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Marital Status and Survival of Patients with Hormone Receptor-Positive Male Breast Cancer: A Surveillance, Epidemiology, and End Results (SEER) Population-Based Study

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Statistical Analysis C
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Background: Although marital status has been reported as a prognostic factor in different cancer types, its prognostic effect on hormone receptor (HR) positive male breast cancer (MBC) is unclear. The objective of the present analysis was to assess the effects of marital status on survival in patients with HR positive MBC.

Material/Methods: Patients diagnosed with HR positive MBC from 1990 to 2014 in the Surveillance, Epidemiology, and End Results (SEER) database were included. Kaplan-Meier survival analysis and Cox proportional hazard regression were used to identify the effects of marital status on cancer-specific survival (CSS) and overall survival (OS).

Results: A total of 3612 cases were identified in this study. Married patients had better 5-year CSS and 5-year OS than unmarried men. In multivariate Cox regression models, unmarried patients also showed higher mortality risk for both CSS and OS, independent of age, race, grade, stage, PR status, HER2 status, and surgery. Subgroup survival analysis according to different ER/PR status showed that married patients had beneficial CSS results only in ER^+/PR^+ subtype, and CSS in the married and unmarried groups did not significantly differ by TNM stage. The results were further confirmed in the 1: 1 matched group.

Conclusions: Marital status was an important prognostic factor for survival in patients with HR positive MBC. Unmarried patients are at greater risk of death compared with married groups. The survival benefit for married patients remained even after adjustment, which indicates the importance of spousal support in MBC.

MeSH Keywords: Breast Neoplasms, Male • Marital Status • Receptors, Estrogen • Survival Analysis

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Background

Male breast cancer (MBC) is a rare disease, accounting for around 1% of all breast cancers [1]. Although rare, its incidence has steadily increased [2]. In 1991, an estimated 900 men in the United States were diagnosed with breast cancer; the number increased to 2550 men by 2018 [3,4]. Although the mortality and survival rates of both male and female breast cancer patients have significantly improved, progress in men has been slower [5]. Due to lack of prospective data and limited retrospective series, MBC usually has been treated according to recommendations for female breast cancer (FBC) [6]. Although MBC shares some features with FBC, it significantly differs in prognostic factors, epidemiological factors, and biological behavior [7,8]. For example, MBC tends to have higher rates of hormone receptor (HR) positivity compared to FBC [5,7]. MBC is frequently positive for ERα (91–95%) and/or PR (80–81%) [5,9,10]. Therefore, identifying prognostic factors in HR positive MBC can help to manage the majority of MBC cases.

Most cancer research focuses on biological aspects; the effect of social or psychological factors, such as marital status, on survival in cancer patients is much less studied. However, marriage has been shown to function as a positive social support with a survival benefit for cancer patients [11]. The relationship between marital status and survival has been studied for some cancers, including hepatocellular cancer [12], gastric cancer [13], biliary tract cancer [14], colorectal cancer [15], prostate cancer [16], pancreatic cancer [17] and breast cancer [18]. Marital status is an independent prognostic factor for survival, and married patients gain a significant survival benefit versus the unmarried, who are single, widowed, or separated/divorced patients [19,20]. As for MBC, only 1 previous study reported that unmarried men were more likely to present with advanced disease at diagnosis and were at greater risk for poorer outcomes compared with married men [21]. However, in that study, researchers did not control for confounding variables and the outcomes may have been subject to a selection bias. Additionally, they only took stage into consideration and could not discuss the effect of marriage on survival from other aspects, such as different ER/PR subtypes.

To our knowledge, no study has analyzed the influence of marital status on prognosis in HR positive MBC. Therefore, data from Surveillance, Epidemiology, and End Results (SEER) database was used to investigate the influence of marital status on survival and on potential subtypes in HR positive MBC.

Material and Methods

Patient population and study design

We obtained permission to access SEER research-data files using the reference number 15983-Nov2016. Because no information from the SEER database requires informed patient consent, it is considered exempt from the ethical approval requirements of the institutional review board. The case listing in this retrospective cohort study was generated by SEER *Stat version 8.3.5, which contained data from 18 population-based cancer registries (1973–2014) and covered approximately 28% of the United States population (*http://seer.cancer.gov/*). Male patients with first primary stages I–III and HR positive breast cancer diagnosed between 1990 and 2014 were selected from the SEER database. We selected the period starting from 1990 because HR status was introduced to SEER in 1990. We choose 3612 patients according to the following criteria: (a) at least 18 years old at diagnosis; (b) male; (c) diagnosed between 1990 and 2014; (d) known marital status; (e) known race; (f) known residence type; (g) pathologically confirmed breast cancer; (h) breast cancer as the first and only malignant cancer diagnosis; (i) known histology; (j) known grade; (k) American Joint Committee on Cancer stages I–III at diagnosis; (l) known tumor size; (m) known lymph node status; (n) HR positive (ER^+ or PR^+); (o) known HER2 status; (p) known surgical condition; (q) known radiotherapy condition; (r) active follow-up; (s) known survival months after diagnosis; and (t) known cause of death. We excluded patients for whom the aforementioned data was missing. Eligible patients were categorized by marital status, age at diagnosis, race, residence type, histology, tumor grade, pathologic T stage, pathologic N stage, ER status, PR status, HER2 status, surgery and radiotherapy. Marital status at diagnosis was the primary variable of interest, and classified as married or unmarried, the latter of which included patients who were single, divorced, separated, and widowed. The methods were performed in accordance with the approved guidelines.

