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Young male breast cancer, a small crowd, the survival, and prognosis?
A population-based study

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Abstract
Women diagnosed with breast cancer at young age often have poorprognoses. Yet, few studies have focused on the prognoses of young men with breast cancer. We therefore used Surveillance, Epidemiology, and End Results (SEER) population-based data and identified 151 male patients with breast cancer aged <40 years between 1988 and 2012. Propensity score matching analysis was used to balance the clinical variables among different groups. Kaplan–Meier curves were applied to compare the survival differences. The subgroup variables on cancer-specific survival (CSS) and overall survival (OS) were analyzed by the Cox proportional hazard model. Results showed that male patients with breast cancer aged <40 had a significant OS benefit compared with those aged ≥40 years ($P < .001$). The significant difference of the CSS was not found ($P > .05$). Compared with the male patients with breast cancer aged ≥40, those aged <40 had significant OS benefit in most subgroups ($P < .05$). Compared with the female patients with breast cancer aged <40, the male patients with breast cancer aged <40 had worse OS and CSS benefit only in the subgroup with progesterone receptor and estrogen receptor positive ($P < .05$). In conclusion, we demonstrated that young male patients with breast cancer had better OS compared with elder male patients with breast cancer. However, the survival benefit was not found compared with young female patients with breast cancer.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, ER = estrogen receptor, HER-2 = human epidermal growth factor receptor 2, HR = hazard ratio, OS = over survival, PR = progesterone receptor, SEER = Surveillance, Epidemiology, and End Results.

Keywords: male breast cancer, prognosis, Surveillance, Epidemiology, and End Results, survival

1. Introduction

Male breast cancer is an uncommon disease. It accounts for only about 1% of all breast carcinomas all over the world and distinguishes from female breast cancer in some aspects of tumor characteristics.[1,2] Importantly, the incidence of male breast cancer has been gradually on the rise during the past decades.[3,4] For a long time, our understanding of male breast cancer, such as genetic characteristics, hormonal conditions, are not as profound as that of female breast cancer. Interestingly, due to its low incidence, studies reporting the clinical characteristics and optimal treatment of male breast cancer are usually referred to those on female breast cancer.[5] In fact, the prognostic factors and treatment strategies in male breast cancer extrapolated from some related studies of female breast cancer are controversial.[6–8] Therefore, it is imperative to comprehensively understand the molecular mechanism and prognostic factors of male breast cancer.

As known to us all, breast cancer has been more prevalent among young women.[9,10] Women diagnosed with breast cancer at young age often have poor prognoses.[9,11] Studies have shown that young women with breast cancer are more likely to be presented with luminal B subtype and at advanced stages, to be of higher grade and with more lymphovascular invasion. Besides, women diagnosed with breast cancer at younger age are more likely to be poorly differentiated, human epidermal growth factor receptor 2 (HER-2)-positive and estrogen receptor (ER)-negative, which contributes to the worsened prognoses.[11–14] Because of the specificity of young male patients with breast cancer, we attempt to investigate if their prognoses differ from those of the young female patients with breast cancer and the old male patients with breast cancer. Relevant researches focusing on the particular population are rare due to its rather smaller proportion. However, it is worth to further study the prognostic factors affecting the survival of young male patients with breast cancer.

In this study, we evaluated the clinicopathologic features and prognosis in men diagnosed with breast cancer prior to 40 years old. The population-based data were extracted from the Surveillance, Epidemiology, and End Results (SEER) registry in the United States published annually by the Data Analysis and Interpretation Branch of the National Cancer Institute, MD.[15]

2. Methods

2.1. Patient selection

The SEER database was used to identify all young male patients with breast cancer diagnosed between 1988 and 2012.[15] A total of 18 population-based cancer registries in the United States were included in the current SEER database. The SEER*Stat software (SEER*Stat 8.2.1) was used to identify patients. All cases before 1988 were excluded because of incomplete information on staging and surgery. The inclusion criteria were malignant behavior and the diagnosis was confirmed microscopically, with known age, active follow-up, and the age at diagnosis with <40 years. The exclusion criteria were benign or borderline tumors, with unknown age, unknown cause of death, unknown survival months.

2.2. Ethics statement

As previously described,[16] this study was mainly based on the SEER database and was conducted in compliance with the Helsinki Declaration. We obtained permission to access the SEER program research data files and the reference number is 11824-Nov2014. The informed consent was not required since personal identifying information was not involved. This study was approved by the ethics committee of the Shandong Cancer Hospital affiliated to Shandong University.

