



# The association between molecular type and prognosis of patients with stage IV breast cancer: an observational study based on SEER database

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**Background:** Molecular subtype, the basis for personalized treatment of breast cancer, is of great value in evaluating prognosis and guiding treatment of early-stage breast cancer. However, its value in stage IV patients remains unclear. In this study, we investigated the association between molecular subtype and prognosis of *de novo* stage IV breast cancer using Surveillance, Epidemiology, and End Results (SEER) database with the purpose to provide evidence for optimal therapeutic options for breast cancer patients.

**Methods:** We retrospectively analyzed *de novo* stage IV breast cancer patients with the SEER Program data from 2010 to 2015. Characteristics of patients with different molecular subtypes were compared by chi-square test and survival curves for breast cancer specific survival (BCSS) according to subtypes were plotted by Kaplan-Meier method. The Cox proportional hazards model was performed to search for independent prognostic factors in stage IV breast cancer patients.

**Results:** A total of 11,974 patients were included in this study, among which 7,100 (59.30%) patients were of HR<sup>+</sup>/HER2<sup>-</sup>, 2,093 (17.48%) of HR<sup>+</sup>/HER2<sup>+</sup>, 1,139 (9.51%) of HR<sup>-</sup>/HER2<sup>+</sup> and 1,642 (13.71%) of HR<sup>-</sup>/HER2<sup>-</sup>. Multivariate Cox analysis revealed that molecular subtype, age, race, marital status, grade, surgery and chemotherapy were independent prognostic factors for BCSS in *de novo* stage IV patients. Taking HR<sup>+</sup>/HER2<sup>-</sup> patients as reference, HR<sup>+</sup>/HER2<sup>+</sup> patients had better BCSS (HR =0.81, 95% CI: 0.75–0.88, P<0.001), HR<sup>-</sup>/HER2<sup>-</sup> patients had worse BCSS (HR =1.42, 95% CI: 1.29–1.46, P<0.001) and HR<sup>-</sup>/HER2<sup>+</sup> patients had no significant difference (HR =1.03, 95% CI: 0.98–1.08, P=0.188). In patients with different single organ metastases, the prognosis of HR<sup>+</sup>/HER2<sup>+</sup> subtype was the best (except brain metastasis), while that of HR<sup>-</sup>/HER2<sup>-</sup> subtype was the worst.

**Conclusions:** Molecular subtypes were closely associated with the prognosis of *de novo* stage IV breast cancer. Among the four subtypes, HR<sup>+</sup>/HER2<sup>+</sup> patients had the best prognosis while HR<sup>-</sup>/HER2<sup>-</sup> patients had the worst. The prognosis of patients with different single organ metastases was the same, but in patients

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with brain metastases, HR<sup>+</sup>/HER2<sup>+</sup> ones did not have a significantly better prognosis than other subtypes except triple-negative type.

**Keywords:** Molecular type; breast cancer; stage IV; prognosis; Surveillance, Epidemiology, and End Results program (SEER program)

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## Introduction

Breast cancer has become the most common malignant tumor in women, among which the *de novo* stage IV breast cancer accounts for about 3–10% of total initially diagnosed cases (1-3). This type of breast cancer is incurable with a poor prognosis as 5-year survival rate is only 25% (4). In order to improve quality and prolong the length of patients' life as much as possible, the therapy in stage IV breast cancer usually focuses on systemic comprehensive treatment (4-6). At present, the treatment of breast cancer has entered the era of molecular subtype-based personal therapeutics. According to the classification by hormone receptor (HR) status and human epidermal growth factor receptor-2 (HER2), breast cancer can be divided into HR<sup>+</sup>/HER2<sup>-</sup>, HR<sup>+</sup>/HER2<sup>+</sup>, HR<sup>-</sup>/HER2<sup>-</sup> and HR<sup>-</sup>/HER2<sup>+</sup> subtypes (7-9). The molecular subtype was found to be useful for evaluating prognosis and guiding treatment in early-stage breast cancer patients by effectively reflecting biological characteristics of tumor and predicting the sensitivity of treatment to a certain extent (10). However, the relationship between molecular subtype and prognosis remains to be studied in *de novo* stage IV patients (11). Andre *et al.* (12) noted that HR<sup>-</sup>, multiple site metastasis, visceral involvement and so on were risk factors for prognosis of *de novo* stage IV patients, and Cortesi *et al.* (13) stated that the 5-year overall survival (OS) was significantly increased for HR<sup>+</sup> and HER2<sup>+</sup> tumors. Although stage IV breast cancer is incurable, classification based on molecular subtype can provide patients with treatment alternatives for better survival rate. The results of our study could give proof and guidance to clinical application of molecular subtype in evaluating prognosis of stage IV breast cancer and provide reference data for clinical treatment.

