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CLINICAL TRIAL

Clinical subtypes and prognosis of pregnancy-associated breast cancer: results from the Korean Breast Cancer Society Registry database

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Abstract

Purpose We analyzed the clinicopathologic characteristics and prognosis of pregnancy-associated breast cancer (PABC) according to clinical subtypes to better understand the characteristics of PABC.

Methods A total of 83,792 female patients between the ages of 20 and 49 were enrolled in the Korean Breast Cancer Society Registry database from January 1, 1996 to December 31, 2015. 'PABC' is defined as breast cancer diagnosed during pregnancy or within 1 year after delivery. Other patients were defined as 'non-PABC' patients.

Results In non-PABC patients, luminal A subtype was the most common (50.2%). In PABC patients, TNBC was the most common (40.4%) subtype, while luminal A comprised 21.2% and HER2 subtype comprised 17.3%. There was a significant difference in overall survival (OS). In non-PABC patients, TNBC had the highest HR (HR 2.3, 95% CI 2.1–2.6). In PABC patients, the luminal B subtype (HR+ HER2-high Ki67) had the highest HR at 7.0 (95% CI 1.7–29.1). In multivariate analysis of OS by subtypes, PABC patients had significantly higher HR than non-PABC patients in the HER2 subtype (HR 2.0, 95% CI 1.1–3.7) and luminal B subtype (HR+ HER2-high Ki67) (HR 4.4, 95% CI 1.6–12.3).

Conclusion PABC showed different biologic features than non-PABC. PABC had a particularly poor prognosis in the luminal B (HR+ HER2-highKi67) and HER2 subtypes. To improve the prognosis of PABC, treatment should be considered according to subtype. Development of drugs that can be used during pregnancy is needed.

Keywords Pregnancy · Breast cancer · Subtype · Prognosis

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Introduction

Although its definition varies widely, pregnancy-associated breast cancer (PABC) refers to breast cancer diagnosed during pregnancy or after delivery, including breast cancer diagnosed within 1 year after delivery. PABC is rare and comprises 0.2–0.4% of all breast cancers [1, 2]. However, it is the most common cancer in pregnancy, and is diagnosed in about 1 of 3000 pregnancies [3].

Recent literature regarding PABC is inconsistent, but a recent meta-analysis showed that PABC has poor prognosis [4–6]. Young women are not commonly screened for breast cancer, and diagnosis is difficult due to changes to the breast during pregnancy. Furthermore, treatment is limited due to concerns for fetal safety. These are considered the main causes of poor prognosis in PABC [7, 8].

Recent studies have found high overexpression of human epidermal growth receptor 2 (HER2) and low expression of estrogen receptor (ER) and progesterone receptor (PR) in PABC [5, 6, 9]. Young women with breast cancer have a high frequency of triple-negative breast cancer (TNBC) and HER2 subtype, resistance to tamoxifen, high relapse and mortality rates, and poor prognosis [10]. However, it is not clear whether the poor prognosis is due to the high frequency of these subtypes or due to the characteristic biology of breast cancer in young women.

Pregnancy and childbirth in women of childbearing age are significant events, both socially and personally. Pregnancy, childbirth, and breastfeeding are also major physiologic changes in the breast. It is not clear whether the poor prognosis of patients with PABC is due to the characteristics of breast cancer or the influence of pregnancy. This study was initiated to understand the characteristics of PABC by analyzing its pathological features and prognosis while considering clinical subtypes.

Methods

Korean Breast Cancer Society Registry (KBCSR)

The Korean Breast Cancer Society Registry (KBCSR) was established in 1996. More than 100 hospitals participate in the nationwide breast cancer registry data management program, which contains hospital-based breast cancer registry data. The KBCSR program includes a variety of clinicopathologic factors, treatment data, and research resources. Further information on the KBCSR database is described in a previous study [10].

