Prognostic factors and survival according to tumour subtype in women presenting with breast cancer bone metastases at initial diagnosis: a SEER based study

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Abstract

Background: Tumour subtype have a significant effect on bone metastasis in breast cancer, but population-based estimates of the prognosis of bone metastases at diagnosis of breast cancer are lacking. The aim of this study was to analyse the influence of tumour subtype and other factors in the prognostic and survival of patients with bone metastases of breast cancer.

Methods: Using the Surveillance, Epidemiology, and End Results Program (SEER) data of 2012 to 2016 conducted a retrospective cohort study to investigate stage IV patients with bone metastases in breast cancer. Stage IV Patients characteristic according subtype were compared using chi-square. Overall survival (OS), prognostic factor calculated using the Kaplan-Meier method and the Cox proportional hazards model.

Results: A total of 3384 stage IV patients were included in this study. 63.42% were HR+/HER2-, 19.86% were HR+/HER2+, 9.34% were HR-/HER2-, and 7.39% were HR-/HER2+. Median OS for the whole population was 38 months, and 33.9% of the patients were alive at five-year. The median OS and five-year survival rate among the different molecular subtype of breast cancer stage IV patients are significant differences (p<0.05). Multivariate Cox regression analysis showed that age of 55-59 (HR=1.270), black race (HR=1.317), grade in III or IV (HR=1.960), HR-/HER2- (HR=2.808), lung metastases (HR=1.378), live metastases (HR=2.085), brain metastases (HR=1.903) are independent risk factors of prognosis; married (HR=0.819), HR+/HER2+ (HR=0.631), HR-/HER2+ (HR=0.716), insurance (HR=0.587) and surgery (HR=0.504) are independent protection factors of prognosis. There is interaction between HR+/HER2+ subtype and other metastases (except bone metastases, HR=0.694, 95%CI: 0.485-0.992), but interaction between race and substype did not reach significance on prognosis.

Conclusions: There were substantial differences in OS according to tumour subtype. In addition to tumour subtype, other independent predictors of OS are age at diagnosis, race, marital status, insurance, grade, surgery and visceral metastases. There is interaction between HR+/HER2+ subtype and other metastases (except bone metastases) on prognosis. Tumour subtype, as a significant prognostic factor, warrant further investigation.

Background

Breast cancer is the second most common type of cancer in women and the second leading cause of cancer-related death in women. In these patients, it is not the primary tumour, but its metastases at distant sites that are the main cause of death [1]. Approximately 5–10% of patients have distant metastases at the time of diagnosis[2, 3], bone is the most common site of metastasis in breast cancer patients, above 55% of breast cancer patients developing bone metastases[4]. Bone metastases are associated with lower survival in patients with advanced breast cancer [5]. And study showed that patients with breast cancer survive a median of 22–57.6 months after detection of bone metastases[6-8]. Breast cancer patients with bone metastases seem to have a longer survival than those with cancer in other metastatic sites [9].

According to the classification by hormone receptor status (HR) and **human epidermal growth factor receptor-2 (**HER2**)**, breast cancer can be divided into HR+/HER2-, HR+/HER2+, HR-/HER2- and HR-/HER2+ [10]. The

strong association of hormonal receptor status with bone metastasis was proposed early in 1991 [11]. With a deeper understanding of the modulated genes and pathways in the various subgroups, it had become more evident that bone metastasis was most abundant among the hormonal receptor-positive subtype [12]. The researchers found that the clinical manifestations, pathological results, gene expression and prognosis of different subtype of breast cancer were very different. The relationship between molecular subtype and the patterns of distant metastases has been documented. Evidence had shown that bone metastases risk depends on breast cancer subtype, HR+ patients were more likely to have bone metastases [13]. The molecular differences in the tumour subtype were often accompanied by differences in clinical features and overall survival [10]. The distribution of molecular subtype is different among different races of breast cancer patients, race are the prognostic factors of breast cancer patients [14, 15]. However, the effect of mixed race and subtype on prognosis was not verified.

Notably, once tumour metastasizes to bone, it is incurable. Bone metastases are associated with lower survival in patients with advanced breast cancer and an increased risk of serious complications during the patients' disease course. The consequences of bone metastases include reduced survival, morbidity, pain and reduced quality of life [16]. Therefore, in order to improve their survival time and outcome, it has great significance to identify the influencing factors of clinical prognosis in patients with bone metastasis of breast cancer. The aim of this study was to analyse the influence of tumour subtype and other factors in the prognostic and survival of patients who present with bone metastases at the time of initial diagnosis of breast cancer.

Methods

Data source and patient selection

We abstracted data from the Surveillance, Epidemiology, and End Results (SEER) 18 registries research database. The SEER of the National Cancer Institute is a coordinated system of population-based cancer registries that collects cancer incidence and survival data from 18 geographic areas throughout the United States that together represent approximately 28% of the U.S. population and includes various diverse ethnic groups. A data use agreement submission was required to access the SEER Research Data File [17]. We submitted the data agreement form to the SEER administration, after acceptance of the agreement, the SEER*Stat Version 8.3.5 software and data files were downloaded directly from the SEER website.

We used SEER*Stat version 8.3.5 to generate a case listing. Extracted cases of woman aged 40-60 with bone metastases breast cancer diagnosed with known breast subtype. Because the SEER database began collecting information on the HER2 status and sites of distant metastasis in 2010, and the most recent of The SEER Cancer Statistics Review (CSR) (1975-2016) was released in April, 2019. We would like to know about the situation of breast cancer patients in the past five years, included women aged 40-60 diagnosed between 2010 and 2013, selected this age group woman because the incidence of breast cancer rises over 50, and the natural mortality of the elderly is high, age is the second important risk factor at primary diagnosis [18].

