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Original Article

The clinicopathological characteristics and survival outcomes of mucinous adenocarcinoma of the breast: a SEER population-based study

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Abstract: Objective: This study aimed to compare the clinicopathological characteristics and survival outcomes of mucinous adenocarcinoma of the breast (BMAC) and infiltrating ductal carcinoma of the breast (BIDC). Methods: A total of 137,029 eligible breast cancer patients were recruited based on the Surveillance, Epidemiology, and End Results (SEER) database, including 2,775 BMAC patients and 134,254 BIDC patients. The demographic and clinicopathological characteristics were captured and compared between the BMAC and BIDC patients. In addition, the overall survival (OS) and disease-specific survival (DSS) rates were estimated, and the prognostic factors of BMAC and BIDC were identified using univariate and multivariate analyses. Results: The BMAC patients presented with older ages, lower histological grades, less advanced stages, smaller tumor sizes, less lymph node involvement, fewer metastases, higher hormone receptor (*HR*) expressions, lower human epidermal growth factor receptor 2 (*HER-2*) expressions, more surgical treatments, and more unmarried women than the BIDC patients, and the BMAC patients had significantly greater 3-year OS (99.1% vs. 94.5%, $P < 0.001$) and DSS rates (96.1% vs. 92.8%, $P < 0.001$) than the BIDC patients. A univariate analysis showed higher OS (hazard ratio = 0.524, 95% *CI*: 0.399-0.668, $P < 0.001$) and DSS rates (hazard ratio = 0.174, 95% *CI*: 0.101-0.301, $P < 0.001$) in the BMAC patients than in the BIDC patients, and a multivariate analysis revealed comparable OS (hazard ratio = 1.219, 95% *CI*: 0.923-1.611, $P = 0.163$) and DSS rates (hazard ratio = 0.617, 95% *CI*: 0.357-1.068, $P = 0.084$) between the BMAC and BIDC patients. Conclusion: BMAC may be a less aggressive histological type of breast cancer than BIDC; however, the histological subtype does not seem to be an independent prognostic factor for BMAC.

Keywords: Breast cancer, clinicopathological characteristics, infiltrating duct carcinoma, mucinous adenocarcinoma, prognosis, SEER database

Introduction

Mucinous carcinoma, which is usually divided into pure and mixed subtypes, consists of many clusters of tumor cells floating in pools of mucin, and commonly occurs in the breasts, colon, lungs, and skin [1]. Mucinous adenocarcinoma of the breast (BMAC), which accounts for 1% to 7% of all breast cancers [2], is a rare histological type of breast cancer with a favorable prognosis in relation to infiltrating ductal carcinoma of the breast (BIDC) [3-5]. In a large retrospective study, patients with pure BMAC had a greater median age than BIDC patients at diagnosis and presented with less aggressive disease behaviors relative to the BIDC patients [6]. However, another retrospective study showed younger ages, less lymph node (LNs) involvement, lower stages, greater expressions of the hormonal receptors (*HR*), and less overexpression of human epidermal growth factor receptor 2 (*HER2*) in the BMAC patients than in the infiltrating ductal carcinoma-not otherwise specified (IDC-NOS) patients [7]. Although previous studies have shown better survival outcomes in patients with BMAC than in those with BIDC [8-10], there is also evidence demonstrating comparable survival outcomes and prognoses between patients with BMAC and BIDC [11]. In addition, the prognostic factors of BMAC and BIDC have remained in dispute until now [7, 11].

In this large-scale population-based retrospective study, a total of 137,029 eligible subjects were recruited based on the Surveillance,

Epidemiology, and End Results (SEER) database during the period 2010 through 2014, including 2,775 patients with BMAC and 134,254 patients with BIDC. The major purpose of the current study was to compare the clinicopathological features of BMAC and BIDC and identify the prognostic factors for BMAC and BIDC, which may provide further understanding of the clinicopathological features and survival of BMAC and BIDC.

Methods

Ethical statement

The study was approved by the Ethical Review Committee of Nanping First Hospital Affiliated to Fujian Medical University. Since all analyses were performed based on public data extracted from the SEER database, written informed consent was not obtained.

Study subjects and data collection

The SEER database was used to identify breast cancer patients using the software SEER *Stat version 8.3.4 [12]. Since *HER2* status is not available in the SEER database before 2010 and the database was only updated before December 31, 2014, we captured data from the SEER database corresponding to the period January 1, 2010 to December 31, 2014.

The inclusion criteria of the potentially eligible patients included (1) females aged 20 to 79 years; (2) unilateral breast cancer; (3) breast cancer as the initial and only cancer type; (4) only a single primary site; (5) pathological diagnosis of IDC-NOS and BMAC; (6) histological grades I to IV; (7) known TNM stage; (8) known estrogen receptor (*ER*), progesterone receptor (*PR*) and *HER2* status; (9) known time at diagnosis; and (10) known survival period. Those who failed to meet the inclusion criteria were excluded from the study. A total of 137,029 patients were enrolled, including 134,254 BIDC cases and 2,775 BMAC cases.

We captured the demographic and clinicopathological characteristics and the treatment and follow-up data from the SEER database using SEER *Stat version 8.3.4. The demographic characteristics included age at diagnosis, marital status and race, and the clinical characteristics included tumor laterality, histological grade, tumor size, LN involvement, metastasis status, *ER* status, *PR* status, and *HER2* status.