Patients

Among 158,740 patients enrolled in the KBCSR database from January 1, 1996 to December 31, 2015, 83,792 female patients between the ages of 20 and 49 were enrolled in this study. 'PABC' is defined as breast cancer diagnosed during pregnancy or within 1 year after delivery. Patients who did not meet these criteria were defined as 'non-PABC' patients.

Clinical subtypes

Patients were classified into five groups according to tumor subtype. (1) Luminal A: hormonal receptor (HR, ER and/or PR) positive and HER2 negative; (2) luminal B (with high Ki67): HR positive and HER2 negative and Ki67 $\geq$ 14.0%; (3) luminal B (with HER2): HR positive and HER2 postive; (4) triple-negative breast cancer (TNBC): ER negative, PR negative, and HER2 negative; and (5) HER2 subtype: HR negative and HER2 positive.

Statistical methods

Clinicopathologic characteristics were analyzed using the Pearson χ^2 test. Overall survival (OS) was based on the date of diagnosis and the date of death; the latter was recorded from data of the Ministry of Health and Welfare, Republic of Korea. A Kaplan–Meier curve was used for univariate analysis, and the Cox proportional hazards model (95% confidence interval, CI) was used for multivariate analysis. Differences were considered significant with $P < 0.05$. IBM SPSS Statistics, version 20.0 was used for statistical analysis (IBM Inc, Chicago, IL).

This study was approved by the institutional review board of Korea University Anam Hospital.

Results

Clinicopathologic characteristics of patients with PABC

The clinicopathologic characteristics of PABC and non-PABC patients are shown in Table 1. With PABC, patients in their 30s were the most common. With non-PABC, patients in their 40s were the most common. Patients with PABC had a higher percentage of stage III and IV and a higher percentage of high nuclear grade (NG, 63.1% vs. 37.3%) than non-PABC patients. In non-PABC patients, Luminal A subtype was the most common (50.2%) and TNBC comprised 16.4% of cases. In PABC patients,

Table 1 Clinicopathologic characteristics of PABC patients and non-PABC patients

	Non-PABC ($n=83,381$)	%	PABC ($n=411$)	%	*P*
Age					
20–29	2057	2.5	50	12.2	< 0.001
30–39	20,628	24.7	313	76.2	
40–49	60,696	72.8	48	11.7	
Family history					
Yes	5571	9.4	50	13.4	< 0.001
No	53,714	90.6	322	86.6	
Unknown	24,096		39		
Menarche					
≤ 13 years	15,375	29.4	173	48.3	< 0.001
> 13 years	36,849	70.6	185	51.7	
Unknown	31,157		53		
First delivery					
≥ 30 years	8544	21.2	142	44.8	< 0.001
< 30 years	31,681	78.8	175	55.2	
Unknown	43,156		94		
Operation (breast)					
Mastectomy	36,036	43.6	199	48.8	< 0.001
BCS	45,949	55.6	193	47.3	
No op	594	0.7	16	3.9	
Unknown	802		3		
Operation (axillary)					
ALND	37,407	45.5	235	57.2	< 0.001
SLN biopsy	37,107	45.1	145	35.3	
No op	7674	9.3	31	7.5	
Unknown	1193		0		
Stage					
O	9959	12.3	16	4.0	< 0.001
I	29,338	36.3	92	22.9	
II	30,926	38.2	186	46.3	
III	9487	11.7	85	21.1	
IV	1148	1.4	23	5.7	
Unknown	2523		9		
Nuclear grade					
Low/intermediate	34,953	62.7	110	36.9	< 0.001
High	20,802	37.3	188	63.1	
Unknown	27,626		113		
Histology					
IDC	61,073	84.3	366	94.8	< 0.001
ILC	2219	3.1	4	1.0	
DCIS	9074	12.5	16	4.1	
etc.	59	0.1	0	0.0	
Unknown	10,956		25		
ER					
Positive	50,452	70.5	143	38.6	< 0.001
Negative	21,145	29.5	227	61.4	
Unknown	11,784		41		
PR					
Positive	46,932	66.1	126	34.2	< 0.001
Negative	24,027	33.9	242	65.8	