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute is a coordinated system of population-based cancer registries that collects cancer incidence and survival data from 18 geographic

regions in United States representing approximately 28% of the country's total land areas. In this study, we retrospectively analyzed *de novo* stage IV breast cancer patients using SEER Program data from 2010 to 2015 to investigate the interaction between molecular type and prognosis of patients. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/gs-21-32>).

## Methods

### Data collection

*De novo* stage IV breast cancer cases were extracted from the SEER database. Inclusion criteria are: (I) female cases; (II) no age limitation; (III) pathological diagnosis; (IV) within the year range from 2010 to 2015; (V) TNM stage as IV. Exclusion criteria are: (I) multiple sites of tumors origins; (II) absence of survival data. Eventually, 11,974 patients were included in the study.

A list with included cases was generated with the data updated in November 2018 from the SEER\*Stat version 8.3.5. The data of year, age at diagnosis, race, marital status, tumor site, histological grade, HR, HER2, American Joint Committee on Cancer (AJCC) stage group 7th edition, surgical operation, chemotherapy, radiotherapy, survival time and survival outcome were extracted. HR includes estrogen receptor (ER) and progesterone receptor (PR), the positivity of which is defined as ER or PR positive. According to HR and HER2 status, 11,974 patients were divided into four molecular subtypes: 7,100 (59.30%) patients of HR<sup>+</sup>/HER2<sup>-</sup>, 2,093 (17.48%) of HR<sup>+</sup>/HER2<sup>+</sup>, 1,139 (9.51%) of HR<sup>-</sup>/HER2<sup>+</sup> and 1,642 (13.71%) of HR<sup>-</sup>/HER2<sup>-</sup>.

### Statistical analysis

In this study, breast cancer specific survival (BCSS) was used to evaluate the prognosis of patients. BCSS was defined as

the interval (month termed) between the time of diagnosis and end of follow-up or time of death, and data of non-breast cancer-related deaths were excluded for analysis. By comparing BCSS among patients with different molecular subtypes, the association between molecular subtype and prognosis of *de novo* stage IV breast cancer was analyzed.

Stata 13.0/MP software was used for statistical analysis. Data with continuous variables were presented as median [interquartile range (IQR)], and data with categorical variables were presented as percentages. The characteristics of different molecular subtypes patients were compared by chi-square test and survival curves were plotted by Kaplan-Meier method. Cox analysis was performed to screen factors governing prognosis in *de novo* stage IV patients. Parameters with a statistical significance in univariate Cox analysis were included in the multivariate Cox model. The adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated in multivariate model. The factors included in the prognostic analysis were molecular subtype, age, race, marital status, histology, grade, lymph node stage, surgery and radiotherapy. They were analyzed by univariate and multivariate Cox proportional hazard mode and variables with  $P < 0.05$  in both univariate and multivariate analysis were identified as independent prognostic factors. In this study, bilateral  $P$  values less than 0.05 were considered statistically significant.

As the data in this study were obtained from the American cancer registry database, detailed treatment regimens and recurrence data are not available, and there may be some bias in the results. Nevertheless, the analysis based on real data can guide the clinical application of molecular subtype to evaluate prognosis of patients with *de novo* stage IV breast cancer and provide reference data for clinical diagnosis and treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

## Results

### Patient characteristics

A total of 11,974 *de novo* stage IV breast cancer patients were included in this study, including 7,100 (59.30%) patients of HR<sup>+</sup>/HER2<sup>-</sup>, 2,093 (17.48%) of HR<sup>+</sup>/HER2<sup>+</sup>, 1,139 (9.51%) of HR<sup>-</sup>/HER2<sup>+</sup> and 1,642 (13.71%) of HR<sup>-</sup>/HER2<sup>-</sup>. The median age of all patients was 60 years (IQR, 51–70 years), and the age distribution was different among patients with different molecular subtypes ( $P < 0.001$ ). The

distribution of histological type, grade, lymph node stage, surgery, radiotherapy and chemotherapy were all different among patients with different molecular subtypes (all  $P < 0.05$ ; Table 1).