2.3. Statistical analysis

For all patients, the following variables were analyzed: Race, American Joint Committee on Cancer (AJCC) stage, Grade, Metastasis status, ER status, progesterone receptor (PR) status, Radiation. In addition, the overall survival (OS) and cancer-specific survival (CSS) were regarded as the primary endpoint of this study and extracted from the SEER database. Chi-squared tests were used to compare the patient's baseline characteristics. The Kaplan–Meier estimates were used to generate the survival curves and the Log Rank test was applied to analyze the differences among the curves. The propensity score matching analysis was used to determine the comparative patients. In detail, the propensity score matching was preformed according to 1:1 matching and the matching tolerance is 0. Between the male patients <40 and the male patients ≥40, a total of 89 patients were matched successfully. Between the male patients <40 and the female patients <40, a total of 86 patients were matched successfully. The Cox proportional hazard analysis was used to analyze the survival based on different subgroup variables, and the concrete results were presented in the forest plot. All statistical tests were 2-sided, and a $P < .05$ was considered statistically significant. The statistical software SPSS 22.0 (SPSS, Chicago, IL) was used for all data analyses.

3. Results

3.1. Patient demographics

There were 151 cases of male patients with breast cancer aged <40 years reported in the SEER database from 1988 to 2012. Importantly, for a better comparison, we also identified 6930 cases of male patients with breast cancer aged ≥40 years and 52,710 cases of female patients with breast cancer aged <40 years in the SEER database from 1988 to 2012. The clinical characteristics and pathologic features of all the patients are summarized in Table 1. There was a statistically significant difference in the composition of Race, AJCC stage, Grade, Metastasis status, ER status, PR status, and Radiation ($P < .001$).

Table 1

Characteristics of patients from SEER database from 1988 to 2012.

Characteristic	Male <40 y (%)	Male ≥40 y (%)	Female < 40 y (%)	P-value
Total	151	6930	52,710	
Race				<.001
White	107 (70.86)	5671 (81.83)	38,480 (73.00)	
Black	28 (18.54)	876 (12.64)	8134 (15.43)	
Other	12 (7.95)	334 (4.82)	5711 (10.83)	
AJCC stage				<.001
I	41 (27.15)	2133 (30.78)	14,275 (27.08)	
II	55 (36.42)	2587 (37.33)	21,579 (40.94)	
III	30 (19.87)	1128 (16.28)	10,361 (19.66)	
IV	9 (5.96)	456 (6.58)	2454 (4.66)	
Grade				<.001
I	10 (6.62)	769 (11.10)	3314 (6.29)	
II	54 (35.76)	3055 (44.08)	14,642 (27.78)	
III	61 (40.40)	2108 (30.42)	26,739 (50.73)	
Metastasis				<.001
Yes	9 (5.96)	456 (6.58)	2454 (4.66)	
No	126 (83.44)	6304 (84.39)	46,215 (87.68)	
ER status				<.001
Positive	102 (67.55)	5341 (76.68)	27,525 (52.22)	
Negative	20 (13.25)	307 (4.43)	16,486 (31.28)	
PR status				<.001
Positive	82 (54.30)	4663 (67.29)	24,319 (46.14)	
Negative	37 (24.50)	831 (11.99)	19,138 (36.31)	
Radiotherapy				<.001
Yes	42 (27.81)	1580 (22.80)	23,727 (45.01)	
No	101 (66.89)	5186 (74.83)	26,898 (51.03)	

AJCC = American Joint Committee on Cancer, ER = estrogen receptor, PR = progesterone receptor, SEER = Surveillance, Epidemiology, and End Results.

In addition, compared with male patients with breast cancer aged ≥40 years, the young male patients with breast cancer were more likely to be black race (18.54% vs 12.64%), less tumor at grade I/II (42.38% vs 55.18%), lower hormone receptor positive (67.5% vs 76.68% for ER status and 54.30% vs 67.29% for PR status). Compared with female patients with breast cancer aged <40 years, the young male patients with breast cancer were more likely to be hormone receptor positive (67.5% vs 52.22 for ER status and 54.30% vs 46.14% for PR status). Interestingly, fewer young male patients with breast cancer received radiation therapy (27.81% vs 45.01%). The detailed statistical results are summarized in Table 1.

3.2. Prognostic analysis of young male patients with breast cancer

The prognoses of male breast cancer and female breast cancer were further analyzed using Kaplan–Meier estimates. As shown in Figure 1, the OS of young male patients with breast cancer was significantly higher than male patients with breast cancer aged ≥40 years ($\chi^2 = 33.929$, $P < .001$) (Fig. 1A). However, there was no significant OS difference between young male patients with breast cancer and young female patients with breast cancer ($\chi^2 = 0.006$, $P = .939$) (Fig. 1A). Interestingly, the significant differences of the CSS among the 3 groups were not found ($\chi^2 = 1.024$, $P = .599$) (Fig. 1B).