Table 1 (continued)

	Non-PABC ($n=83,381$)	%	PABC ($n=411$)	%	*P*
Unknown	12,422		43		
HER2					
Positive	12,649	21.6	91	29.4	< 0.001
Negative	45,880	78.4	218	70.6	
Unknown	24,852		102		
Subtypes					
Luminal A	31,642	50.6	65	21.2	< 0.001
Luminal B (HER2+)	7937	12.7	37	12.1	
TNBC	10,230	16.4	124	40.4	
HER2	5720	9.1	53	17.3	
Luminal B (high Ki67)	7017	11.2	28	9.1	
Unknown	20,835		104		
Chemotherapy					
Yes	47,431	68.7	345	88.5	< 0.001
No	21,604	31.3	45	11.5	
Unknown	14,346		21		
Chemotherapy					
Neoadjuvant	4502	10.1	61	18.2	< 0.001
Adjuvant	39,422	88.9	265	79.1	
Palliative	443	1.0	9	2.7	
Unknown	3064		10		
Radiotherapy					
Yes	43,391	65.0	230	63.2	0.464
No	23,342	35.0	134	36.8	
Unknown	16,648		47		

BCS breast conserving surgery, *ALND* axillary lymph node dissection, *SLN* sentinel lymph node, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in site, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer

TNBC was the most common subtype (40.4%), while luminal A comprised 21.2% and HER2 subtype comprised 17.3% of cases.

The differences in clinicopathologic characteristics between PABC and non-PABC were also different according to age group. In non-PABC patients, the proportion of luminal A was the highest in patients in their 20s and 30s (42–43%). In PABC patients, TNBC was the most common subtype (42–48%). In patients in their 40s, luminal A comprised 48.3% of cases and TNBC comprised 17.2% in PABC patients, which was not significantly different from non-PABC patients.

In univariate analysis for OS, PABC patients had a lower survival rate than non-PABC patients. In multivariate analysis adjusted for age, stage, and subtype, PABC had 1.3-fold increased risk compared to non-PABC. After adjusting for age, stage, NG, and subtype in multivariate analysis, there was no difference in risk between PABC and non-PABC patients (Table 2).

Survival analysis according to subtype

In univariate analysis for OS, luminal B (with HER2+) subtype showed no difference in survival rates for PABC and non-PABC. However, PABC patients had worse survival than non-PABC patients in all other subtypes. After adjusting for age, stage, NG, and subtype in multivariate analysis, the risk of PABC was higher in HER2 subtype and luminal B subtype (with high Ki67) than in non-PABC (Table 2; Fig. 1).

Prognostic factors in PABC and non-PABC patients

The non-PABC and PABC groups showed differences in prognostic factors as a result of multivariate analysis for OS. There was a significant difference in risk between subtypes. For non-PABC patients, TNBC showed the highest risk (Hazard ratio, HR 2.3, 95% CI 2.1–2.6). In PABC patients, luminal B (with high Ki67) had the highest HR of 7.0 (95% CI 1.7–29.1) (Table 3; Fig. 2).