### Molecular subtypes and prognosis

During a median follow-up of 20 months (IQR, 8–37 months), 6,496 (54.25%) patients died of breast cancer, including 3,732 (52.56%) patients of HR<sup>+</sup>/HER2<sup>-</sup>, 933 (44.58%) of HR<sup>+</sup>/HER2<sup>+</sup>, 574 (50.40%) HR<sup>-</sup>/HER2<sup>+</sup> and 1,257 (76.55%) of HR<sup>-</sup>/HER2<sup>-</sup>. Univariate Cox analysis showed that molecular subtype, age, race, marital status, histological type, grade, lymph node stage, surgery, radiotherapy and chemotherapy were all associated with BCSS. BCSS-related prognostic factors were included in multivariate Cox regression model. Compared to HR<sup>+</sup>/HER2<sup>-</sup> breast cancer patients, HR<sup>+</sup>/HER2<sup>+</sup> patients had better BCSS (HR = 0.81, 95% CI: 0.75–0.88,  $P < 0.001$ ), HR<sup>-</sup>/HER2<sup>-</sup> patients had worse BCSS (HR = 1.42, 95% CI: 1.29–1.46,  $P < 0.001$ ) and HR<sup>-</sup>/HER2<sup>+</sup> patients had no significant difference (HR = 1.03, 95% CI: 0.98–1.08,  $P = 0.188$ ), as shown in Figure 1. Multivariate Cox analysis showed that age, race, marital status, grade, surgery and chemotherapy were independent prognostic factors for BCSS in patients with *de novo* stage IV breast cancer (Table 2).

### Analysis of single organ metastasis

Subgroup multivariate Cox regression analysis was performed in patients with single organ metastasis. In patients with bone, lung or liver metastasis, the HR<sup>+</sup>/HER2<sup>+</sup> subtype had a better prognosis than other molecular subtypes. In patients with brain metastasis, there was no statistically significant difference in the prognosis among HR<sup>+</sup>/HER2<sup>+</sup>, HR<sup>+</sup>/HER2<sup>-</sup> and HR<sup>-</sup>/HER2<sup>+</sup> subtypes. Patients with triple negative breast cancer had the worst prognosis in all single organ metastasis subgroups (Table 3, Figures 2,3).

## Discussion

*De novo* stage IV breast cancer is a breast cancer with distant metastasis at the time of initial diagnosis and is an incurable systemic disease with prognosis closely related to biological characteristics and metastatic site (10,14). Because of distant