Estimation of survival outcomes

In this study, overall survival (OS) and disease-specific survival (DSS) were defined as the main endpoints. OS was identified as the duration from diagnosis to any cause of death, and DSS was recognized as the duration from diagnosis to death caused by breast cancer. The 3-year OS and DSS rates were calculated using the Kaplan-Meier method [13].

Data analysis

In this study, age at diagnosis, which was classified into two groups, 20 to 49 years and 50 to 79 years, was defined as a binary variable. T stage was defined as a categorical variable according to the tumor size: T1, ≤ 2 cm; T2, > 2 and ≤ 5 cm; T3, > 5 cm; and T4, tumor of any size, with direct extension to the chest wall or the skin. N stage was processed as a categorical variable according to the number of LNs involved: N0, no LN involvement; N1, involvement of 1 to 3 LNs; N2, involvement of 4 to 9 LNs; and N3, involvement of 10 and more LNs. M stage, which was classified into M0 (no metastasis) and M1 (presence of metastasis), was processed as a binary variable. The surgical treatment was also defined as a categorical variable as follows: surgery, no surgery, or unknown, and the follow-up duration was treated as a continuous variable.

Differences of proportions were tested for statistical significance using Pearson's chi-square test. The prognostic factors of breast cancer were identified with univariate and multivariate Cox proportional hazard regression models, and the hazard ratio and 95% confidence interval (*CI*) were calculated. In addition, the survival analysis was performed with the Kaplan-Meier method, and the differences between the Kaplan-Meier curves were compared using a log-rank test. All statistical analyses were conducted using the software SPSS version 21.0 (SPSS, Inc.; Chicago, IL, USA), and a P value < 0.05 was indicative of statistical significance.

Results

Subject characteristics

Based on the inclusion and exclusion criteria, a total of 137,029 eligible patients with breast cancer were enrolled in our study, including 2,775 BMAC cases (2.0%) and 134,254 BIDC cases (98.0%). **Table 1** describes the demo-

Table 1. Comparison of the demographic and clinicopathological characteristics between the BIDC and BMAC patients

Variables	No. of patients (%)			*P* value*
	BIDC (*n* = 134,254)	BMAC (*n* = 2,775)	Total (*n* = 137,029)	
Age (years)				
20-49	35,852 (26.7)	471 (17)	36,323 (26.5)	< 0.001
50-79	98,402 (73.3)	2,304 (83)	100,706 (73.5)	
Marital status				
Married	78,194 (58.2)	1,464 (52.8)	79,658 (58.1)	< 0.001
Unmarried†	49,422 (36.9)	1,179 (42.4)	50,601 (37)	
Unknown	6,638 (4.9)	132 (4.8)	6,770 (4.9)	
Race				
Black	15,746 (11.7)	323 (11.6)	16,069 (11.7)	0.013
White	103,719 (77.3)	2,093 (75.5)	105,812 (77.3)	
Others‡	13,833 (10.3)	339 (12.2)	14,172 (10.3)	
Unknown	956 (0.7)	20 (0.7)	976 (0.7)	
Laterality				
Left	67,893 (50.6)	1,442 (52)	69,335 (50.6)	0.146
Right	6,631 (49.4)	1,333 (48)	67,694 (49.4)	
Grade				
I	27,038 (20.1)	1,679 (60.5)	28,717 (21)	< 0.001
II	54,753 (40.8)	985 (35.5)	55,738 (40.6)	
III or IV	52,463 (39.1)	111 (4)	52,574 (38.4)	
T stage				
T1	80,969 (60.3)	1,843 (66.4)	82,812 (60.4)	< 0.001
T2	41,197 (30.7)	752 (27.1)	41,949 (30.6)	
T3	7,167 (5.3)	142 (5.1)	7,309 (5.3)	
T4	4,921 (3.7)	38 (1.4)	4,959 (3.7)	
N stage				
N0	87,806 (65.4)	2,496 (90)	90,302 (65.9)	< 0.001
N1	34,455 (25.7)	220 (7.9)	34,675 (25.3)	
N2	7,658 (5.7)	41 (1.5)	7,699 (5.6)	
N3	4,355 (3.2)	18 (0.6)	4,353 (3.2)	
M stage				
M0	128,948 (96)	2,739 (98.7)	131,687 (96.1)	< 0.001
M1	5,306 (4)	36 (1.3)	5,342 (3.9)	
HR status				
Positive	92,340 (68.8)	2,599 (93.7)	94,939 (69.3)	< 0.001
Negative	41,914 (31.2)	176 (6.3)	42,090 (30.7)	
HER2 status				
Positive	23,871 (17.8)	166 (6)	24,037 (17.5)	< 0.001
Negative	110,383 (82.2)	26.9 (94)	112,992 (82.5)	
Surgery				
No	7,286 (5.4)	81 (2.9)	7,367 (5.4)	< 0.001
Yes	126,820 (94.5)	2,691 (97)	129,551 (94.5)	
Unknown	148 (0.1)	3(0.1)	151 (0.1)	

T stage, tumor stage; N stage, lymph node stage; M stage, metastasis stage; *HR*, hormone receptor; *HER2*, human epidermal growth factor receptor 2; BMAC, mucinous adenocarcinoma of the breast; MIDC, infiltrating ductal carcinoma of the breast; SEER, Surveillance, Epidemiology and End Results. *P value is calculated using the chi-square test comparing the BMAC patients and BIDC patients. †Including divorced, unmarried, single (never married), separated, domestic partner and widowed. ‡Including Asian/Pacific Islander, and American Indian/Alaskan native, and others-unspecified.