Statistical analyses

Clinicopathological features were compared between different marital groups using the *t*-test and the χ^2 test as appropriate. Cancer-specific survival (CSS) and overall survival (OS) were estimated with the Kaplan-Meier method; differences were calculated by the log rank test. Multivariate Cox proportional hazards regression models were built for analyzing hazard ratios of different prognostic variables. OS was defined as the interval from breast cancer diagnosis until death due to all causes (including breast cancer) or last follow-up. CSS was measured from the date of diagnosis to either the date of breast cancer death or the date of last contact. All variables for which $P<0.05$ in univariate analyses were initially included in

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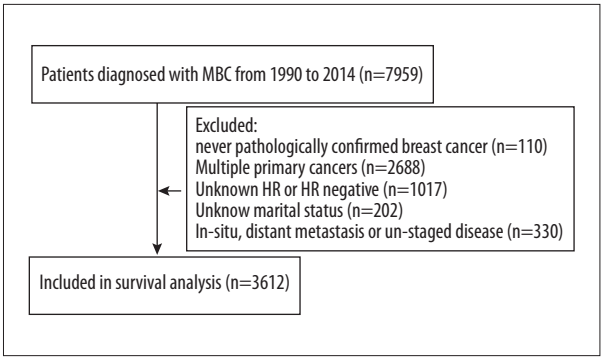

Figure 1. Diagram of analytic cohort for survival analysis. HR – hormone receptor; MBC – male breast cancer.

multivariate analyses; for the Cox proportional hazards regression, age, race, PR, and radiotherapy were included although *P*>0.05 for their respective univariate analyses, because they are common confounders of MBC. We performed a 1: 1 case-matched analysis based on marital status and matching for age, race, residence, histology, grade, T-stage, N-stage, ER status, PR status, HER2 status, surgery and radiotherapy, using the propensity score matching method to control for confounding variables. These analyses were performed with SPSS software version 23.0 (IBM Corporation, Armonk, NY, USA). *P*<0.05 (2-sided) was considered significant.

Results

Patient baseline characteristics

From 1990 to 2014, 7959 men were diagnosed with invasive breast cancer in the SEER database. From these records, we excluded patients with missing records or exact data on any of the abovementioned variables. The flow diagram of the study selection process is shown in Figure 1. Finally, we identified 3612 eligible patients with MBC.

When we stratified HR positive MBC patient by marital status, significant differences emerged (Table 1). Of these patients, 2548 (70.5%) were married and 1064 (29.5%) were unmarried. The 2 groups significantly differed in age, race, pathologic T stage, pathologic N stage, and surgical history. The mean age of the entire cohort was 65 years (range: 23–103 years). Unmarried patients were younger (64.8±14.3 *vs.* 65.3±12.3 years old, *P*=0.003), and had a lower proportion (77.0% *vs.* 89.2%, *P*<0.0001) of white patients and a higher proportion (19.7% *vs.* 9.9%, *P*<0.0001) of black patients than the married group. The married group was also more likely to have tumors that were smaller in size (35.0% *vs.* 26.6%, *P*<0.0001), less likely to have lymph node metastases (50.3% *vs.* 43.6%, *P*<0.0001) and had a higher rate of surgery (87.5% *vs.* 85.2%, *P*=0.013).

Impact of marital status on cancer-specific survival of HR positive MBC patients

We used Kaplan-Meier analysis and log-rank test to evaluate the impact of marital status on CSS of HR positive MBC patients (Figure 2A). The married group had a better 5-year CSS rate than the unmarried group (90.8% *vs.* 83.8%, χ^2=28.501, *P*<0.0001). In univariate analyses, race (*P*<0.0001), histology (*P*<0.0001), grade (*P*<0.0001), pathologic T stage (*P*<0.0001), pathologic N stage (*P*<0.0001), PR status (*P*<0.0001), HER2 status (*P*=0.039), surgery (*P*<0.0001), and radiotherapy (*P*<0.0001) were also significantly associated with CSS in HR positive MBC patients (Table 2). In multivariate Cox regression analysis of these factors, the unmarried group were found to have a significantly greater risk for cancer-specific mortality (hazards ratio: 1.394, 95% CI: 1.153–1.687, *P*=0.001). Race, histology, grade, pathologic T stage, pathologic N stage, PR status, and surgery were validated as independent prognostic factors as well.

Interestingly, we observed a better 5-year CSS in the no-radiotherapy group (90.1%) than among those who received radiotherapy (85.3%). Complicated influence of unadjusted confounders was a possible reason, but the 2 groups showed no significant difference in the multivariate analysis (Table 2).

Impact of marital status on overall survival (OS) of HR positive MBC patients

Univariate analysis (Kaplan-Meier analysis) and multivariate analysis (multivariate Cox regression analysis) were also used to evaluate the effect of marital status on the overall survival (OS) of HR positive MBC patients (Table 3). Unmarried men had worse 5-year OS than did married men (64.2% *vs.* 78.6%; χ^2=79.335, *P*<0.0001; Figure 2B and Table 3). In univariate analysis, age (*P*<0.0001), race (*P*<0.0001), histology (*P*=0.002), grade (*P*<0.0001), pathologic T stage (*P*<0.0001), pathologic N stage (*P*<0.0001), PR status (*P*=0.017), HER2 status (*P*=0.008), and surgery (*P*<0.0001) were also associated with OS and they were further included in multivariate Cox regression analyses (Table 3). Marital status was also an independent prognostic factor in the multivariate analysis after adding the other prognostic factors. Unmarried status significantly increased overall mortality risk (hazard ratio: 1.548, 95% CI: 1.373–1.746, *P*<0.0001). We also included radiotherapy in the multivariate analysis because it is an important confounder of MBC, although the *P* value of radiotherapy in univariate analysis was >0.05; radiotherapy still demonstrated a protective effect on OS (hazard ratio: 0.824, 95% CI: 0.717–0.947, *P*=0.006) after multivariate Cox regression. Age, race, grade, pathologic T stage, pathologic N stage, HER2 status, and surgery were also associated with OS in multivariate analysis (Table 3).

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Table 1. Baseline characteristic of male patients with HR positive breast cancer in SEER database, by marital status.