Table 2 Multivariate analysis for overall survival of patients by subtype

	B	Standard error	Wald	*P*	HR	95.0% CI	
						Lower	Upper
Total patients							
Age at diagnosis	−0.031	0.004	77.564	0.000	0.970	0.963	0.976
Stage	1.099	0.028	1570.088	0.000	3.003	2.844	3.170
NG, high versus low/intermediate	0.306	0.044	47.890	0.000	1.358	1.245	1.481
PABC versus non-PABC	0.026	0.166	0.024	0.878	1.026	0.741	1.420
Luminal A (ref)					1		
Luminal B (HR+ HER2+)	0.362	0.066	30.186	0.000	1.436	1.262	1.634
TNBC	0.850	0.055	241.571	0.000	2.339	2.101	2.603
HER2 subtype	0.785	0.065	146.237	0.000	2.192	1.930	2.490
Luminal B (HR+ HER2−, high Ki67)	0.074	0.088	0.700	0.403	1.076	0.906	1.279
CTx, no versus yes	0.084	0.083	1.035	0.309	1.088	0.925	1.279
Luminal A subtype							
Age	−0.053	0.006	70.510	0.000	0.949	0.937	0.960
Stage	1.074	0.050	461.098	0.000	2.928	2.655	3.230
NG, high versus low/intermediate	0.514	0.074	47.828	0.000	1.673	1.446	1.935
PABC versus non-PABC	−0.555	0.503	1.214	0.270	0.574	0.214	1.540
CTx, no versus yes	−0.234	0.140	2.775	0.096	0.792	0.601	1.042
Luminal B (HR+ HER2+) subtype							
Age	−0.050	0.009	28.524	0.000	0.951	0.934	0.969
Stage	0.895	0.075	142.060	0.000	2.447	2.112	2.835
NG, high versus low/intermediate	0.053	0.110	0.236	0.627	1.055	0.850	1.308
PABC versus non-PABC	−0.262	0.585	0.200	0.655	0.770	0.245	2.422
CTx, no versus yes	−0.114	0.212	0.287	0.592	0.893	0.589	1.353
TNBC subtype							
Age	−0.010	0.006	2.856	0.091	0.990	0.978	1.002
Stage	1.102	0.049	510.836	0.000	3.011	2.736	3.313
NG, high versus low/intermediate	0.091	0.080	1.302	0.254	1.095	0.937	1.281
PABC versus non-PABC	−0.028	0.257	0.012	0.912	0.972	0.587	1.610
CTx, no versus yes	0.546	0.165	11.001	0.001	1.726	1.250	2.382
HER2 subtype							
Age	−0.008	0.009	0.808	0.369	0.992	0.974	1.010
Stage	1.247	0.068	336.071	0.000	3.478	3.044	3.974
NG, high versus low/intermediate	0.190	0.113	2.815	0.093	1.209	0.969	1.510
PABC versus non-PABC	0.713	0.314	5.148	0.023	2.041	1.102	3.780
CTx, no versus yes	0.643	0.212	9.170	0.002	1.901	1.254	2.882
Luminal B (HR+ HER2−, high Ki67) subtype							
Age	−0.045	0.014	10.172	0.001	0.956	0.931	0.983
Stage	1.201	0.114	111.768	0.000	3.323	2.660	4.152
NG, high versus low/intermediate	0.650	0.166	15.375	0.000	1.916	1.384	2.653
PABC versus non-PABC	1.492	0.521	8.196	0.004	4.445	1.601	12.344
CTx, no versus yes	0.586	0.262	5.005	0.025	1.797	1.075	3.003

NG nuclear grade, *PABC* pregnancy-associated breast cancer, *CTx* chemotherapy, *HR* hormonal receptor, *HER2* human epidermal growth factor 2, *TNBC* triple-negative breast cancer

PABC patients versus nulliparous women in non-PABC patients

Clinicopathologic characteristics of PABC patients were compared with nulliparous women in non-PABC patients. In the nulliparous women (non-PABC), luminal A was the most common subtype (47.9%) and HER2 subtype was the least common (7.9%) ($P < 0.001$, Supplemental Table 1). Univariate analysis and multivariate analysis showed that PABC patients had worse prognosis than