**Table 1** Patient characteristics according to tumor subtype

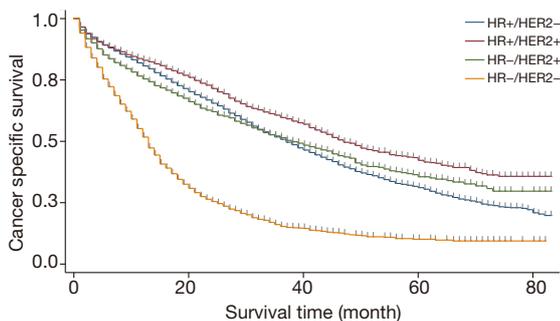
Parameters	N	HR <sup>+</sup> /HER2 <sup>-</sup> (N=7,100), n (%)	HR <sup>+</sup> /HER2 <sup>+</sup> (N=2,093), n (%)	HR <sup>-</sup> /HER2 <sup>+</sup> , (N=1,139), n (%)	HR <sup>-</sup> /HER2 <sup>-</sup> (N=1,642), n (%)	P
Year of diagnosis						0.103
2010	1,778	1,061 (14.94)	284 (13.57)	160 (14.05)	273 (16.63)	
2011	1,959	1,184 (16.68)	328 (15.67)	175 (15.36)	272 (16.57)	
2012	1,932	1,138 (16.03)	361 (17.25)	176 (15.45)	257 (15.65)	
2013	2,112	1,273 (17.93)	348 (16.63)	196 (17.21)	295 (17.97)	
2014	2,087	1,226 (17.27)	364 (17.39)	217 (19.05)	280 (17.05)	
2015	2,106	1,218 (17.15)	408 (19.49)	215 (18.88)	265 (16.14)	
Race						<0.001
White	8,909	5,447 (76.72)	1,541 (73.63)	820 (71.99)	1,101 (67.05)	
Black	2,064	1,060 (14.93)	374 (17.87)	200 (17.56)	430 (26.19)	
Other	964	567 (7.99)	174 (8.31)	114 (10.01)	109 (6.64)	
Unknown	37	26 (0.37)	4 (0.19)	5 (0.44)	2 (0.12)	
Marital status						0.267
Married	5,147	3,035 (42.75)	931 (44.48)	502 (44.07)	679 (41.35)	
Unmarried	5,153	3,668 (51.66)	1,043 (49.83)	564 (49.52)	878 (53.47)	
Unknown	674	397 (5.59)	119 (5.69)	73 (6.41)	85 (5.18)	
Age (years)						<0.001
<60	5,743	3,080 (43.38)	1,175 (56.14)	671 (58.91)	817 (49.76)	
≥60	6,231	4,020 (56.62)	918 (43.86)	486 (41.09)	825 (50.24)	
Histology						<0.001
IDC	8,584	4,720 (66.48)	1,685 (80.51)	920 (80.77)	1,259 (76.67)	
ILC	1,199	1,053 (14.83)	81 (3.87)	23 (2.02)	42 (2.56)	
Others	2,191	1,327 (18.69)	327 (15.62)	196 (17.21)	341 (20.77)	
Grade						<0.001
1	739	665 (9.37)	47 (2.25)	4 (0.35)	23 (1.40)	
2	4,171	2,990 (42.11)	692 (33.06)	252 (22.12)	237 (14.43)	
3/4	5,026	2,112 (29.75)	1,053 (50.31)	703 (61.72)	1,158 (70.52)	
Unknown	2,038	1,333 (18.77)	301 (14.38)	180 (15.80)	224 (13.64)	
Lymph node stage						<0.001
N0	2,313	1,484 (20.90)	385 (18.39)	152 (13.35)	292 (17.78)	
N1	4,307	2,547 (35.87)	773 (36.93)	430 (37.75)	557 (33.92)	
N2	1,117	673 (9.48)	187 (8.93)	112 (9.83)	145 (8.83)	
N3	3,355	1,827 (25.37)	603 (28.81)	374 (32.84)	551 (33.56)	
Unknown	882	569 (8.01)	145 (6.93)	71 (6.23)	97 (5.91)	

**Table 1** (continued)

Table 1 (continued)

Parameters	N	HR <sup>+</sup> /HER2 <sup>-</sup> (N=7,100), n (%)	HR <sup>+</sup> /HER2 <sup>+</sup> (N=2,093), n (%)	HR <sup>-</sup> /HER2 <sup>+</sup> , (N=1,139), n (%)	HR <sup>-</sup> /HER2 <sup>-</sup> (N=1,642), n (%)	P
Surgery						<0.001
No	8,167	5,020 (70.70)	1,424 (68.04)	725 (63.65)	998 (60.78)	
Yes	3,561	1,939 (27.31)	631 (30.15)	377 (33.10)	614 (37.39)	
Unknown	246	141 (1.99)	38 (1.82)	37 (3.25)	30 (1.83)	
Radiotherapy						0.034
No/unknown	7,992	4,665 (65.70)	1,422 (67.94)	779 (68.39)	1,126 (68.57)	
Yes	3,982	2,435 (34.30)	671 (32.06)	360 (31.61)	516 (31.43)	
Chemotherapy						<0.001
No/unknown	5,277	4,010 (56.48)	574 (27.42)	235 (20.63)	458 (27.89)	
Yes	6,697	3,090 (43.52)	1,519 (72.58)	904 (79.37)	1,184 (72.11)	
Cancer specific death	6,496	3,732 (52.56)	933 (44.58)	574 (50.40)	1,257 (76.55)	<0.001
All death	7,351	4,160 (60.00)	1,042 (49.78)	640 (56.19)	1,409 (86.81)	<0.001

HR<sup>+</sup>, hormone receptor (HR) includes estrogen receptor (ER) and progesterone receptor (PR), and HR<sup>+</sup> is defined as ER or PR positive; HER2, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.