Characteristic (%)	Total (%)		Married (%)		Unmarried (%)		P value
	3612 (100.0)		2548 (70.5)		1064 (29.5)		
Age							**0.003**
<50	445	(12.3)	283	(11.1)	162	(15.2)	
50–64	1259	(34.9)	895	(35.1)	364	(34.2)	
≥65	1908	(52.8)	1370	(53.8)	538	(50.6)	
Race							**<0.0001**
White	2932	(81.2)	2113	(82.9)	819	(77.0)	
Black	462	(12.8)	252	(9.9)	210	(19.7)	
Other	202	(5.6)	171	(6.7)	31	(2.9)	
Unknown	16	(0.4)	12	(0.5)	4	(0.4)	
Residence type							0.935
Metropolitan	3238	(89.6)	2287	(89.8)	951	(89.4)	
Non-metropolitan	360	(10.0)	251	(9.9)	109	(10.2)	
Unknown	14	(0.4)	10	(0.4)	4	(0.4)	
Histology							0.103
Ductal	3153	(87.3)	2230	(87.5)	923	(86.7)	
Lobular	33	(0.9)	28	(1.1)	5	(0.5)	
Others	426	(11.8)	290	(11.4)	136	(12.8)	
Grade							0.369
Well/moderately differentiated	2208	(61.1)	1574	(61.8)	634	(59.6)	
Poorly/undifferentiated	1183	(32.8)	825	(32.4)	358	(33.6)	
Unknown	221	(6.1)	149	(5.8)	72	(6.8)	
Pathologic T stage							**<0.0001**
T0–T1	1174	(32.5)	891	(35.0)	283	(26.6)	
T2	1166	(32.3)	778	(30.5)	388	(36.5)	
T3	139	(3.8)	86	(3.4)	53	(5.0)	
Unknown	1133	(31.4)	793	(31.1)	340	(32.0)	
Pathologic N stage							**<0.0001**
N0	1746	(48.3)	1282	(50.3)	464	(43.6)	
N1	1008	(27.9)	729	(28.6)	279	(26.2)	
N2	335	(9.3)	227	(8.9)	108	(10.2)	
N3	172	(4.8)	109	(4.3)	63	(5.9)	
Unknown	351	(9.7)	201	(7.9)	150	(14.1)	
ER status							0.192
Negative	31	(0.9)	19	(0.7)	12	(1.1)	
Positive	3578	(99.1)	2528	(99.2)	1050	(98.7)	
Unknown	3	(0.1)	1	(0.0)	2	(0.2)	
PR status							0.549
Negative	374	(10.4)	265	(10.4)	109	(10.2)	
Positive	3161	(87.5)	2233	(87.6)	928	(87.2)	
Unknown	77	(2.1)	50	(2.0)	27	(2.5)	

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Table 1 continued. Baseline characteristic of male patients with HR positive breast cancer in SEER database, by marital status.

Characteristic (%)	Total (%)	Married (%)	Unmarried (%)	P value
	3612 (100.0)	2548 (70.5)	1064 (29.5)	
HER2 status				0.866
Negative	1130 (31.3)	792 (31.1)	338 (31.8)	
Positive	144 (4.0)	100 (3.9)	44 (4.1)	
Unknown	2338 (64.7)	1656 (65.0)	682 (64.1)	
Surgery				**0.013**
No	101 (2.8)	58 (2.3)	43 (4.0)	
Yes	3143 (87.0)	2230 (87.5)	913 (85.8)	
Unknown	368 (10.2)	260 (10.2)	108 (10.2)	
Radiation				0.605
No	2696 (74.6)	1908 (74.9)	788 (74.1)	
Yes	916 (25.4)	640 (25.1)	276 (25.9)	

ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; PR – progesterone receptor. SEER – The Surveillance Epidemiology and End Results.

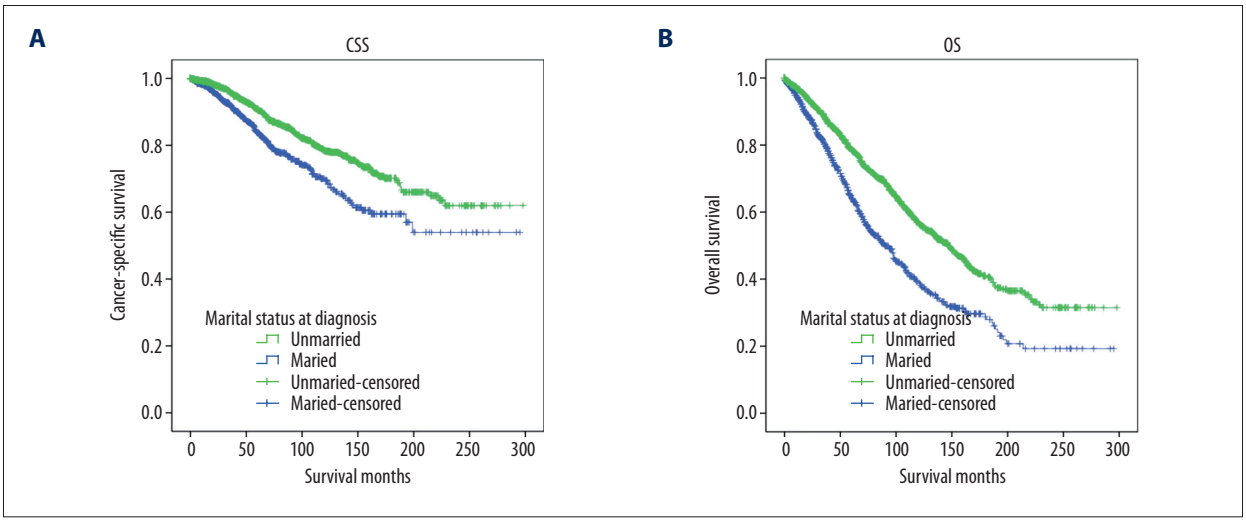

Figure 2. Kaplan-Meier survival curves for cancer-specific survival (CSS) and overall survival (OS) in married *vs.* unmarried male patients with hormone receptor (HR) positive breast cancer. (**A**) CSS: χ^2=28.501, *P*<0.0001; (**B**) OS: χ^2=79.335, *P*<0.0001.