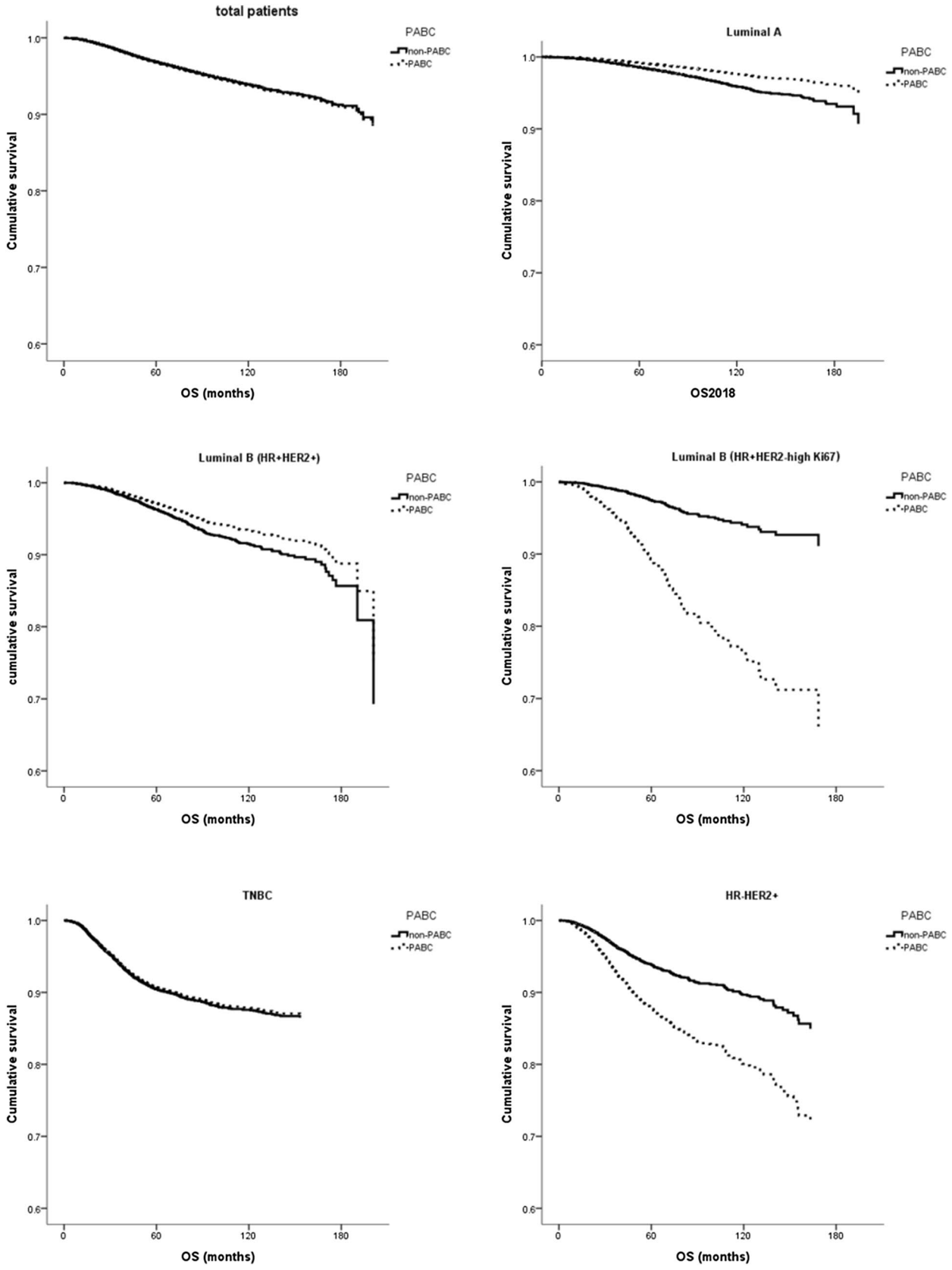

Fig. 1 Overall survival of PABC patients and non-PABC patients by subtype: **a** all patients, **b** luminal A, **c** luminal B (HER2+), **d** luminal B (high Ki67), **e** triple-negative breast cancer, and **f** HER2 subtypes