**Figure 1** Kaplan-Meier curve for BCSS according to tumor subtype. BCSS, breast cancer specific survival. HR, hormone receptor; HER2, human epidermal growth factor receptor-2.

metastasis, stage IV patients are substantially different from early-stage patients in terms of treatment objectives and strategies. Molecular subtype, which reflects the biological characteristics of the tumor, is of great value in evaluating prognosis and guiding treatment in early-stage breast cancer patients, while its value in *de novo* stage IV remains unclear. In this study, a large sample case analysis using SEER database showed that molecular subtype was closely related to the prognosis of *de novo* stage IV breast cancer, in which HR<sup>+</sup>/HER2<sup>+</sup> had the best prognosis and HR<sup>-</sup>/HER2<sup>-</sup> had the worst prognosis, and there were slight differences in

the relationship between molecular subtype and prognosis in patients with different metastatic sites.

Breast cancer is a highly heterogeneous disease and initially classified into different genotypes by genetic testing which is a good predictor of prognosis (15-17). Due to the poor availability and accessibility of genetic testing, patients are divided into four immunohistochemical molecular subtypes—HR<sup>+</sup>/HER2<sup>-</sup>, HR<sup>+</sup>/HER2<sup>+</sup>, HR<sup>-</sup>/HER2<sup>+</sup> and HR<sup>-</sup>/HER2<sup>-</sup>, based on the status of ER, PR and HER2 to replace genotyping in clinical evaluation of prognosis and guidance of treatment. HR<sup>+</sup>/HER2<sup>+</sup> had the best prognosis and HR<sup>-</sup>/HER2<sup>-</sup> had the worst prognosis in patients with early breast cancer. However, breast cancer subtypes are not associated with prognosis in untreated patient and, in contrast, significantly associated with prognosis in patients with conventional therapy (18). There are significant differences in therapeutic objectives and strategies between early breast cancer and *de novo* stage IV breast cancer, and the relationship between molecular subtypes and the prognosis of the latter is still unclear.

The results of this study showed that among patients with *de novo* stage IV breast cancer, patients with HR<sup>+</sup>/HER2<sup>+</sup> subtype had a better prognosis than those with other subtypes while patients with HR<sup>-</sup>/HER2<sup>-</sup> subtype had the worst prognosis, which was the same as those with