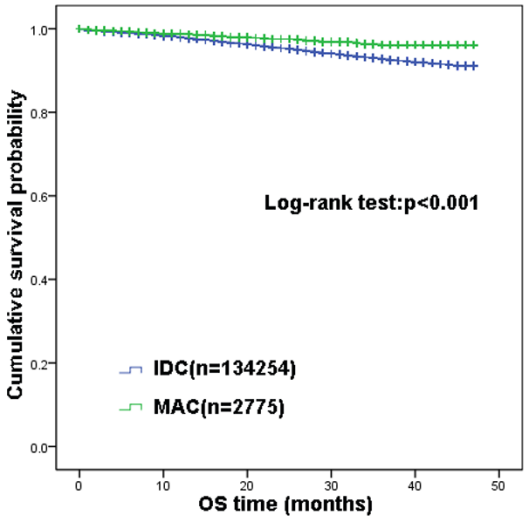

Figure 1. Comparison of the 3-year overall survival rates between the BMAC and BIDC patients.

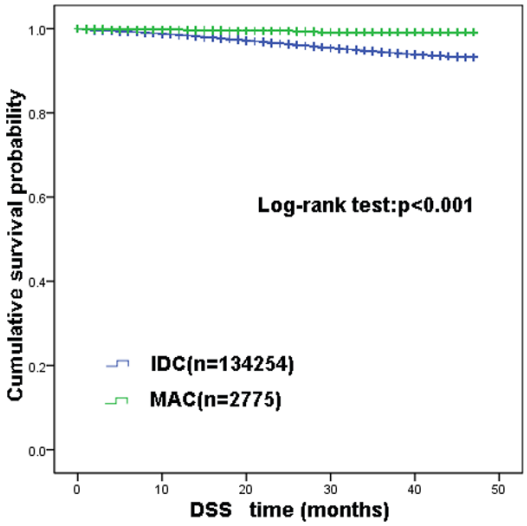

Figure 2. Comparison of the 3-year disease-specific survival rates between the BMAC and BIDC patients.

graphic and clinicopathological characteristics of the study subjects. The BMAC patients presented with a higher age (83.0% vs. 73.3% at ages of > 50 years, $P < 0.001$), more unmarried women (42.4% vs. 36.9%, $P < 0.001$), more well-differentiated diseases (60.5% vs. 20.1%, $P < 0.001$), smaller tumor sizes (66.4% vs. 60.3%, $P < 0.001$), lower prevalence of distant metastasis (1.3% vs. 4.0%, $P < 0.001$), and a higher proportion of surgical treatment (97.0% vs. 94.5%, $P < 0.001$) than the BIDC patients. In addition, higher *HR* expression (93.7% vs. 68.8%, $P < 0.001$), lower *HER2* expression (6.0% vs. 17.8%, $P < 0.001$) and a higher proportion of N0 stage (90.0% vs. 65.4%, $P < 0.001$) were found in the BMAC patients than in BIDC patients.

Comparison of the survival outcomes between the BMAC and BIDC patients

Significantly greater 3-year OS and (96.1% vs. 92.8%, $P < 0.001$) and DSS rates (99.1% vs. 94.5%, $P < 0.001$) were estimated in the BMAC patients than in the BIDC patients, as revealed by the Kaplan-Meier curves (**Figures 1** and **2**). A univariate Cox proportional hazard regression analysis showed significantly better OS (hazard ratio = 0.524, 95% *CI*: 0.399-0.668, $P < 0.001$) and DSS (hazard ratio = 0.174, 95% *CI*: 0.101-0.301, $P < 0.001$) in the BMAC patients than in the BIDC patients, and unmarried status, black women, infiltrating ductal carcinoma, grades III and IV, T4 stage, the number of LN involvement, distant metastasis, absent *ER* and *PR* expression, *HER2* over-amplification, and non-surgical treatment were identified as significantly correlating with poor OS and DSS (**Table 2**), which were included in the subsequent multivariate analysis. To our surprise, after adjusting for age at diagnosis, marital status, histological grade, TNM stage, *HR* status, *HER2* status and surgery, the BMAC patients had no more favorable OS (hazard ratio = 1.219, 95% *CI*: 0.923-1.611, $P = 0.163$) or DSS (hazard ratio = 0.617, 95% *CI*: 0.357-1.068, $P = 0.084$) than the BIDC patients (**Table 3**).