Survival analysis in matched groups

To control for confounding variables, we used case matching to determine if these factors were responsible for the benefit seen with marital status. A total of 1049 cases in the married group were successfully matched with 1049 cases from the unmarried group (Table 4). We also analyzed CSS and OS by marital status with the case-matched cohorts. As with the total group, the married group showed significant CSS and OS benefits in stratified log-rank tests with matched pairs (Figure 3), which was confirmed through multivariate analysis with the Cox proportional hazards model performed on the propensity-matched cohort. Univariate analysis of CSS and OS in matched groups also showed results similar to Tables 2 and 3. However, when compared with an unmatched cohort, race and histology were not significantly associated with OS in the matched cohort. In addition to marital status, multivariate Cox analyses further confirmed the independent prognostic significance of tumor grade, pathologic T stage, and pathologic N stage in CSS and OS. We also found that PR status and surgery were significantly associated with CSS (hazard ratio: 0.473,95% CI: 0.555–0.995, *P*=0.046), but not OS. Although race did not reach significance in univariate analysis, white race was associated with improved OS in multivariate analysis when compared to black race (hazard ratio: 1.285,95% CI: 1.063–1.553, *P*=0.009). The results are summarized in Tables 5 and 6.

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Table 2. Univariate and multivariate analyses for of CSS predictors in men with hormone receptor-positive breast cancer.

Variables	5-year CSS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
Marital status		28.501	**<0.0001**			
Married	90.8				Reference	
Unmarried	83.8			1.394	1.153–1.687	**0.001**
Age		1.214	0.545			
<50	89.8				Reference	
50–64	91.0			0.950	0.728–1.238	0.702
≥65	87.0			1.203	0.925–1.566	0.169
Race		37.467	**<0.0001**			
White	89.9				Reference	
Black	79.9			1.731	1.369–2.189	**<0.0001**
Other	91.5			0.935	0.617–1.417	0.753
Residence type		0.734	0.693			
Metropolitan	89.1					
Non-metropolitan	86.4					
Histology		16.697	**<0.0001**			
Ductal	88.1				Reference	
Lobular	92.4			0.761	0.240–2.412	0.642
Others	93.9			0.600	0.416–0.867	**0.007**
Grade		55.794	**<0.0001**			
Well/moderately differentiated	92.1				Reference	
Poorly/undifferentiated	82.8			1.611	1.336–1.942	**<0.0001**
Pathologic T stage		69.301	**<0.0001**			
T0–T1	96.5				Reference	
T2	84.9			2.199	1.577–3.067	**<0.0001**
T3	77.2			2.838	1.649–4.883	**<0.0001**
Pathologic N stage		313.683	**<0.0001**			
N0	95.2				Reference	
N1	88.7			2.366		**<0.0001**
N2	79.4			4.235		**<0.0001**
N3	67.7			6.261		**<0.0001**
ER status		0.156	0.925			
Negative	89.2					
Positive	88.9					

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Table 2. Univariate and multivariate analyses for of CSS predictors in men with hormone receptor-positive breast cancer.

Variables	5-year CSS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
PR status		26.386	**<0.0001**			
Negative	84.2				Reference	
Positive	89.3			0.669	0.531–0.844	**0.001**
HER2 status		6.467	**0.039**			
Negative	93.1				Reference	
Positive	83.8			1.316	0.575–3.012	0.516
Surgery		57.175	**<0.0001**			
No	74.2				Reference	
Yes	90.3			0.505	0.290–0.880	**0.016**
Radiation		17.788	**<0.0001**			
No	90.1				Reference	
Yes	85.3			0.982	0.802–1.203	0.860

CI – confidence interval; CSS – cause-specific survival; ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; R – hazard ratio; PR – progesterone receptor.

Table 3. Univariate and multivariate analyses of OS predictors in men with hormone receptor-positive breast cancer.

Variables	5-year OS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
Marital status		79.335	**<0.0001**			
Married	78.6				Reference	
Unmarried	64.2			1.548	1.373–1.746	**<0.0001**
Age		280.203	**<0.0001**			
<50	86.9				Reference	
50–64	85.4			1.167	0.930–1.464	0.182
≥65	64.0			3.126	2.534–3.857	**<0.0001**
Race		18.314	**<0.0001**			
White	74.9				Reference	
Black	67.4			1.378	1.166–1.629	**<0.0001**
Other	82.5			0.791	0.601–1.043	0.097
Residence type		1.771	0.412			
Metropolitan	74.6					
Non-metropolitan	72.7					
Histology		12.566	**0.002**			
Ductal	73.5				Reference	
Lobular	92.4			0.435	0.179–1.056	0.066
Others	80.2			0.825	0.679–1.001	0.052

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Table 3 continued. Univariate and multivariate analyses of OS predictors in men with hormone receptor-positive breast cancer.

Variables	5-year OS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
Grade		35.760	**<0.0001**			
Well/moderately differentiated	78.8				Reference	
Poorly/undifferentiated	66.5			1.327	1.175-1.498	**<0.0001**
Pathologic T stage		113.607	**<0.0001**			
T0–T1	87.4				Reference	
T2	68.0			1.858	1.531-2.255	**<0.0001**
T3	58.9			2.363	1.680-3.324	**<0.0001**
Pathologic N stage		470.864	**<0.0001**			
N0	85.2				Reference	
N1	74.4			1.669	1.444-1.930	**<0.0001**
N2	66.0			2.479	2.035-3.019	**<0.0001**
N3	58.6			2.805	2.226-3.534	**<0.0001**
ER status		0.265	0.876			
Negative	76.1					
Positive	74.5					
PR status		8.173	**0.017**			
Negative	71.6				Reference	
Positive	74.5			0.870	0.738–1.026	**0.098**
HER2 status		9.636	**0.008**			
Negative	76.7				Reference	
Positive	66.1			1.625	1.019–2.591	**0.041**
Surgery		109.767	**<0.0001**			
No	39.7				Reference	
Yes	77.1			0.694	0.494–0.976	**0.036**
Radiation		0.113	0.737			
No	74.0				Reference	
Yes	75.8			0.824	0.717–0.947	**0.006**

CI – confidence interval; ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; HR – hazard ratio; OS – overall survival; PR – progesterone receptor.