3.3. Propensity score matching analysis

The clinical baseline was significantly different among the patients, which may lead to different prognosis. To eliminate the
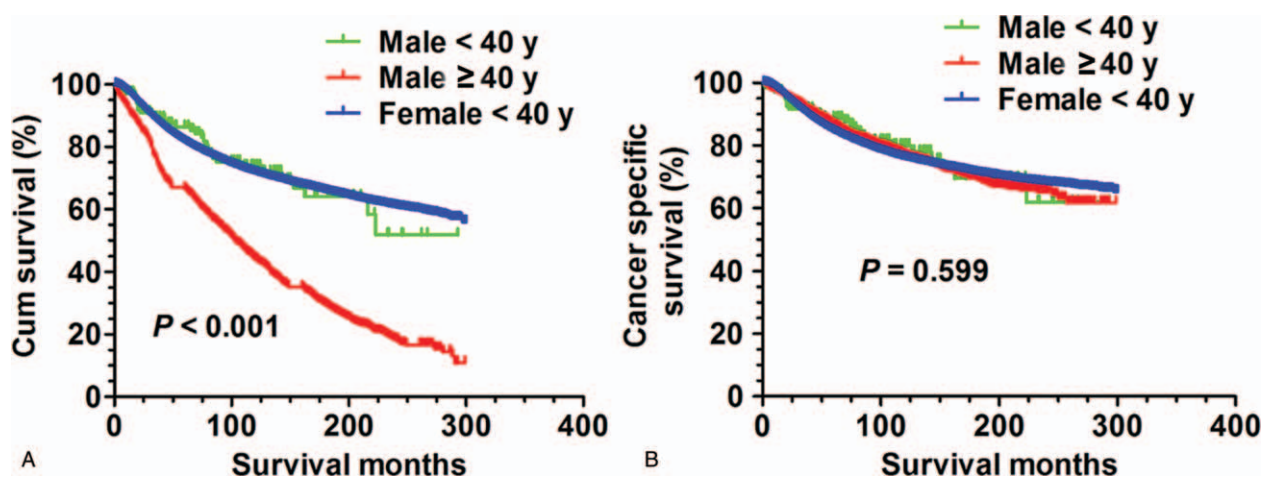
Figure 1. The over survival (OS) and cancer-specific survival (CSS) curves in male breast cancer aged <40 years, male breast cancer aged ≥40 years, female breast cancer aged <40 years between 1988 and 2012. (A) The OS curves: male breast cancer aged <40 years vs male breast cancer aged ≥40 years (χ^2 = 33.929, P < .001); male breast cancer aged <40 years vs female breast cancer aged <40 years (χ^2 = 0.006, P = .939). (B) The CSS curves of 3 different groups (χ^2 = 1.024, P = .599).
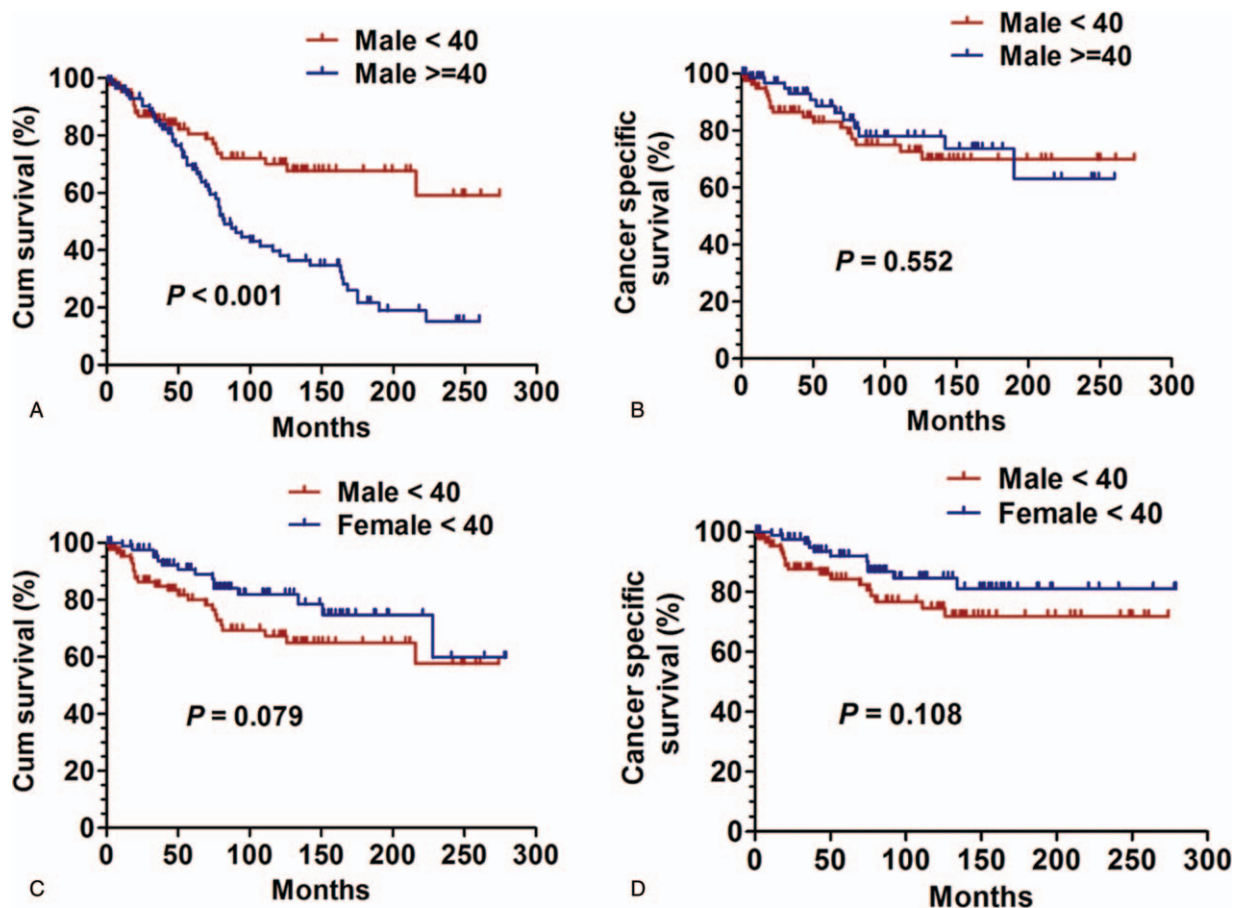
Figure 2. The over survival (OS) and cancer-specific survival (CSS) curves in male breast cancer aged <40 years, male breast cancer aged ≥40 years, female