Subgroup analysis of the survival outcomes

To further evaluate the effects of molecular subtype on survival in the BMAC and BIDC patients, we performed a univariate analysis stratified by breast cancer molecular subgroup. The $HR^+/HER2^-$ BMAC patients had a better DSS rate than the $HR^+/HER2^-$ IDC patients (hazard ratio = 0.284, 95% *CI*: 0.399-0.668, $P < 0.001$); however, the OS was comparable between the $HR^+/HER2^-$ BMAC and BIDC patients (hazard ratio = 0.785, 95% *CI*: 0.593-1.039, $P = 0.09$). In the $HR^+/HER2^+$ subgroup, the BMAC patients had a comparable OS (hazard ratio = 0.188, 95% *CI*: 0.026-1.34, $P = 0.095$) and DSS (hazard ratio = 0.25, 95% *CI*: 0.035-1.781, $P = 0.167$) to the BIDC patients. Similarly, there were no statistical differences in the OS or DSS between the BMAC and BIDC patients in the $HR^-/HER2^+$ subgroup (OS: haz-

Table 2. Univariate and multivariate analyses of OS predictors using a Cox proportional hazard regression model

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% *CI*)	*P* value	Hazard ratio (95% *CI*)	*P* value
Age at diagnosis (years)				
18-49	Reference	-	Reference	-
50-79	1.259 (1.177-1.347)	< 0.001	1.596 (1.490-1.709)	< 0.001
Marital status				
Married	Reference	-	Reference	-
Unmarried	1.915 (1.806-2.030)	< 0.001	1.406 (1.324-1.493)	< 0.001
Unknown	1.522 (1.338-1.731)	< 0.001	1.357 (1.193-1.544)	< 0.001
Race				
Black	Reference	-	Reference	-
White	0.495 (0.462-0.531)	< 0.001	0.869 (0.808-0.934)	< 0.001
Others	0.355 (0.314-0.402)	< 0.001	0.614 (0.541-0.696)	< 0.001
Unknown	0.088 (0.037-0.212)	< 0.001	0.159 (0.066-0.383)	< 0.001
Laterality				
Left	Reference	-	Reference	-
Right	0.944 (0.892-0.999)	0.047	0.984 (0.930-1.041)	0.574
Histology type				
IDC	Reference	-	Reference	-
MAC	0.524 (0.399-0.688)	< 0.001	1.219 (0.923-1.611)	0.163
Grade				
I	Reference	-	Reference	-
II	2.074 (1.838-2.340)	< 0.001	1.171 (1.034-1.327)	0.013
III or IV	5.297 (4.728-5.934)	< 0.001	1.825 (1.608-2.070)	< 0.001
T stage				
T1	Reference		Reference	-
T2	3.197 (2.968-3.443)	< 0.001	1.817 (1.676-1.970)	< 0.001
T3	7.806 (7.110-8.569)	< 0.001	2.724 (2.450-3.029)	< 0.001
T4	20.604 (18.984-22.362)	< 0.001	3.218 (2.894-3.578)	< 0.001
N stage				
N0	Reference	-	Reference	-
N1	2.768 (2.588-2.961)	< 0.001	1.367 (1.269-1.472)	< 0.001
N2	4.782 (4.377-5.225)	< 0.001	2.016 (1.830-2.221)	< 0.001
N3	9.334 (8.553-10.186)	< 0.001	3.218 (2.894-3.578)	< 0.001
M stage				
M0	Reference	-	Reference	-
M1	17.151 (16.152-18.211)	< 0.001	3.951 (3.627-4.303)	< 0.001
HR status				
Positive	Reference	-	Reference	-
Negative	3.124 (2.924-2.338)	< 0.001	2.424 (2.253-2.604)	< 0.001
HER2 status				
Positive	Reference	-	Reference	-
Negative	0.865 (0.805-0.929)	< 0.001	2.716 (2.498-2.953)	< 0.001
Surgery				
No	Reference	-	Reference	-
Yes	0.08 (0.076-0.086)	< 0.001	0.31 (0.286-0.337)	< 0.001
Unknown	0.567 (0.347-0.929)	0.024	0.938 (0.572-1.536)	0.846

OS, overall survival; *CI*, confidence interval; *HR*, hormone receptor; *HER2*, human epidermal growth factor receptor 2; MAC, mucinous adenocarcinoma; IDC, infiltrating ductal carcinoma.

Table 3. Univariate and multivariate analyses of DSS predictors using a Cox proportional hazard regression model

