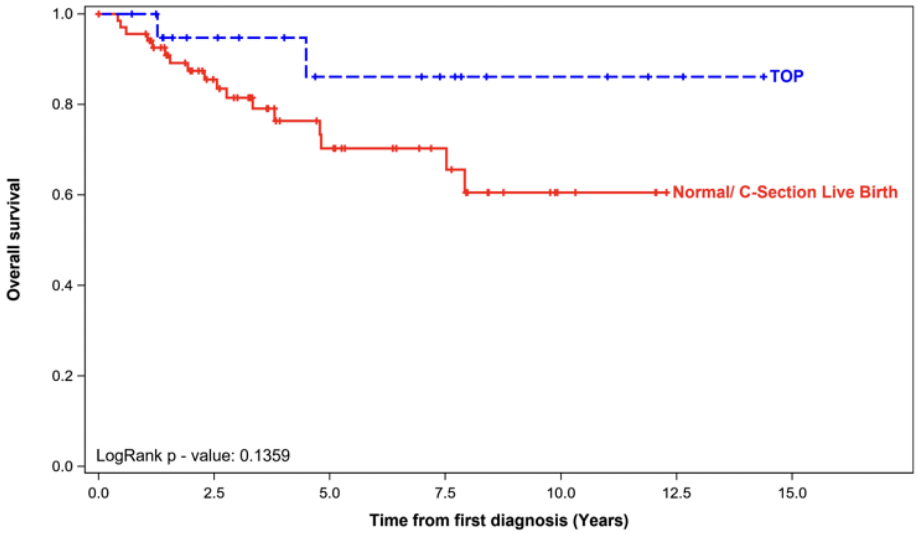

Fig. 9 Comparison based on the overall survival between patients who terminated their pregnancy upon diagnosis of breast cancer to those who continued with their pregnancy during treatment

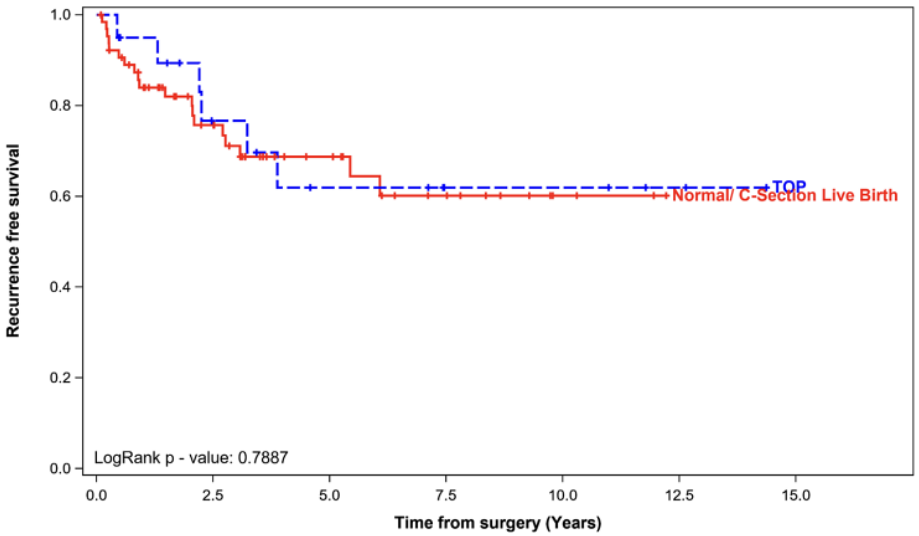

Fig. 10 Disease-free survival between pregnant patient who terminated their pregnancy upon diagnosis of breast cancer compared to those who continued with their pregnancy during treatment

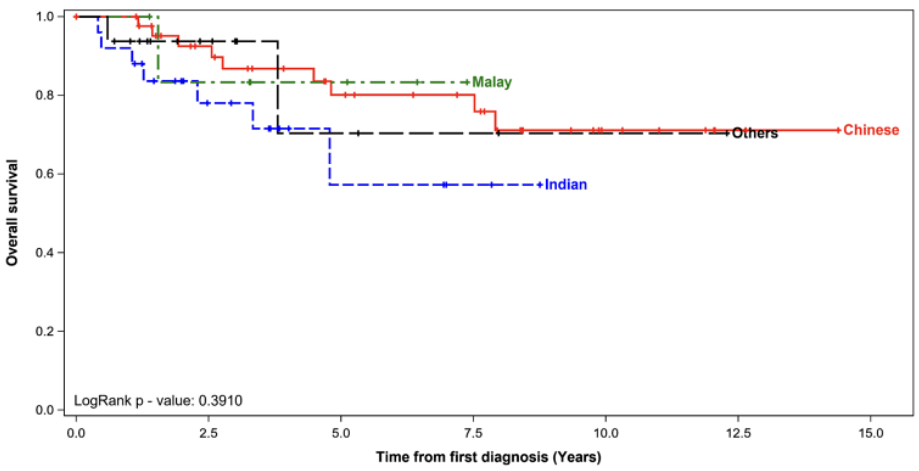

Fig. 11 Comparison in overall survival between races among pregnancy-associated breast cancer patients