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Table 4. Characteristics of male patients with breast cancer by marital status, in 1: 1 matched groups.

Characteristic (%)	Total (%)	Married (%)	Unmarried (%)	P value
	2098 (100.0)	1049 (100.0)	1049 (100.0)	
Age				**0.088**
<50	349(16.6)	189(18.0)	160(15.3)	
50–64	686(32.7)	323(30.8)	363(34.6)	
≥65	1063(50.7)	537(51.2)	526(50.1)	
Race				**0.633**
White	1649 (78.6)	830 (79.1)	819 (78.1)	
Black	372 (17.7)	177 (16.9)	195 (18.6)	
Other	67 (3.2)	36 (3.4)	31 (3.0)	
Unknown	10 (0.5)	6 (0.6)	4 (0.4)	
Residence type				0.599
Metropolitan	1861 (88.7)	924 (88.1)	937 (89.3)	
Non-metropolitan	227 (10.8)	119 (11.3)	108 (10.3)	
Unknown	10 (0.5)	6 (0.6)	4 (0.4)	
Histology				0.929
Ductal	1818 (86.7)	908 (86.6)	910 (86.7)	
Lobular	9 (0.4)	4 (0.4)	5 (0.5)	
Others	271 (12.9)	137 (13.1)	134 (12.8)	
Grade				0.649
Well/moderately differentiated	1246 (59.4)	619 (59.0)	627 (59.8)	
Poorly/undifferentiated	701 (33.4)	349 (33.3)	352 (33.6)	
Unknown	151 (7.2)	81 (7.7)	70 (6.7)	
Pathologic T stage				**0.706**
T0–T1	563 (26.8)	280 (26.7)	283 (27.0)	
T2	747 (35.6)	365 (34.8)	382 (36.4)	
T3	100 (4.8)	48 (4.6)	52 (5.0)	
Unknown	688 (32.8)	356 (33.9)	332 (31.6)	
Pathologic N stage				**0.756**
N0	958 (45.7)	494 (47.1)	464 (44.2)	
N1	539 (25.7)	260 (24.8)	279 (26.6)	
N2	207 (9.9)	100 (9.5)	107 (10.2)	
N3	125 (6.0)	62 (5.9)	63 (6.0)	
Unknown	269 (12.8)	133 (12.7)	136 (13.0)	
ER status				0.732
Negative	26 (1.2)	15 (1.4)	11 (1.0)	
Positive	2070 (98.7)	1033 (98.5)	1037 (98.9)	
Unknown	2 (0.1)	1 (0.1)	1 (0.1)	
PR status				0.397
Negative	237 (11.3)	128 (12.2)	109 (10.4)	
Positive	1812 (86.4)	898 (85.6)	914 (87.1)	
Unknown	49 (2.3)	23 (2.2)	26 (2.5)	

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Table 4 continued. Characteristics of male patients with breast cancer by marital status, in 1: 1 matched groups.

Characteristic (%)	Total (%)		Married (%)		Unmarried (%)		P value
	2098 (100.0)		1049 (100.0)		1049 (100.0)		
HER2 status							0.418
Negative	688	(32.8)	356	(33.9)	332	(31.6)	
Positive	93	(4.4)	49	(4.7)	44	(4.2)	
Unknown	1317	(62.8)	664	(61.4)	673	(64.2)	
Surgery							0.792
No	68	(3.2)	32	(3.1)	36	(3.4)	
Yes	1813	(86.4)	905	(86.3)	908	(86.6)	
Unknown	217	(10.3)	112	(10.7)	105	(10.0)	
Radiation							1.000
No	1550	(73.9)	775	(73.9)	775	(73.9)	
Yes	548	(26.1)	274	(26.1)	274	(26.1)	

ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; PR – progesterone receptor.