**Table 2** Analysis of prognostic factors

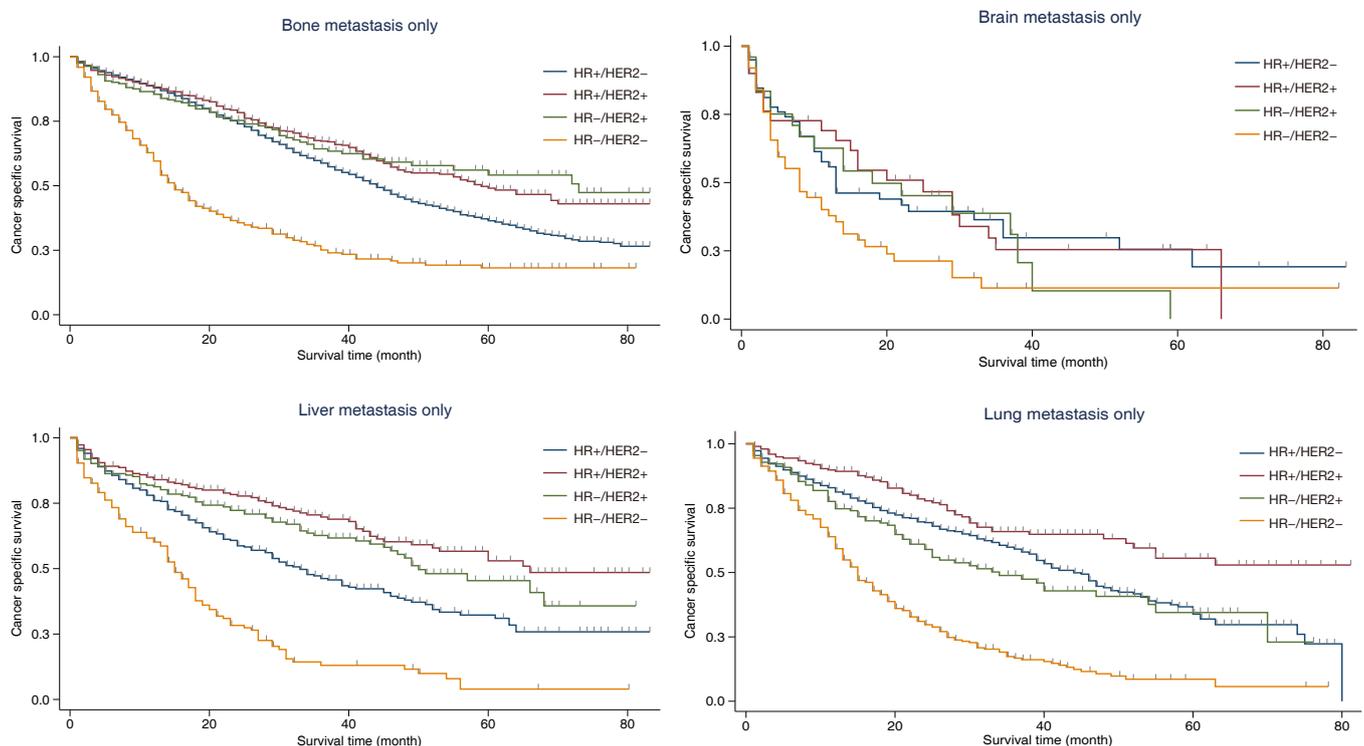
Parameters	Breast cancer specific survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
<b>Subtype</b>				
HR <sup>+</sup> /HER2 <sup>-</sup>	1 (reference)		1 (reference)	
HR <sup>+</sup> /HER2 <sup>+</sup>	0.76 (0.71–0.82)	<0.001	0.81 (0.75–0.88)	<0.001
HR <sup>-</sup> /HER2 <sup>+</sup>	1.00 (0.95–1.05)	0.941	1.03 (0.98–1.08)	0.188
HR <sup>-</sup> /HER2 <sup>-</sup>	1.39 (1.35–1.42)	<0.001	1.42 (1.29–1.46)	<0.001
<b>Age (years)</b>				
<60	1 (reference)		1 (reference)	
≥60	1.35 (1.28–1.42)	<0.001	1.26 (1.20–1.33)	<0.001
<b>Race</b>				
White	1 (reference)		1 (reference)	
Black	1.33 (1.23–1.42)	<0.001	1.26 (1.18–1.35)	<0.001
Others	0.95 (0.90–1.00)	0.045	0.97 (0.92–1.02)	0.227
<b>Marital status</b>				
Married	1 (reference)		1 (reference)	
Unmarried	1.36 (1.29–1.44)	<0.001	1.26 (1.20–1.33)	<0.001
<b>Histology</b>				
IDC	1 (reference)		1 (reference)	
ILC	1.01 (0.93–1.10)	0.812	1.08 (0.99–1.18)	0.09
Others	1.05 (1.02–1.09)	0.003	0.99 (0.96–1.03)	0.716
<b>Grade</b>				
1	1 (reference)		1 (reference)	
2	1.30 (1.14–1.47)	<0.001	1.30 (1.14–1.47)	<0.001
3/4	1.38 (1.30–1.47)	<0.001	1.40 (1.31–1.50)	<0.001
<b>Node stage</b>				
N0	1 (reference)		1 (reference)	
N1	0.96 (0.90–1.04)	0.343	1.01 (0.94–1.09)	0.716
N2	0.98 (0.93–1.03)	0.439	1.07 (1.01–1.13)	0.014
N3	1.07 (1.04–1.10)	<0.001	1.09 (1.06–1.11)	<0.001
<b>Surgery</b>				
No	1 (reference)		1 (reference)	
Yes	0.59 (0.56–0.63)	<0.001	0.59 (0.56–0.63)	<0.001
<b>Radiotherapy</b>				
No	1 (reference)		1 (reference)	
Yes	0.92 (0.87–0.97)	0.001	1.04 (0.98–1.09)	0.196
<b>Chemotherapy</b>				
No	1 (reference)		1 (reference)	
Yes	0.79 (0.75–0.83)	<0.001	0.70 (0.66–0.74)	<0.001