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% *CI*)	*P* value	Hazard ratio (95% *CI*)	*P* value
Age at diagnosis (years)				
18-49	Reference	-	Reference	-
50-79	0.997 (0.927-1.074)	0.945	1.338 (1.242-1.442)	< 0.001
Marital status				
Married	Reference	-	Reference	-
Unmarried	1.814 (1.696-1.941)	< 0.001	1.274 (1.189-1.366)	< 0.001
Unknown	1.347(1.154-1.573)	< 0.001	1.183 (1.013-1.382)	0.030
Race				
Black	Reference	-	Reference	-
White	0.46 (0.425-0.497)	< 0.001	0.883 (0.813-0.959)	0.003
Others	0.318 (0.275-0.368)	< 0.001	0.583 (0.503-0.676)	< 0.001
Unknown	0.022 (0.003-0.158)	< 0.001	0.048 (0.007-0.342)	0.002
Laterality				
Left	Reference	-	Reference	-
Right	0.972 (0.910-1.038)	0.391	1.019 (0.955-1.088)	0.569
Histology type				
IDC	Reference	-	Reference	-
MAC	0.174 (0.101-0.301)	< 0.001	0.617 (0.357-1.068)	0.084
Grade				
I	Reference	-	Reference	-
II	4.909 (3.656-6.092)	< 0.001	2.214 (1.778-2.758)	< 0.001
III or IV	15.923 (12.920-19.624)	< 0.001	3.932 (3.16-4.893)	< 0.001
T stage				
T1	Reference	-	Reference	-
T2	4.897 (4.437-5.405)	< 0.001	2.265 (2.04-2.516)	< 0.001
T3	14.182 (12.659-15.887)	< 0.001	3.703 (3.261-4.203)	< 0.001
T4	37.675 (33.985-41.766)	< 0.001	4.235 (3.729-4.809)	< 0.001
N stage				
N0	Reference	-	Reference	-
N1	3.951(3.639-4.290)	< 0.001	1.59 (1.453-1.740)	< 0.001
N2	6.95 (6.266-7.709)	< 0.001	2.31 (2.064-2.584)	< 0.001
N3	14.742 (13.341-16.290)	< 0.001	2.761 (2.466-3.092)	< 0.001
M stage				
M0	Reference	-	Reference	-
M1	24.601 (23.015-26.297)	< 0.001	5.106 (4.652-5.605)	< 0.001
HR status				
Positive	Reference	-	Reference	-
Negative	4.082 (3.823-4.358)	< 0.001	2.838 (2.616-3.079)	< 0.001
HER2 status				
Positive	Reference	-	Reference	-
Negative	0.808 (0.745-0.877)	< 0.001	3.145 (2.865-3.452)	< 0.001
Surgery				
No	Reference	-	Reference	-
Yes	0.064 (0.06-0.069)	< 0.001	0.32 (0.292-0.349)	< 0.001
Unknown	0.623 (0.374-1.036)	0.068	1.105 (0.664-1.841)	0.701

DSS, disease-specific survival; *CI*, confidence interval; *HR*, hormone receptor; *HER2*, human epidermal growth factor receptor 2; MAC, mucinous adenocarcinoma; IDC, infiltrating ductal carcinoma.

Table 4. Comparison of DSS and OS between BMAC and BIDC patients using a Cox proportional hazard regression model

Molecular Subtype	DSS			OS		
	Events No./ Sum No.	Hazard ratio (95% *CI*)	*P* value	Events No./ Sum No.	Hazard ratio (95% *CI*)	*P* value
HR$^+$/*HER2*$^-$						
IDC	1,510/92,340	Reference	-	2,277/92,340	Reference	-
MAC	12/2,599	0.284 (0.161-0.501)	＜0.001	50/2,599	0.785 (0.593-1.039)	0.09
HR$^+$/*HER2*$^+$						
IDC	380/16,443	Reference	-	506/16,443	Reference	-
MAC	1/147	0.25 (0.035-1.781)	0.167	1/147	0.188 (0.026-1.340)	0.095
HR$^-$/*HER2*$^+$						
IDC	349/7,428	Reference	-	422/7,428	Reference	-
MAC	0/19	0.05 (0.00-257.919)	0.491	0/19	0.05 (0.00-121.296)	0.45
Triple negative						
IDC	1,332/18,043	Reference	-	1,557/18,043	Reference	-
MAC	0/10	0.5 (0.000-828.348)	0.545	1/10	1.052 (0.148-7.465)	0.96

DSS, disease-specific survival; OS, overall survival; MAC, mucinous adenocarcinoma; IDC, infiltrating ductal carcinoma; *CI*, confidence interval; *HR*, hormone receptor; *HER2*, human epidermal growth factor receptor 2; triple negative, negative for *ER*, *PR,* and *HER2*.

ard ratio = 0.05, 95% *CI*: 0-121.296, *P* = 0.45; DSS: hazard ratio = 0.05, 95% *CI*: 0-257.919, *P* = 0.491) and the triple-negative subgroup (OS: hazard ratio = 1.052, 95% *CI*: 0.148-7.465, *P* = 0.960; DSS: hazard ratio = 0.5, 95% *CI*: 0-828.348, *P* = 0.545) (**Table 4**).

Comparison of the clinicopathological characteristics and survival outcomes between the HR$^+$*/HER2*$^-$ *BMAC and BIDC patients*

In terms of the molecular subtype of breast cancer, the BMAC patients had a tendency to present more *HR*$^+$*/HER2*$^-$ tumors than the BIDC patients did (93.7% vs. 68.8%, *P* < 0.001), so we compared the clinicopathological characteristics and survival outcomes between the *HR*$^+$*/HER2*$^-$ BMAC patients (2,599 cases) and the BIDC patients (92,340 cases). The *HR*$^+$*/HER2*$^-$ BMAC patients were found to have more women over 50 years old (83.8% vs. 76.0%, *P* < 0.001), more unmarried women (42.6% vs. 36.5%, *P* < 0.001), more grade I disease (62.7% vs. 28%, *P* < 0.001), less LN involvement (91.1% vs. 68.4%, *P* < 0.001), a lower prevalence of distal metastasis (1.2% vs. 3.0%, *P* < 0.001), and a higher proportion of surgical treatment (96.9% vs. 95.7%, *P* < 0.001) than the *HR*$^+$*/HER2*$^-$ BIDC patients (**Table 5**). In addition, the *HR*$^+$*/HER2*$^-$ BMAC patients presented with a higher 3-year DSS rate than the *HR*$^+$*/HER2*$^-$ BIDC patients (99.2% vs. 96.5%, *P* < 0.001) (**Figure 3**); however, there was no significant difference in the 3-year OS rates between the *HR*$^+$*/HER2*$^-$ BMAC and BIDC patients (96% vs. 94.9%, *P* < 0.09) (**Figure 4**).