Table 4 Univariate and multivariable Cox regression analysis for overall survival

Variables	Unadjusted hazard ratio (95%CI)	*P* value	Adjusted hazard ratio (95%CI)	*P* value
Age (years)	0.96 (0.93, 0.99)	0.0202		
Race (Ref = Chinese)		< 0.0001 +		
Malay	2.70 (1.82, 4.02)	< 0.0001		
Indian	3.20 (1.96, 5.25)	< 0.0001		
Others	0.81 (0.44, 1.48)	0.4930		
Pregnancy associated (Ref = No)				
Yes	2.95 (1.82, 4.77)	< 0.0001	1.76 (1.06, 2.93)	0.0291
Histology (Ref = Invasive ductal carcinoma)		0.0341 +		
Invasive lobular carcinoma	1.01 (0.45, 2.29)	0.9772		
Mucinous carcinoma	0.36 (0.11, 1.12)	0.0764		
Other types	0.74 (0.30, 1.80)	0.5071		
Ductal carcinoma in situ	0.10 (0.01, 0.73)	0.0233		
Estrogen receptor status (Ref = Positive)				
Negative	2.83 (2.08, 3.86)	0.0001		
Progesterone receptor status (Ref = Positive)				
Negative	2.54 (1.86, 3.46)	0.0001		
Her2 status (Ref = Positive)				
Negative	1.47 (0.99, 2.19)	0.0555	2.51 (1.62, 3.90)	< 0.0001
Grade (Ref = Grade 1)		< 0.0001 +		0.0068 +
Grade 2	8.17 (1.98, 33.70)	0.0037	4.7 (1.29, 17.15)	0.0192
Grade 3	16.16 (3.99, 65.44)	0.0001	6.69 (1.84, 24.28)	0.0039
T stage (Ref = T1)		< 0.0001 +		0.0119 +
T2	3.13 (2.10, 4.66)	< 0.0001	1.69 (0.98, 2.90)	0.0595
T3	5.38 (3.23, 8.97)	< 0.0001	2.25 (1.18, 4.31)	0.0142
T4	12.79 (6.73, 24.28)	< 0.0001	3.46 (1.58, 7.56)	0.0019
N stage (Ref = N0)		< 0.0001 +		
N1	2.04 (1.36, 3.05)	0.0005		
N2	4.09 (2.67, 6.25)	0.0001		
N3	5.60 (3.52, 8.92)	0.0001		
TNM stage (Ref = Stage 1)		< 0.0001 +		< 0.0001 +
Stage 2	3.40 (1.96, 5.90)	0.0001	1.43 (0.69, 3.00)	0.3383
Stage 3	8.14 (4.74, 13.98)	0.0001	3.18 (1.49, 6.76)	0.0027
Stage 4	29.67 (12.67, 69.50)	0.0001	8.98 (3.05, 26.45)	0.0001
Stage 0/DCIS	0.40 (0.05, 3.02)	0.3744	0.07 (0.003, 1.88)	0.1129
Focality (Ref = Unifocality)				
Multifocality	1.92 (1.31, 2.81)	0.0008		
Centricity (Ref = Unicentric)				
Multicentric	0.50 (0.12, 2.02)	0.3292		
Neoadjuvant chemotherapy (Ref = No)				
Yes	3.12 (2.15, 4.54)	< 0.0001	2.24 (1.47, 3.40)	0.0002
Adjuvant chemotherapy (Ref = No)				
Yes	0.98 (0.70,1.37)	0.9101		
Adjuvant radiotherapy (Ref = No)				
Yes	0.94 (0.66, 1.33)	0.7235	0.39 (0.27, 0.56)	< 0.0001
Adjuvant targeted therapy (Ref = No)				
Yes	0.74 (0.47, 1.15)	0.1789		
Adjuvant hormonal therapy (Ref = No)				
Yes	0.35 (0.26, 0.49)	< 0.0001		

+ Type 3 or omnibus *P* value

Table 5 Univariate and multivariable Cox regression analysis for disease-free survival