HR, hazard ratio; CI, confidence interval; HR<sup>+</sup>, hormone receptor (HR) includes estrogen receptor (ER) and progesterone receptor (PR), and HR<sup>+</sup> is defined as ER or PR positive; HER2, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

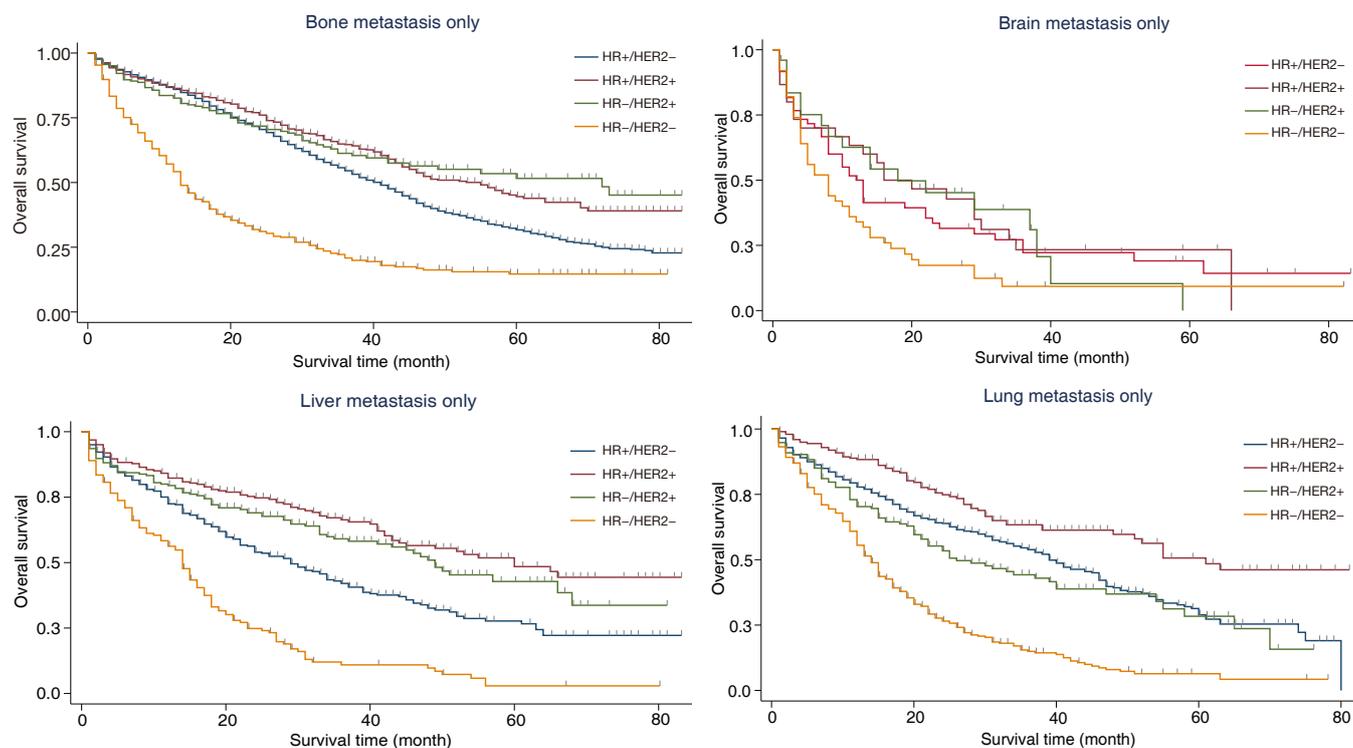
**Table 3** Multivariate Cox analysis of tumor subtype and prognosis of patients with single organ metastasis