To further identify the prognostic factors of DSS, univariate and multivariate Cox proportional hazard regression analyses were performed in *HR*$^+$*/HER2*$^-$ breast cancer patients. The univariate analysis showed that unmarried status, black women, infiltrating ductal carcinoma, grades III or IV, large tumor size, increased number of LN involvement, distant metastasis, and non-surgical treatment were significantly associated with poor DSS, which were included in the multivariate analysis. After adjustment for age at diagnosis, marital status, histological grade, TNM stage and surgery, however, the *HR*$^+$*/HER2*$^-$ BMAC patients had a favorable 3-year DSS rate that was no longer than the *HR*$^+$*/HER2*$^-$ BIDC patients (hazard ratio = 0.699, 95% *CI*: 0.394-1.241, *P* = 0.221) (**Table 6**).

Discussion

In this study, BMAC accounted for approximately 2% of all breast cancer patients, a proportion consistent with previous studies [14, 15]. Our findings demonstrated that BMAC patients are

Table 5. Comparison of the clinicopathological characteristics between the $HR^+/HER2^-$ BIDC and BMAC patients

Variables	No. of patients (%)			*P* value
	IDC	MAC	Total	
Age (years)				
20-49	22,172 (24)	422 (16.2)	22,594 (23.8)	< 0.001
50-79	70,168 (76)	2,177 (83.8)	72,345 (76.2)	
Marital status				
Married	54,126 (58.6)	1,365 (52.5)	55,491 (58.4)	< 0.001
Unmarried	33,663 (36.5)	1,106 (42.6)	34,769 (36.6)	
Unknown	4,551 (4.9)	128 (4.9)	4,679 (5)	
Race				
Black	8,811 (9.5)	305 (11.7)	9,116 (9.6)	< 0.001
White	73,399 (79.6)	1,954 (75.2)	75,353 (79.4)	
Others	9,462 (10.2)	321 (12.4)	9,783 (10.3)	
Unknown	668 (0.7)	19 (0.7)	687 (0.7)	
Laterality				
Left	46,381 (50.2)	1,337 (51.4)	47,718 (50.3)	< 0.001
Right	45,959 (49.8)	1,262 (48.6)	47,221 (49.7)	
Grade				
I	25,820 (28)	1,629 (62.7)	27,449 (28.9)	< 0.001
II	43,953 (47.6)	892 (34.3)	44,845 (47.2)	
III or IV	22,567 (24.4)	78 (3)	22,645 (23.9)	
T stage				
T1	61,838 (67)	1742 (67.0)	63,580 (67.0)	< 0.001
T2	24,447 (26.4)	700 (26.9)	25,147 (26.5)	
T3	3,674 (4)	123 (4.8)	3,797 (4.0)	
T4	2,381 (2.6)	34 (1.3)	2,415 (2.5)	
N stage				
N0	63,170 (68.4)	2,367 (91.1)	65,537 (69)	< 0.001
N1	22,262 (24.1)	185 (7.1)	22,447 (23.6)	
N2	4,667 (5.1)	32 (1.2)	4,699 (5)	
N3	2,241 (2.4)	15 (0.6)	2,256 (2.4)	
M stage				
M0	89,536 (97)	2,568 (98.8)	92,104 (97)	< 0.001
M1	2,804 (3)	31 (1.2)	2,835 (3)	
Surgery				
No	3,881 (4.2)	77 (3)	3958 (4.2)	0.007
Yes	88,381 (95.7)	2,519 (96.9)	90,900 (95.7)	
Unknown	78 (0.1)	3 (0.1)	81 (0.1)	

HR, hormone receptor; *HER2*, human epidermal growth factor receptor 2; MAC, mucinous adenocarcinoma; IDC, infiltrating ductal carcinoma; SEER, Surveillance, Epidemiology and End Results.

older at diagnosis, have a higher unmarried rate, a lower histological grade, a smaller tumor size, less LN involvement, a low prevalence of distant metastases, a higher percentage of *ER* and *PR* expressions, a lower proportion of *HER2* expression, and a bigger proportion of surgical treatments than BIDC patients. Among middle and south Taiwanese women, the BMAC patients showed favorable clinicopathological characteristics in terms of tumor grade, *HR* status and LN involvement relative to the BIDC patients [16], which is similar to the findings

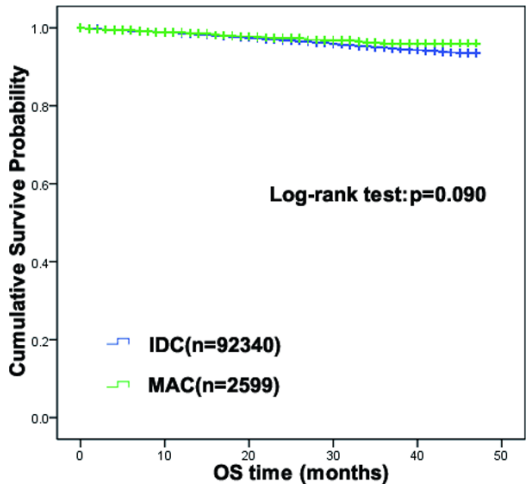

Figure 3. Comparison of the 3-year disease-specific survival rates between the *HR*$^{+}$/*HER2*$^{-}$ BMAC and BIDC patients.