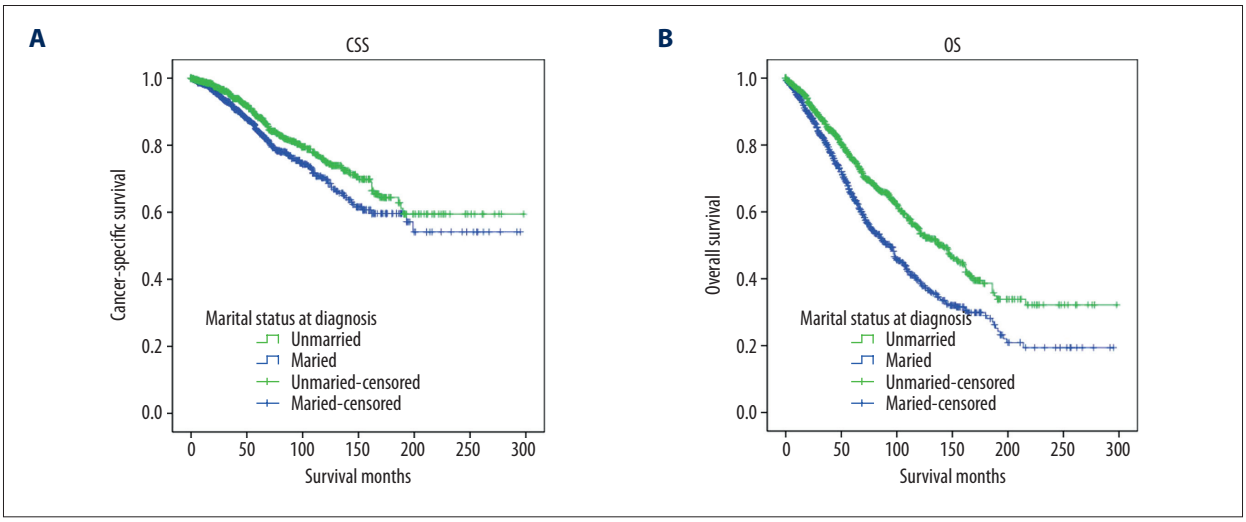

Figure 3. Kaplan-Meier survival curves of 1: 1 matched group for cancer-specific survival (CSS) and overall survival (OS) in married *vs.* unmarried male patients with hormone receptor (HR) positive breast cancer: (**A**) CSS: χ^2=4.730, *P*=0.030. (**B**) OS: χ^2=30.037, *P*<0.0001.

Stratification analysis according to ER/PR status and tumor stage

Based on ER and PR expression, HR positive MBC can be further classified as ER^-/PR^+, ER^+/PR^- and ER^+/PR^+ subtypes. To further investigate the prognostic effect of marital status on CSS and OS in different subtypes, we stratified all the cases by ER and PR expression and performed univariate analyses. Of the 3532 cases, 31 were ER^-/PR^+, 374 were ER^+/PR^- and 3127 were ER^+/PR^+. Distribution of these subgroups did not significantly differ among the married and unmarried groups (*P*=0.513; Supplementary Table 1). Kaplan-Meier curves for the 3 subgroups showed that only married patients with ER^+/PR^+ subtypes had better 5-year CSS and OS, but not the other 2 subtypes (Figure 4). Consequently, marriage clearly benefited HR positive MBC prognosis among patients with ER^+/PR^+ subtype. Relevance between marital status and stage at diagnosis was also shown by univariate logistic regression models (see Supplementary Table 2), which found no significant difference in CSS between the married and unmarried groups with respect to TNM stage, which was further confirmed in matched groups.

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Table 5. Univariate and multivariate analyses of CSS predictors in 1: 1 matched groups of men with breast cancer.

Variables	5-year CSS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
Marital status		4.730	**0.030**			
Married	87.4				Reference	
Unmarried	84.3			1.273	1.021–1.586	**0.032**
Age		1.737	0.420			
<50	88.8				Reference	
50–64	86.7			1.028	0.754–1.401	0.863
≥65	84.2			1.203	0.882–1.641	0.242
Race		12.183	**0.007**			
White	87.0				Reference	
Black	80.6			1.475	1.130–1.926	**0.004**
Other	84.9			0.889	0.454–1.744	0.733
Residence type		1.899	0.387			
Metropolitan	86.4					
Non-metropolitan	81.5					
Histology		7.669	**0.022**			
Ductal	85.0				Reference	
Lobular	85.7			1.358	0.187–9.867	0.762
Others	90.9			0.749	0.505–1.109	0.149
Grade		28.095	**<0.0001**			
Well/moderately differentiated	89.0				Reference	
Poorly/undifferentiated	79.4			1.438	1.142–1.811	**0.002**
Pathologic T stage		27.715	**<0.0001**			
T0–T1	94.0				Reference	
T2	81.2			1.879	1.248–2.828	**0.003**
T3	76.6			2.370	1.287–4.365	**0.006**
Pathologic N stage		169.063	<0.0001			
N0	92.9				Reference	
N1	85.3			2.354	1.728–3.207	**<0.0001**
N2	77.6			3.979	2.764–5.727	**<0.0001**
N3	67.1			5.452	3.745–7.939	**<0.0001**
ER status		0.519	0.772			
Negative	90.8					
Positive	85.8					

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Table 5 continued. Univariate and multivariate analyses of CSS predictors in 1: 1 matched groups of men with breast cancer.

Variables	5-year CSS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
PR status		8.441	**0.015**			
Negative	85.0				Reference	
Positive	85.6			0.743	0.555–0.995	**0.046**
HER2 status		5.322	0.070			
Negative	90.9				Reference	
Positive	77.3			1.448	0.581–3.608	0.427
Surgery		30.247	**<0.0001**			
No	71.5				Reference	
Yes	87.0			0.438	0.227–0.848	**0.014**
Radiation		11.689	**0.001**			
No	87.1				Reference	
Yes	82.7			1.054	0.821–1.352	0.681

CI – confidence interval; CSS – cause-specific survival; ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; HR – hazard ratio; PR – progesterone receptor.

Table 6. Univariate and multivariate analysis of OS predictors in 1: 1 matched groups of men with breast cancer.

Variables	5-year OS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
Marital status		30.037	**<0.0001**			
Married	74.5				Reference	
Unmarried	64.8			1.519	1.315–1.754	**<0.0001**
Age		176.879	**<0.0001**			
<50	85.8				Reference	
50–64	79.9			1.207	0.929–1.569	0.159
≥65	58.0			2.965	2.332–3.769	**<0.0001**
Race		5.568	0.135			
White	69.6				Reference	
Black	68.6			1.285	1.063–1.553	**0.009**
Other	69.5			0.835	0.547–1.275	0.403
Residence type		3.073	0.215			
Metropolitan	70.1					
Non-metropolitan	65.0					

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Table 6 continued. Univariate and multivariate analysis of OS predictors in 1: 1 matched groups of men with breast cancer.