Variables	Unadjusted hazard ratio	*P* value	Adjusted hazard ratio	*P*-value
Age	0.954 (0.93, 0.98)	0.0004		
Race (Ref = Chinese)		< 0.0001 +		
Malay	2.23 (1.63, 3.04)	< 0.0001		
Indian	2.27 (1.49, 3.45)	0.0001		
Other	1.16 (0.81, 1.67)	0.4162		
Pregnancy associated (Ref = No)				
Yes	2.10 (1.39, 3.16)	0.0004	1.7 (1.11, 2.60)	0.0147
Histology (Ref = Invasive ductal carcinoma)		0.6003		
Invasive lobular carcinoma	0.96 (0.51, 1.81)	0.9012		
Mucinous carcinoma	0.86 (0.48 1.53)	0.5954		
Other types	0.67 (0.33, 1.35)	0.2626		
Ductal carcinoma in situ	0.71 (0.40, 1.26)	0.2376		
Estrogen receptor status (Ref = Positive)				
Negative	1.64 (1.29, 2.07)	< 0.0001	1.77 (1.35, 2.32)	< 0.0001
Progesterone receptor status (Ref = Positive)				
Negative	1.48 (1.17, 1.87)	0.0010		
Her2 status (Ref = Positive)				
Negative	1.30 (0.98, 1.73)	0.0662		
Grade (Ref = Grade 1)		< 0.0001		
Grade 2	2.62 (1.53, 4.51)	0.0005		
Grade 3	3.47 (2.05, 5.89)	< 0.0001		
T stage (Ref = T1)		< 0.0001 +		
T2	1.65 (1.27, 2.13)	0.0002		
T3	2.54 (1.73, 3.73)	< 0.0001		
T4	5.03 (2.76, 9.16)	< 0.0001		
N stage (Ref = N0)		< 0.0001 +		
N1	1.41 (1.07, 1.87)	0.0158		
N2	2.24 (1.61, 3.10)	< 0.0001		
N3	3.10 (2.14, 4.48)	< 0.0001		
TNM stage (Ref = Stage 1)		< 0.0001 +		< 0.0001 +
Stage 2	1.55 (1.13, 2.12)	0.0064	1.50 (1.05, 2.16)	0.0274
Stage 3	3.12 (2.28, 4.28)	< 0.0001	3.69 (2.58, 5.27)	< 0.0001
Stage 4	44.36 (23.07, 85.29)	< 0.0001	51.29 (26.14, 100.66)	< 0.0001
Stage 0/DCIS	1.26 (0.68, 2.34)	0.4660	1.33 (0.66, 2.71)	0.4264
Focality (Ref = Unifocality)				
Multifocality	1.50 (1.11, 2.03)	0.0088		
Centricity (Ref = Unicentric)				
Multicentric	1.78 (0.97, 3.27)	0.0607	2.20 (1.21, 4.03)	0.0104
Neoadjuvant chemotherapy (Ref = No)				
Yes	1.95 (1.41, 2.71)	0.0001		
Adjuvant chemotherapy (Ref = No)				
Yes	1.10 (0.85,1.43)	0.4593		
Adjuvant radiotherapy (Ref = No)				
Yes	1.02 (0.78, 1.32)	0.9114		
Adjuvant targeted therapy (Ref = No)				
Yes	0.69 (0.50, 0.97)	0.0310	0.46 (0.32, 0.67)	< 0.0001
Adjuvant hormonal therapy (Ref = No)				
Yes	0.62 (0.49, 0.79)	0.0001		

+ Type 3 or omnibus *P* value

To our knowledge, this is the first multicenter study in Southeast Asia examining the characteristics and outcomes of PABC. The limitations of our study include retrospective nature, small sample size of pregnant patients, limited access to infant data and loss to follow up. Due to the relatively low incidence of PABC larger scale studies on an international level would increase the study population and enable investigators to reach more nuanced conclusions regarding this challenging disease.

Conclusion

Patients with PABC had worse recurrence and survival outcomes compared to non-PABC patients, likely due to higher stage at diagnosis. Diagnosis of cancer during or after pregnancy did not affect survival and termination of pregnancy did not improve survival. Tumor size and axillary nodal involvement after surgery did not differ significantly between PABC and non-PABC patients suggesting comparable effects of neoadjuvant treatment in both groups. Delay in diagnosis and treatment could be a contributing factor to poorer outcomes. Greater awareness among women and their healthcare specialists may help to expedite diagnosis and treatment and improve outcomes by actively investigating pregnant and breastfeeding patients who report a new breast lump.

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Declarations

Conflict of interests The authors have no relevant financial or non-financial interests to disclose.

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