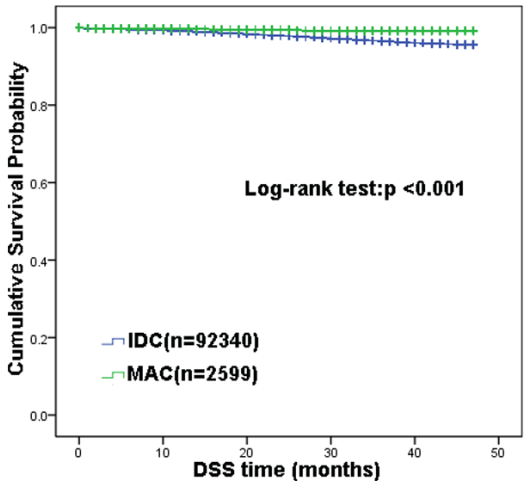

Figure 4. Comparison of the 3-year overall survival rates between the *HR*$^{+}$/*HER2*$^{-}$ BMAC and BIDC patients.

from this study. In addition, a Kaplan-Meier survival analysis revealed greater favorable 3-year OS and DSS rates in BMAC patients than in BIDC patients, rates in agreement with previous reports [7, 17]. Surprisingly, the multivariate Cox proportional hazard regression analysis showed no more favorable OS or DSS in the BMAC patients when compared with the OS and DSS in the BIDC patients, after adjustment for age at diagnosis, marital status, histological grade, TNM stage, *HR* status, *HER2* status, and surgery. This is different from previous studies [17, 18], and histological subtype was determined not to be an independent prognostic factor for BMAC in the present study.

In our study, the BMAC patients had a higher prevalence rate of *HR* expression (93.7% vs. 68.8%) and a lower prevalence rate of *HER2* expression (6.0% vs. 17.8%) than BIDC patients, which is consistent with previous studies [17]. In a previous case series of pure mucinous carcinomas, all were positive for ER expression, all were negative for *HER2* amplification, and 94.4% were positive for *PR* expression, but neither the triple-negative nor the *HER2* subtype was detected [19]. In the current study, the subgroup analysis showed better DSS in the *HR*$^{+}$/*HER2*$^{-}$ BMAC patients than in the *HR*$^{+}$/*HER2*$^{-}$ BIDC patients and a comparable OS between the *HR*$^{+}$/*HER2*$^{-}$ BMAC and BIDC patients. Based on our findings, it is hypothesized that BMAC seems to predominantly occur in older women who are likely to die from causes other than breast cancer. In the *HR*$^{+}$/*HER2*$^{+}$, *HR*$^{-}$/*HER2*$^{+}$ and *HR*$^{-}$/*HER2*$^{-}$ subgroups, comparable OS and DSS were found between the BMAC and BIDC patients, indicating the molecular subtype may play a significant role in the prognosis of breast cancer. Additionally, after adjustment for potential prognostic factors, a multivariate Cox proportional hazard regression analysis revealed, as expected, that the *HR*$^{+}$/*HER2*$^{-}$ BMAC patients had no longer favorable 3-year DSS rate than the *HR*$^{+}$/*HER2*$^{-}$ BIDC patients. It is therefore assumed that age at diagnosis, race, histological grade, TNM stage, and surgical treatment may play a synergic role in the prognosis of breast cancer. However, further studies are required to validate our hypothesis.

Our findings have several potential implications for both clinical practice and breast cancer research. First, our data demonstrate that histological subtype is not an independent prognostic factor for BMAC after adjustment for other prognostic factors, including age at diagnosis, marital status, histological grade, TNM stage, *HR* status, *HER2* status, and surgical treatment. Therefore, therapeutic decisions for BMAC cannot be made based on histological subtype, notably molecular subtype, and BMAC patients may be treated with the same intensive care as BIDC patients. Since molecular subtype and tumor stage were identified as major prognostic factors responsible for the statistical differences in the survival outcomes between BMAC and BIDC patients, clinicopath-

Table 6. Univariate and multivariate analyses of the DSS predictors in the *HR*$^{+}$/*HER2*$^{-}$ BMAC and BIDC patients