Subtypes	N	Bone only (n=4,599)		Lung only (n=1,245)		Liver only (n=940)		Brain only (n=174)	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<b>BCSS</b>									
HR <sup>+</sup> /HER2 <sup>-</sup>	7,100	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
HR <sup>+</sup> /HER2 <sup>+</sup>	2,093	0.83 (0.72–0.96)	0.014	0.64 (0.48–0.87)	0.005	0.55 (0.41–0.73)	<0.001	1.14 (0.60–2.16)	0.688
HR <sup>-</sup> /HER2 <sup>+</sup>	1,139	0.91 (0.80–1.03)	0.146	1.19 (1.03–1.38)	0.022	0.85 (0.73–0.98)	0.022	1.12 (0.78–1.61)	0.524
HR <sup>-</sup> /HER2 <sup>-</sup>	1,642	1.43 (1.36–1.51)	<0.001	1.46 (1.36–1.56)	<0.001	1.41 (1.29–1.54)	<0.001	1.26 (1.04–1.54)	0.018
<b>OS</b>									
HR <sup>+</sup> /HER2 <sup>-</sup>	7,100	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
HR <sup>+</sup> /HER2 <sup>+</sup>	2,093	0.84 (0.73–0.96)	0.011	0.66 (0.50–0.88)	0.004	0.56 (0.43–0.72)	<0.001	1.05 (0.58–1.91)	0.862
HR <sup>-</sup> /HER2 <sup>+</sup>	1,139	0.91 (0.81–1.03)	0.135	1.22 (1.06–1.40)	0.004	0.85 (0.74–0.97)	0.017	1.17 (0.82–1.66)	0.384
HR <sup>-</sup> /HER2 <sup>-</sup>	1,642	1.45 (1.38–1.52)	<0.001	1.44 (1.35–1.54)	<0.001	1.40 (1.28–1.52)	<0.001	1.23 (1.03–1.47)	0.024

HR, hazard ratio; CI, confidence interval; BCSS, breast cancer specific survival; OS, overall survival; HR<sup>+</sup>, hormone receptor (HR) includes estrogen receptor (ER) and progesterone receptor (PR), and HR<sup>+</sup> is defined as ER or PR positive; HER2, human epidermal growth factor receptor-2.



**Figure 2** Kaplan-Meier curves for cancer specific survival according to the metastatic site. HR, hormone receptor; HER2, human epidermal growth factor receptor-2.



**Figure 3** Kaplan-Meier curves for overall survival according to the metastatic site. ER, estrogen receptor.

early breast cancer. However, the relationship between molecular subtype and prognosis was slightly different in patients with different metastatic sites. Comparing patients with the same organ metastasis, we found that the prognosis of HR<sup>-</sup>/HER2<sup>-</sup> subtype was the worst in patients with bone, liver, lung, or brain metastases, while the prognosis of HR<sup>+</sup>/HER2<sup>+</sup> subtype was the best in patients with bone, liver, or lung metastases (excluding brain metastases). To a certain extent, molecular subtypes reflect the biological characteristics of tumor and predict the sensitivity of treatment. HR-positive patients are sensitive to endocrine therapy, while HER2-positive can be treated with anti-HER2 targeted therapy (5,8,19). The prognosis of HR<sup>+</sup>/HER2<sup>+</sup> patients is better than that of other subtypes possibly due to sensitivity to endocrine therapy and anti-HER2 therapy. In contrast, HR<sup>-</sup>/HER2<sup>-</sup> (triple negative) patients who lack endocrine therapy and anti-HER2 therapy had the worst prognosis (20). Although stage IV breast cancer is incurable, classification based on molecular subtype can provide patients with more choices of treatment to improve survival. In the study, lack of data about detailed treatment and recurrence information from American cancer registry database inevitably cause some bias in the results. However,

the analysis based on real data is meaningful for the application of molecular subtype in stage IV breast cancer and provide reference for clinical diagnosis and treatment.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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