breast cancer aged <40 years between 1988 and 2012 after doing propensity score matching analysis. (A) The OS curves: male breast cancer aged <40 years vs male breast cancer aged ≥40 years (χ^2 = 14.64, P < .001). (B) The CSS curves: male breast cancer aged <40 years vs male breast cancer aged ≥40 years (χ^2 = 0.354, P = .552). (C) The OS curves: male breast cancer aged <40 years vs female breast cancer aged <40 years (χ^2 = 3.085, P = .079). (D) The CSS curves: male breast cancer aged <40 years vs female breast cancer aged <40 years (χ^2 = 2.589, P = .018).
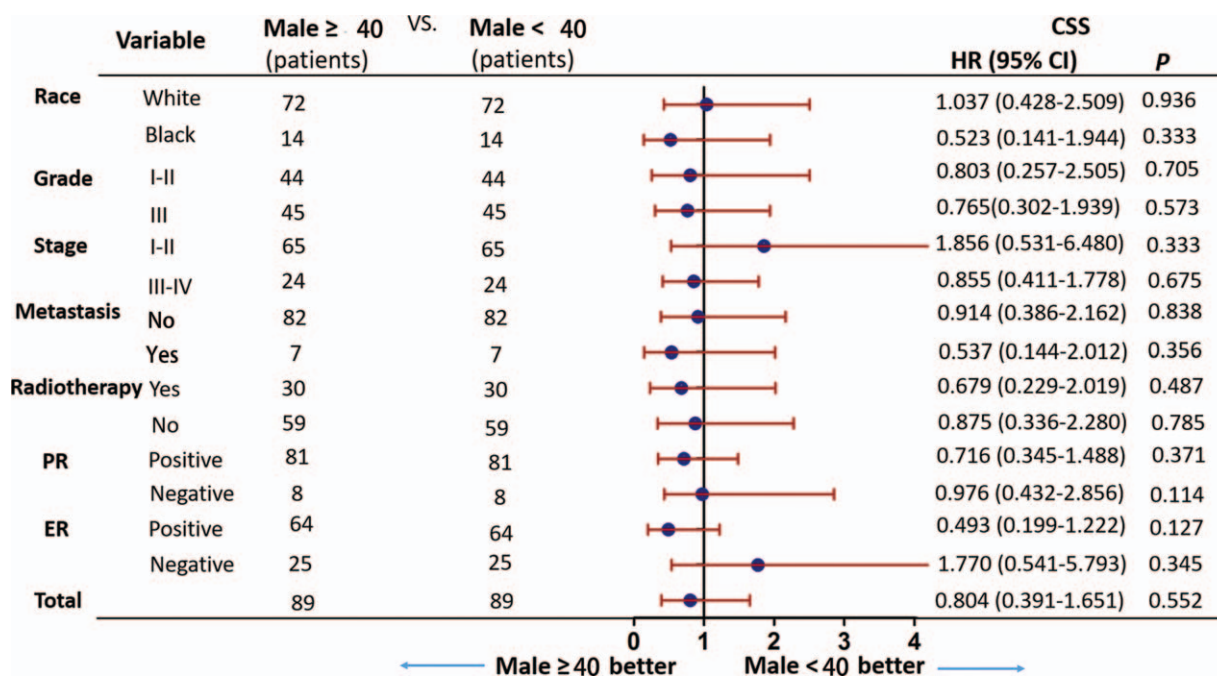
Figure 3. The forest plot for hazard ratio to compare cancer-specific survival (CSS) between male breast cancer aged <40 years and male breast cancer aged ≥40 years according to different variables. CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, PR = progesterone receptor.