Table 3 Multivariate analysis for overall survival of PABC and non-PABC patients

	B	Standard error	*P*	HR	95.0% CI	
					Lower	Upper
non-PABC						
Age	−0.031	0.004	0.000	0.969	0.963	0.976
Luminal A (ref)						
Luminal B (HER2+)	0.364	0.066	0.000	1.439	1.264	1.638
TNBC	0.854	0.055	0.000	2.349	2.109	2.616
HER2 subtype	0.773	0.066	0.000	2.167	1.905	2.464
Luminal B (high Ki67)	0.054	0.089	0.546	1.055	0.886	1.256
Stage	1.096	0.028	0.000	2.992	2.833	3.161
NG, high versus low/intermediate	0.306	0.045	0.000	1.358	1.244	1.482
Chemotherapy, no versus yes	0.086	0.083	0.298	1.090	0.927	1.282
PABC						
Age	−0.035	0.044	0.422	0.965	0.885	1.052
Luminal A (ref)						
Luminal B (HR+ HER+)	0.030	0.785	0.970	1.030	0.221	4.798
TNBC	0.757	0.600	0.207	2.132	0.658	6.914
HER2 subtype	1.469	0.602	0.015	4.346	1.336	14.132
Luminal B (high Ki67)	1.958	0.722	0.007	7.085	1.721	29.167
Stage	1.456	0.251	0.000	4.291	2.626	7.011
NG, high versus low/intermediate	0.619	0.417	0.138	1.857	0.820	4.207
Chemotherapy, no versus yes	−11.320	401.778	0.978	0.000	0.000	

PABC pregnancy-associated breast cancer, *NG* nuclear grade, *CTx* chemotherapy, *HER2* human epidermal growth factor 2, *TNBC* triple-negative breast cancer

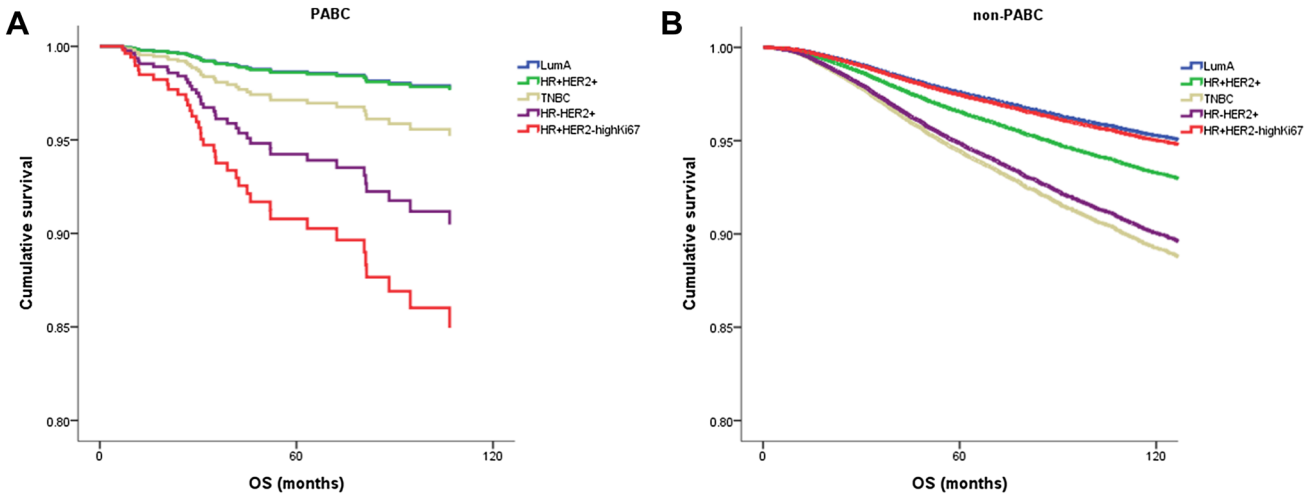

Fig. 2 Overall survival graph of five subtypes in PABC patients (**a**) and non-PABC patients (**b**)

nulliparous patients. After adjusting for age, stage, and NG in multivariate analysis, PABC patients had 1.9-fold higher HR (95% CI 1.3–2.7, $P < 0.001$) than non-PABC patients. After adjusting for age, stage, NG, and subtype in multivariate analysis, PABC patients showed 1.5-fold higher HR (95% CI 1.0–2.3, $P = 0.05$) than non-PABC patients.