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% *CI*)	*P* value	Hazard ratio (95% *CI*)	*P* value
Age at diagnosis (years)				
18-49	Reference	-	Reference	-
50-79	0.984 (0.875-1.105)	0.780	1.351 (1.200-1.521)	< 0.001
Marital status				
Married	Reference	-	Reference	-
Unmarried	1.759 (1.587-1.950)	< 0.001	1.136 (1.020-1.264)	0.020
Unknown	1.196 (0.933-1.535)	0.158	1.077 (0.839-1.382)	0.561
Race				
Black	Reference	-	Reference	-
White	0.425 (0.375-0.482)	< 0.001	0.725 (0.637-0.825)	< 0.001
Others	0.272 (0.216-0.343)	< 0.001	0.412 (0.326-0.521)	< 0.001
Unknown	0.047 (0.007-0.331)	0.002	0.095 (0.013-0.675)	0.019
Laterality				
Left	Reference		Reference	-
Right	0.994 (0.899-1.099)	0.900	1.03 (0.931-1.139)	0.564
Histology type				
IDC	Reference	-	Reference	-
MAC	0.284 (0.161-0.501)	< 0.001	0.699 (0.394-1.241)	0.221
Grade				
I	Reference	-	Reference	-
II	4.109 (3.230-5.228)	< 0.001	1.923 (1.502-2.461)	< 0.001
III or IV	14.837 (11.744-18.746)	< 0.001	4.628 (3.625-5.91)	< 0.001
T stage				
T1	Reference		Reference	-
T2	6.459 (5.552-7.514)	< 0.001	2.943 (2.498-3.466)	< 0.001
T3	20.345 (17.156-24.268)	< 0.001	4.777 (3.898-5.855)	< 0.001
T4	57.009 (48.625-66.840)	< 0.001	5.313 (4.339-6.506)	< 0.001
N stage				
N0	Reference	-	Reference	-
N1	4.3 (3.793-4.875)	< 0.001	1.414 (1.233-1.622)	< 0.001
N2	8.09 (6.911-9.470)	< 0.001	1.953 (1.643-2.322)	< 0.001
N3	18.159 (15.549-21.208)	< 0.001	2.283 (1.914-2.723)	< 0.001
M stage				
M0	Reference	-	Reference	-
M1	34.503 (31.178-38.182)	< 0.001	4.816 (4.152-5.585)	< 0.001
Surgery				
No	Reference	-	Reference	-
Yes	0.043 (0.039-0.048)	< 0.001	1.057 (0.437-2.559)	< 0.001
Unknown	0.477 (0.198-1.149)	0.024	0.699 (0.394-1.241)	0.846

HR, hormone receptor; *HER2*, human epidermal growth factor receptor 2; MAC, mucinous adenocarcinoma; IDC, infiltrating ductal carcinoma.

ological features, but not histological types, should be taken into account when deciding on the treatment option. Second, the majority of BMAC patients are characterized as luminal A or luminal B subtypes, and these types of breast cancer usually have an indolent nature and a lower possibility of distant metastasis [20-23]. Previous studies have shown that breast-

conserving surgery and endocrine therapy are crucial for the treatment of BMAC with luminal A or luminal B subtypes [22, 24]. Even after the development of metastasis, luminal A or luminal B types of breast cancer seem to benefit from endocrine therapy and present fewer opportunities for rapid progression or visceral crisis, and therefore, less aggressive regimens could be taken into account for these specific patients to avoid unnecessary treatment and adverse effects [22, 24]. In the era of molecular subtyping, a 21-gene recurrence score assay was reported to be feasible to predict the likelihood of chemotherapy benefit and distant recurrence at the early stage of *ER*$^{+}$/*HER2*$^{-}$ breast cancer [25]. Further studies to investigate the clinicopathological features, diagnosis, treatment, and survival predictors of *ER*$^{+}$/*HER2*$^{-}$ breast cancer are warranted.

Although this study was performed with a large cohort of patients, the results of this study still have several limitations. First, the records of *Ki-67* expression were not available in the SEER database, which is of great importance in distinguishing the luminal A and luminal B subtypes, and the differences in treatment and prognosis of these two subtypes may contribute some bias to the clinical applications [22, 24]. Second, the information concerning *HER2* expression was not recorded in the SEER database until 2010, and the follow-up duration in this study is relatively inadequate for these types of patients with favorable prognoses. Given that breast cancer has a long natural history [26, 27], a 14-month (median) follow-up study may not identify the difference in the survival outcomes between groups. Third, BMAC is classified into the pure and mixed subtypes, and different subtypes present diverse prognoses [4]. In the SEER database, the proportion of pathological subtypes is not available, and the data pertaining to systemic treatments such as endocrine therapy, chemotherapy, or *HER2* targeted therapy are insufficient. The absence of these prognostic factors may cause deviations in our study. Moreover, this is a retrospective study, and further prospective clinical trials are required to validate the findings from the present study. Despite these limitations, this study is very trustworthy and believable because it is based on a large population.

In summary, the results of the present study demonstrate that BMAC patients present specific clinicopathological characteristics and more favorable survival outcomes relative to BIDC patients. Nevertheless, these more favorable prognoses disappear after an adjustment for demographic and clinicopathological factors. Subgroup analyses indicate that molecular subtype may be a major prognostic factor for BMAC, and age at diagnosis, race, histological grade, TNM stage and surgical treatment may play a synergic role in the prognosis of BMAC. Our data provide new insights into the understanding of the biological features of BMAC. When deciding the treatment regimen, clinicians should strictly comply with evidence-based guidelines, which are based on clinicopathological and molecular subtype and not based on histological subtype.

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Disclosure of conflict of interest

None.

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