influence of clinical baseline and the sample size on survival, propensity score matching was conducted to reevaluate the prognosis. After performing the propensity score matching analysis according to 1:1 matching, all variable factors were well balanced between the 3 groups (all, $P > .05$) (Supplemental Table 2, http://links.lww.com/MD/C540, Supplemental Table 3, http://links.lww.com/MD/C540). Then the prognoses of male breast cancer and female breast cancer were further analyzed using Kaplan–Meier estimates. The results showed that the OS of young male patients with breast cancer was still significantly longer than male patients with breast cancer aged ≥40 years ($\chi^2 = 14.64$, $P < .001$) (Fig. 2A). However, the significant difference between young male patients with breast cancer and male patients with breast cancer aged ≥40 was not found in CSS ($\chi^2 = 0.354$, $P = .552$) (Fig. 2B). Interestingly, there was no significant difference between young male patients with breast cancer and young female patients with breast cancer in CSS and OS ($\chi^2 = 3.085$, $P = .079$ for OS; $\chi^2 = 2.589$, $P = .018$ for CSS) (Fig. 2C and D).

3.4. Subgroup analysis between male patients with breast cancer aged <40 and ≥40

The univariate and multivariate Cox proportional hazard analysis was used to analyze the survival prognosis factors. Then the forest plot was applied to depict the subgroup analysis to adjust for other variables including grade, stage, metastasis, radiotherapy, and PR/ER. The result showed that the patients aged <40 had no significant CSS benefit compared with the patients aged ≥40 among all the subgroup variables (Fig. 3). However, the result showed that the patients aged <40 had significant OS benefit compared with the patients aged ≥40 among most of the subgroup variables (Fig. 4). The subgroup variables including white race (hazard ratio [HR]: 3.156; 95%

confidence interval [CI]: 1.881–5.295; $P < .001$); grades I and II (HR: 2.665; 95% CI: 1.367–5.196; $P = .004$); grade III (HR: 2.173; 95% CI: 1.181–3.996; $P = .013$); stages I and II (HR: 4.516; 95% CI: 2.555–7.982; $P < .001$); no metastasis (HR: 3.065; 95% CI: 1.887–4.980; $P < .001$); no radiotherapy (HR: 2.649; 95% CI: 1.548–4.533; $P < .001$); PR positive (HR: 2.025; 95% CI: 1.270–3.230; $P = .003$); PR negative (HR: 2.235; 95% CI: 1.378–3.907; $P = .002$); ER positive (HR: 2.158; 95% CI: 1.256–3.708; $P < .001$); ER negative (HR: 2.932; 95% CI: 1.309–6.568; $P < .001$).

3.5. Subgroup analysis between young male patients with breast cancer and young female patients with breast cancer

Analogously, the univariate and multivariate Cox proportional hazard analysis was used to analyze the survival prognostic factors. Then forest plot was applied to depict the subgroup analysis to adjust for other variables including grade, stage, metastasis, radiotherapy, and PR/ER. Results showed that the male patients with breast cancer aged <40 had no significant survival benefit including CSS and OS compared with the female patients with breast cancer aged <40 among most of the subgroup variables (Fig. 5). Only in the PR and ER positive subgroup, the male patients with breast cancer had worse CSS benefit compared to the female patients with breast cancer aged <40 (HR: 0.470; 95% CI: 0.223–0.990; $P = .047$ for PR; HR: 0.287; 95% CI: 0.114–0.728; $P = .009$ for ER) (Fig. 5). Importantly, compared with the female patients with breast cancer aged <40, the male patients with breast cancer aged <40 also had worse OS benefit in PR and ER positive subgroup (HR: 0.482; 95% CI: 0.254–0.914; $P = .025$ for PR; HR: 0.375; 95% CI: 0.170–0.827; $P = .015$ for ER) (Fig. 6).
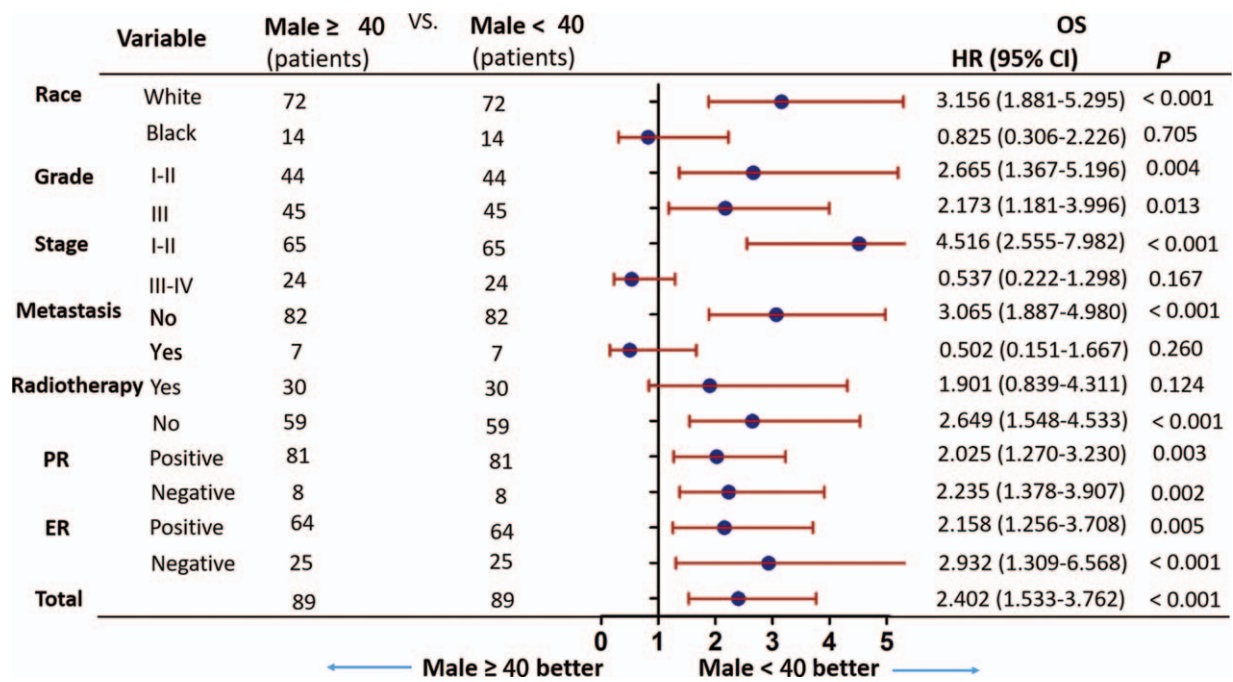
Variable		Male ≥ 40 (patients)	VS.	Male < 40 (patients)		OS HR (95% CI)	P
Race	White	72		72		3.156 (1.881-5.295)	< 0.001
	Black	14		14		0.825 (0.306-2.226)	0.705
Grade	I-II	44		44		2.665 (1.367-5.196)	0.004
	III	45		45		2.173 (1.181-3.996)	0.013
Stage	I-II	65		65		4.516 (2.555-7.982)	< 0.001
	III-IV	24		24		0.537 (0.222-1.298)	0.167
Metastasis	No	82		82		3.065 (1.887-4.980)	< 0.001
	Yes	7		7		0.502 (0.151-1.667)	0.260
Radiotherapy	Yes	30		30		1.901 (0.839-4.311)	0.124
	No	59		59		2.649 (1.548-4.533)	< 0.001
PR	Positive	81		81		2.025 (1.270-3.230)	0.003
	Negative	8		8		2.235 (1.378-3.907)	0.002
ER	Positive	64		64		2.158 (1.256-3.708)	0.005
	Negative	25		25		2.932 (1.309-6.568)	< 0.001
Total		89		89		2.402 (1.533-3.762)	< 0.001