Discussion

Pregnancy is a significant change that affects both individuals and society, and it is also the most significant physiologic change in the breast. Pregnancy is known to lower the risk of breast cancer, but this is the result of studies

in postmenopausal women. Recent studies have shown that in premenopausal women, the risk of breast cancer increases 3–5 years after delivery [11–13]. By univariate analysis for OS, PABC patients had a lower survival rate than non-PABC patients. In multivariate analysis adjusted for age, stage, and subtype, PABC had 1.3-fold increased risk compared with non-PABC. However, the importance of PABC is overlooked because breast cancer is rare in women in their 20s–30s.

PABC often is advanced stage at diagnosis and poor prognosis. Screening for young women is uncommon, and it is difficult to detect tumors early during pregnancy or lactation. In addition, treatment is also limited during pregnancy. In the past, these are considered the main causes for the poor prognosis of PABC. However, recent studies have shown that estrogen receptor expression is low and HER2 overexpression is high in PABC [5, 6, 9]. This suggests that the biology of PABC itself may be aggressive. This phenotype is also characteristic of breast cancer occurring in young women [14].

In this study, we investigated whether the biomarker subtypes of PABC are different from those of breast cancer in young women and whether they are related to prognosis. TNBC and HER2 subtypes were more common than in non-PABC patients. Compared with nulliparous women, patients with PABC had lower expression of hormone receptors and higher expression of HER2, indicating that this breast cancer subtype is associated with pregnancy. In PABC patients, there was no difference between breast cancer in the 20s and 30s and breast cancer in the 40s. There was also no statistically significant difference in the expression of hormone receptors between PABC and non-PABC patients in their 40s.

PABC and non-PABC had different prognostic factors. In non-PABC, TNBC subtype had the worst prognosis and luminal B (with high Ki67) had the best prognosis with no difference from the luminal A subtype. However, in PABC, the HER2 and luminal B (with high Ki67) subtypes had the worst outcomes. The poor prognosis of the HER2 subtype could not be confirmed in this study, but the relevance of treatment with trastuzumab should be considered. Compared with other subtypes, luminal B (with high Ki67) showed the highest frequency of family history (28.6%) and significantly different rates from non-PABC (10.4%). The rate of chemotherapy for luminal B (with high Ki67) was the lowest, with 76.4%. Family history and age at diagnosis of breast cancer are related to the prevalence of BRCA1/BRCA2 mutation [15, 16], and a recent study showed that BRCA1/BRCA2 pathogenic mutations are more prevalent in younger Asian women with breast cancer than in the TCGA cohort [17].

Recent literature has shown that younger women are more resistant to hormone therapy for breast cancer than middle-aged women with breast cancer [18], and luminal subtype has a poor prognosis [19]. In addition, the higher incidence of luminal B breast cancer in young women is itself considered a poor prognostic factor [20, 21]. Recent clinical trial studies have shown that luminal B cancer is less dependent on the estrogen pathway, which is aimed at an alternative pathway EGFR [18] and PI3K/Akt/mTOR in advanced ER+ cancer [22].

This study suggests that PABC has different biologic features than breast cancer in young women. PABC has some characteristics of breast cancer in young women, but it seems to have more aggressive characteristics due to pregnancy. PABC showed a particularly poor prognosis in the luminal B (with high Ki67) and HER2 subtypes. Treatment is limited because fetal health must be considered during pregnancy. Chemotherapy can be performed from the second trimester, but endocrine therapy and target therapy are contraindications during pregnancy. To improve the prognosis of PABC, treatment should be considered according to each subtype. In addition, development of drugs that can be used during pregnancy is needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.

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