Variables	5-year OS (%)	Univariate analysis		Multivariate analysis		
		Log Rank χ^2 test	*P* value	HR	95% CI	*P* value
Histology		6.614	**0.037**			
Ductal	68.5				Reference	
Lobular	85.7			0.747	0.183–3.054	0.685
Others	76.4			0.815	0.646–1.028	0.084
Grade		28.177	**<0.0001**			
Well/moderately differentiated	75.0				Reference	
Poorly/undifferentiated	59.6			1.379	1.184–1.607	**<0.0001**
Pathologic T stage		63.425	**<0.0001**			
T0–T1	84.4				Reference	
T2	63.2			1.971	1.516–2.561	**<0.0001**
T3	57.1			2.420	1.621–3.613	**<0.0001**
Pathologic N stage		279.309	**<0.0001**			
N0	81.6				Reference	
N1	69.9			1.588	1.310–1.926	**<0.0001**
N2	64.0			2.332	1.815–2.996	**<0.0001**
N3	59.6			2.517	1.908–3.319	**<0.0001**
ER status		0.656	0.720			
Negative	75.1					
Positive	69.5					
HER2 status		9.335	**0.009**			
Negative	72.8				Reference	
Positive	61.3			1.557	0.882–2.748	0.127
Surgery		64.162	**<0.0001**			
No	36.9				Reference	
Yes	72.2			0.694	0.464–1.040	0.077
Radiation		0.324	0.569			
No	68.1				Reference	
Yes	73.7			0.865	0.728–1.029	0.101

CI – confidence interval; ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; HR – hazard ratio; OS – overall survival; PR – progesterone receptor.

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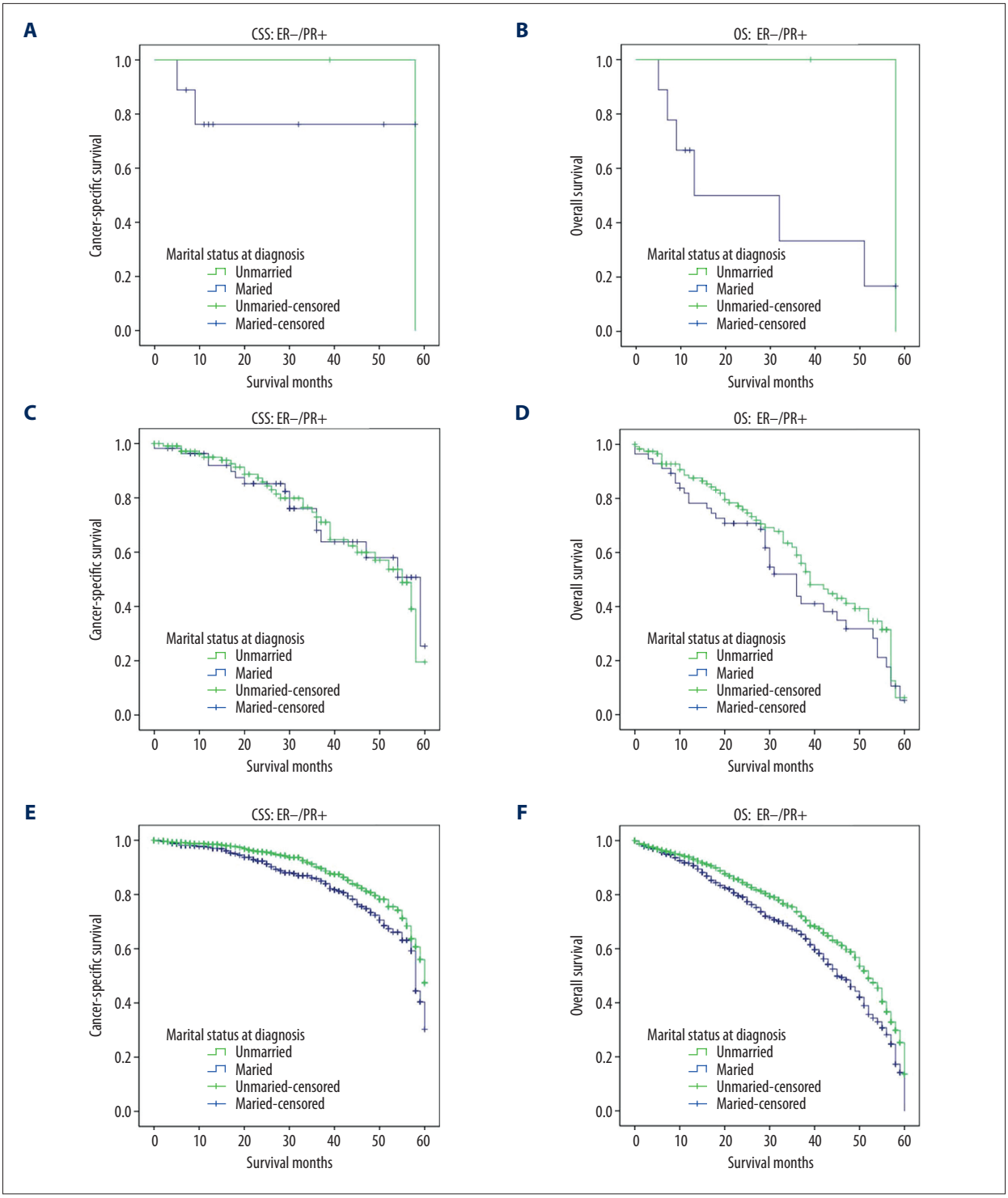

Figure 4. Kaplan-Meier survival analysis of the effect of marital status on cancer-specific survival (CSS) and overall survival (OS) in 3612 male patients with breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status. (**A**) CSS ER$^-$/PR$^+$: χ^2=0.016, *P*=0.899; (**B**) OS ER$^-$/PR$^+$: χ^2=0.968, *P*=0.325; (**C**) CSS ER$^+$/PR$^-$: χ^2=0.030, *P*=0.862; (**D**) OS ER$^+$/PR$^-$: χ^2=1.578, *P*=0.209; (**E**) CSS ER$^+$/PR$^+$: χ^2=9.557, *P*=0.002; (**F**) OS ER$^+$/PR$^+$: χ^2=16.475, *P*<0.001.