Male ≥ 40 better ←——— | ———→ Male < 40 better

Figure 4. The forest plot for hazard ratio to compare over survival between male breast cancer aged <40 years and male breast cancer aged ≥40 years according to different variables. CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, OS = over survival, PR = progesterone receptor.

4. Discussion

Male breast cancer is a rare disease, accounting for about 1% of all breast malignancies.[1] Most male patients with breast cancer are diagnosed between the age of 60 and 70 years old.[17,18] However, there are few literatures reporting the clinicopathologic features and prognostic factors of young male breast cancer.

Interestingly, studies have reported that the tumor biologic behavior of younger women diagnosed with breast cancer tend to be more aggressive, which would consequently lead to a worsened prognosis compared with older women.[9,11–14] Therefore, an in depth understanding of young male breast cancer is urgently needed.
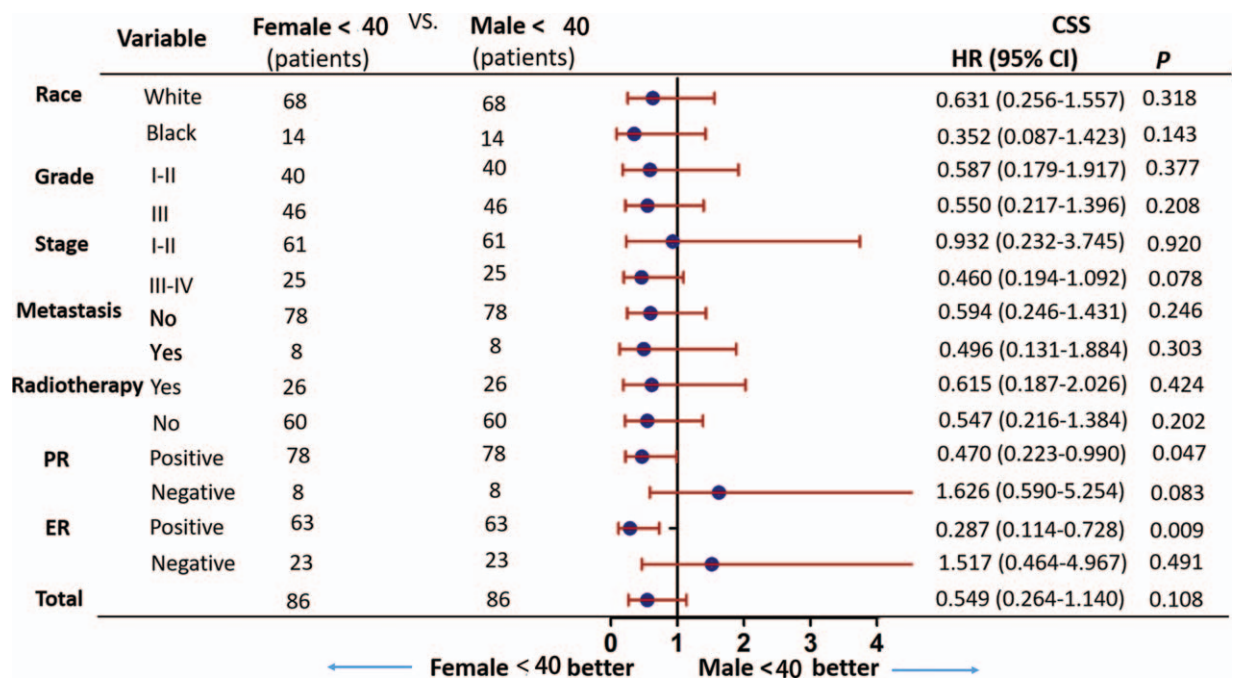
Variable		Female < 40 (patients)	VS.	Male < 40 (patients)		CSS HR (95% CI)	P
Race	White	68		68		0.631 (0.256-1.557)	0.318
	Black	14		14		0.352 (0.087-1.423)	0.143
Grade	I-II	40		40		0.587 (0.179-1.917)	0.377
	III	46		46		0.550 (0.217-1.396)	0.208
Stage	I-II	61		61		0.932 (0.232-3.745)	0.920
	III-IV	25		25		0.460 (0.194-1.092)	0.078
Metastasis	No	78		78		0.594 (0.246-1.431)	0.246
	Yes	8		8		0.496 (0.131-1.884)	0.303
Radiotherapy	Yes	26		26		0.615 (0.187-2.026)	0.424
	No	60		60		0.547 (0.216-1.384)	0.202
PR	Positive	78		78		0.470 (0.223-0.990)	0.047
	Negative	8		8		1.626 (0.590-5.254)	0.083
ER	Positive	63		63		0.287 (0.114-0.728)	0.009
	Negative	23		23		1.517 (0.464-4.967)	0.491
Total		86		86		0.549 (0.264-1.140)	0.108

Female < 40 better ←——— | ———→ Male < 40 better

Figure 5. The forest plot for hazard ratio to compare cancer-specific survival (CSS) between male breast cancer aged <40 years and female breast cancer aged <40 years according to different variables. CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, PR = progesterone receptor.
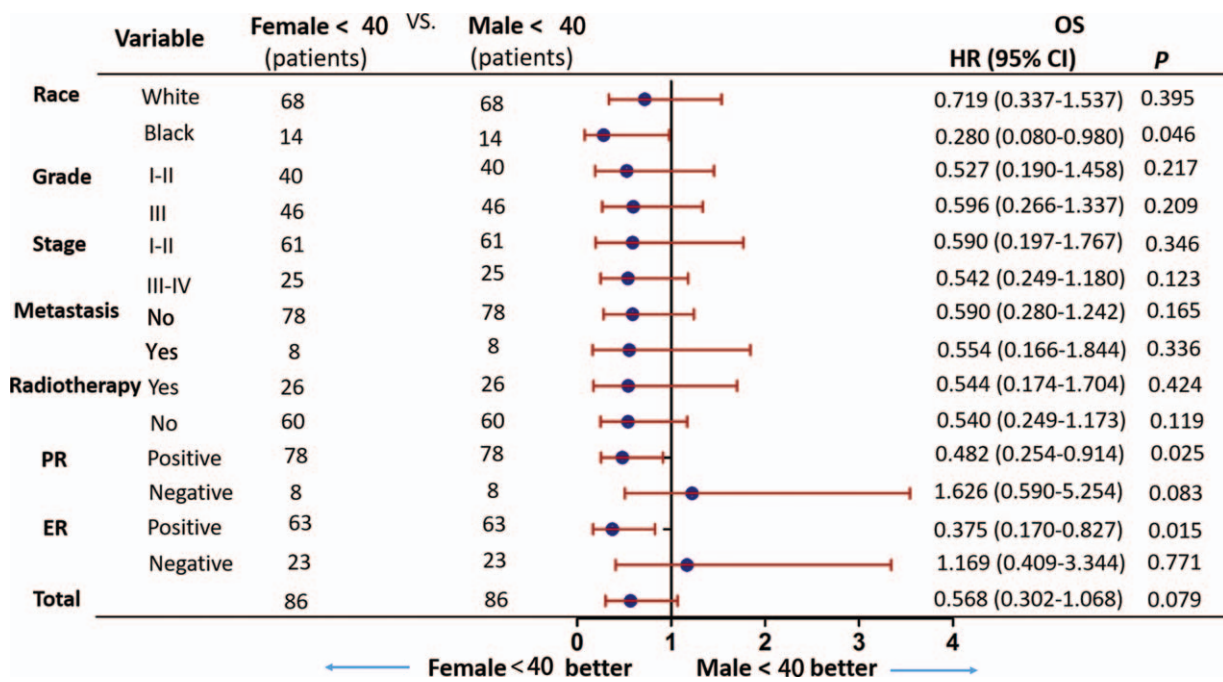
Figure 6. The forest plot for hazard ratio to compare over survival (OS) between male breast cancer aged <40 years and female breast cancer aged <40 years according to different variables. CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, PR = progesterone receptor.