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Discussion

Because MBC is a relatively rare disease, prognostic evaluation in MBC is often modeled after FBC. However, it is known that FBC and MBC differ biologically. Incidence of hormone receptor expression is strikingly different, and it is reportedly higher in MBC than in FBC [22]. Among MBC cases, receptor phenotypes were: ER^+/PR^+ (86%), ER^+/PR^- (6%), ER^-/PR^+ (3%) and ER^-/PR^- (5%) [23]. Moreover, the presence of HR positive tumors in men does not increase with age, which is common observed in FBC [24]. As most MBC are HR positive, we carried out this population-based study to better characterize prognostic factors.

It has been confirmed that marital status is considered as a protective survival factor in different cancer types [25–27]. However, effects of marital status on HR positive MBC survival have not been fully examined. In this study, we first explored the influence of marital status on CSS and OS in patients with HR positive MBC; we found that both CSS and OS were better in married patients than in their single, divorced, separated, or widowed counterparts. In multivariable analyses, the beneficial effect for married patients remained, even after adjusting for age, race, residence, histology, grade, pathologic T stage, pathologic N stage, ER status, PR status, HER2 status, surgery, and radiotherapy. As HR status is an important biologic prognostic indicator in breast cancer, subgroup analysis later evaluated the impact of marital status on survival by different HR phenotypes.

To our knowledge, this is the first study to find that marriage is only associated with improved CSS among patients with the ER^+/PR^+ subtype. An earlier hypothesis for worse survival among unmarried patients was that they tended to present with delayed diagnoses at advanced tumor stages [18,20]. However, we found no significant difference in CSS between the married and unmarried groups by TNM stage, which was confirmed in matched groups. Obviously, delayed diagnosis alone cannot explain the poorer survival outcomes in unmarried patients.

Our result show that marital status is associated with survival in patients with HR positive MBC and have emphasized the relationship between marital status and survival rather than causal relationships. Why marital status of married patients serves as a protective factor warrants further study. However, accumulating evidence suggested that physiological changes that accompany stress and depression may affect cancer outcomes through different mechanisms. Decreased psychosocial support and psychological stress has been reportedly associated with immune dysfunction, which may contribute to tumor progression and mortality [28,29]; and lack of social support can depress natural killer cell activity [30], which could result in disorders of various endocrine hormones [31,32]. Sex hormone disorder is closely related to occurrence and development of breast cancer. A cohort study has associated depression and anxiety with breast cancer recurrence [33]. Breast cancer patients, and male patients in particular, suffer from significant psychological and socioeconomic stress [34]. With no spouses to share their emotional burdens, unmarried cancer patients may experience more distress, depression, and anxiety than married patients [35,36]. Although unmarried patients may have support from friends and family, this support did not lead to lower psychological distress, whereas any beneficial social support received by male cancer patients from friends and family may be mediated by spousal support [36]. Psychosocial support from a spouse may ultimately translate to less distress and greater fighting spirit to improve adherence to cancer treatment [37,38]. Married patients are also more likely than unmarried patients to have better family financial circumstances, to seek treatment at more prestigious medical centers, to accept curative therapies, and to comply with treatment, all of which may contribute to better outcomes [39–41].

This study had some limitations. First, as important information regarding chemotherapy or systemic therapy was not provided in SEER database, and could not be adjusted by our analyses, whether they contributed to survival differences by marital status is unclear. Second, the SEER database only provides the marital status at diagnosis, but details about the duration or quality of the marriage, or any changes in marital status, were not tracked, which might influence the prognosis of MBC patients. Third, some important demographic factors were not recorded in the SEER databases, such as education, insurance, income status, and family status, all of which may influence the effect of marital status on cancer survival [42,43]. Fourth, data on ER, PR, and HER2 status were collected from different local pathology laboratories and could not be further verified, which might increase the possibilities of bias.

Conclusions

Despite these potential limitations, this study demonstrated that marital status is an independent prognostic factor for survival in HR positive MBC patients. Unmarried patients are at greater risk for overall and tumor cause-specific mortality independent of age, race, grade, stage, surgery, and radiotherapy. Particularly, subgroup analysis showed that the beneficial survival results of married patients in HR positive MBC is associated with ER^+/PR^+ subtype. The main reasons for poor survival in unmarried patients can be explained hypothetically by social support and psychological factors. Therefore, more social and psychological supports should be provided for unmarried patients. Further understanding of the potential associations among the marital status, psychosocial factors and survival outcomes may help to identify sound strategies of treatment in HR positive MBC patients.

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Disclosure

The authors declare that they have no competing interests.

Supplementary Tables

Supplementary Table 1. Men with breast cancer by ER/PR status.

Subtype	Total (%)	Married (%)	Unmarried (%)	P value
	3532 (100.0)	2497 (100.0)	1035 (100.0)	
ER^-PR^+	31 (0.9)	19 (0.8)	12 (1.2)	0.513
ER^+PR^-	374 (10.6)	265 (10.6)	109 (10.5)	
ER^+PR^+	3127 (88.5)	2213 (88.6)	914 (88.3)	

ER – estrogen receptor; PR – progesterone receptor.

Supplementary Table 2. Characteristics and subgroup analysis of the effect of marital status on CSS by tumor stage in men with hormone receptor-positive breast cancer.

Stage	Married (%)	Unmarried (%)	Log rank χ^2 test (c)	*P* value	Log rank χ^2 test (c)	*P* value
I	13.8%	11.3%	0.117	0.732	2.462	0.117
II	16.4%	18.5%	3.677	0.055	0.678	0.410
III	6.0%	7.7%	1.120	0.290	1.181	0.277

CSS – cause-specific survival; Log Rank χ^2 test (a), adjusted Log Rank χ^2 test (adjusted for age, race, residence, histology, grade, pathologic T stage, pathologic N stage, ER status, PR status, HER2 status, surgery and radiotherapy); Log Rank χ^2 test (c), crude Log Rank χ^2 test.

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