Most studies have recommended that breast cancer should be screened as early as 40 years old for average-risk women.[19] In our study, male patients with breast cancer younger than 39 years old were classified into the category of young male breast cancer. Some studies have shown that the incidence of breast cancer is on the rise for young women.[9,10] Similarly, our results indicated that the incidence of young male breast cancer also demonstrated a trend of gradual increase, which is consistent with previous studies.[4,20] In addition, the prognoses of male breast cancer were demonstrated to be worse than those of their female counterparts.[8,20] However, in our study, we found that there was no obvious difference in OS or CSS between young men and young women with breast cancer. Interestingly, some studies also showed that the prognoses were similar if patients' age, cancer stage, and other prognostic factors are controlled between male patients with breast cancer and female patients with breast cancer.[21,22] Importantly, we found that the OS of young male patients was significantly longer than those of elder male patients with breast cancer. Interestingly, there was no obvious difference in CSS between young men and old men with breast cancer. In this regard, our study differs from some studies documenting that young female patients with breast cancer are often associated with unfavorable prognosis compared with their elder counterpart.[9,11] In addition, the average age of male patients diagnosed with breast cancer was higher than that of female patients with breast cancer, which could possibly increase the risk of suffering from other diseases.[17,18] Undeniably, the rather relatively smaller sample size in young patients in our study may be also an influencing factor.

Importantly, due to the clinical baseline imbalances intrinsic in a retrospective study, the propensity score matching analysis according to 1:1 matching was applied to regenerate clinical baseline data. Our results also showed male patients with breast cancer aged <40 had a significantly OS benefit only compared with the male patients with breast cancer aged ≥40. The significant difference of the CSS among the 3 groups was not found. Up till now, no related studies have focused on young male patients with breast cancer. Interestingly, compared with the male patients with breast cancer aged ≥40 years, our subgroup analysis showed that male patients with breast cancer aged <40 had no significantly CSS benefit in all variables; however, the significant OS benefit could be found in most variables including white race, grades I and II/III, stages I and II, no metastasis, no radiotherapy, PR positive/negative, and ER positive/negative. In fact, some studies have shown that race is a prognostic factor for male patients with breast cancer.[23,24] Interestingly, in our study, we found that young white race patients had a better OS in male patients with breast cancer. Tumor stage was a prognostic factor for OS by univariate analysis. However, it was not an independent factor by multivariate analysis.[25] In our study, we found that for patients at tumor stages I and II, the young male patients with breast cancer had a better prognosis. For the ER/PR status, studies indicated that the expressions of ER and PR were higher in male patients with breast cancer as compared with those in female patients with breast cancer.[26,27] However, due to the distinct functions in male breast cancer compared to the female breast cancer, some studies demonstrated that the hormone receptor status has no effect on survival in male breast cancer.[25,28] In our study, regardless of the ER/PR state, the young male patients with breast cancer had a better prognosis compared to the patients aged ≥40. However, compared to the female patients with breast cancer aged <40, the subgroup young male patients with breast cancer with ER/PR positive had a worse OS and CSS. Our results demonstrated that young male patients with breast cancer did not benefit from endocrine therapy. Interestingly, some studies showed that patients with male breast cancer received fewer chemotherapy, whereas no statistical difference was observed in the use of hormone treatment.[28]

Undeniably, this study has several limitations. First, due to the absence of information on chemotherapy or minimally invasive treatment included in the SEER database, its effect on survival could not be evaluated. Second, as a retrospective registry assessment, this study has some intrinsic defects of a retrospective study. Third, due to the low incidence in young men with breast cancer, the sample size in our study is rather small. In fact, male breast cancer may be presented with more aggressive behavior and the lymph node metastasis rate ranges from 35% to 84%.[29–31] Pitifully, some molecular characteristics affecting the prognosis of male patients with breast cancer were not analyzed in our study. Several studies have pointed that a significant number of patients (mostly BRCA2 mutation positive) developed multiple cancers including male breast cancer; most male cancers are ER positive but without a corresponding increase in PR positivity and only a weaker association with estrogen-controlled markers such as PS2, HSP27, and Cathepsin D; increased methylation defines a subset of familial male breast cancer and with average methylation index may be a useful prognostic marker.[32–34]

In fact, some disputes can be discovered about the prognosis of young patients in all tumor types. For example, a study found that gastric cancer in young patients more aggressive; however, colorectal cancer had a better prognostic in young patients by another study demonstrated.[35,36] In our study, we analyzed the different clinical and pathologic factors and prognosis of young male breast cancer compared with old male breast cancer and young female breast cancer for the first time. And more relevant researches are needed.

Author contributions

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Methodology: Naikun Li.
Software: Haiyong Wang.
Supervision: Haiyong Wang.
Validation: Haiyong Wang.
Writing – original draft: Naikun Li.
Writing – review & editing: Haiyong Wang.

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