Patients diagnosed by either autopsy or death certificate were excluded. Patients must be have complete dates of survival month and the follow-up must be active. The analysis was restricted to a diagnosis

confirmed by histopathology, and only duct, lobular and other carcinomas based on the primary site were included (International Classification of Disease for Oncology, Third Edition (ICD-O-3) codes 8500 to 8543). Tumour stage was registered according to the American Joint Committee on Cancer Staging System six edition.

We generated a case listing with information on the following variables: year of diagnosis, age at diagnosis, race/ethnicity, marital status at diagnosis, grade, laterality, ICD-O-3 Hist/behav, American Joint Committee on Cancer (AJCC) Stage Group 6th edition, surgery prim site, bone/ lung/ liver /brain metastases, tumour subtype, cause-specific death classification, vital status, and survival (months). Race was classified as white, black or other. Marital status was categorized as married, single (including never married single, divorced, separated, and widowed) or other. Insured was classified as uninsured, insured (including Any Medicaid, Insured, Insured - No Specifics) or unknown. Because the stage was supposed to be the most powerful prognostic factor in other study and clinical, stage IV patients exhibited worse survival rates than stage I–III patients, so we only select stage IV patients according AJCC Stage Group 6th edition.

Statistical Analyses

Descriptive statistics were used to examine the following baseline characteristics of the breast cancer with bone metastases stage IV patients: year of diagnosis, age, race/ethnicity, insurance, marital status, grade, surgery, laterality, histology, liver, lung, brain, bone only metastases, BCSS (time from the breast cancer diagnosis to death due to breast cancer) and OS (the time from the breast cancer diagnosis to death due to any cause). Age at diagnosis, race/ethnicity, insurance, marital status, grade, surgery, laterality, histology, liver metastases, lung metastases, brain metastases, interaction terms between visceral metastases and subtype were used in multivariate Cox model.

These variables were stratified by molecular subtype. *P*-values for comparing the frequency distributions among the subgroups were calculated using the chi-squared () test. Within each variable, patients with unknown data were excluded from the comparative analysis. OS were used as the primary study outcomes, we used the Kaplan-Meier method to generate survival curves and analyse the differences between the curves using the log-rank test. A Cox proportional hazards regression was used to assess the independent association of several variables with OS, interaction analysis by adding interaction items to the next layer. Hazard ratios (HR) and their 95% confidence interval (95%CI) were estimated using the Cox model. *P*-value of 0.05 or less was considered statistically significant. All *P*-values were 2-tailed. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc) and IBM SPSS version 23.0.

Results

Patient characteristics

A total of 3384 stage IV patients were diagnosed with bone metastases from breast cancer at initial presentation between 2012 and 2016 and were included in this study. 2146 stage IV patients (63.41%) were diagnosed with HR+/HER2- breast cancer, 672 stage IV patients (19.86%) were HR+/HER2+ breast cancer, 316

stage IV patients (9.34%) were HR-/HER2- breast cancer, and 250 stage IV patients (7.39%) were HR-/HER2+ breast cancer.

The demographic and clinical characteristics of the study based on breast cancer subtype showed in table1. Stage IV Patients with bone metastases from HR-/HER2- breast cancer more likely were white race ($P < 0.001$). HR-/HER2- and HR+/HER2+ and HR-/HER2+ breast cancer more likely were higher tumour grade and histology type classification of duct carcinoma than HR+/HER2- ($P < 0.001$). Visceral and only bone metastases were less frequent in HR+/HER2- ($P < 0.001$). HR-/HER2- breast cancer patients more likely to die ($P < 0.001$).

Table1 Patient characteristics according to tumour subtype						
Characteristics	HR+/HER2-	HR+/HER2+	HR-/HER2-	HR-/HER2+	Total	*P*-value
	2146(63.41)	672(19.86)	316(9.34)	250(7.39)	3384(100)	
Year of diagnosis						0.981
2012	422(19.66)	133(19.79)	55(17.41)	51(20.40)	661(19.53)	
2013	441(20.55)	138(20.54)	68(21.52)	52(20.80)	699(20.66)	
2014	425(19.80)	125(18.60)	65(20.57)	46(18.40)	661(19.53)	
2015	428(19.94)	143(21.28)	59(18.67)	45(18.00)	675(19.95)	
2016	430(20.04)	133(19.79)	69(21.84)	56(22.40)	688(20.33)	
Age at diagnosis						0.221
40-44 years	283(13.19)	107(15.92)	31(9.81)	28(11.20)	449(13.27)	
45-49 years	465(21.67)	128(19.05)	65(20.57)	50(20.00)	708(20.92)	
50-54 years	638(29.73)	202(30.06)	110(34.81)	81(32.40)	1031(30.47)	
55-59 years	760(35.41)	235(34.97)	110(34.81)	91(36.40)	1196(35.34)	
Race						<0.001
White	1574(73.35)	481(71.58)	218(68.99)	170(68.00)	2443(72.19)	
Black	353(16.45)	127(18.90)	81(25.63)	43(17.20)	604(17.85)	
Other [a]	211(9.83)	64(9.52)	16(5.06)	33(13.20)	324(9.57)	
Unknown	8(0.37)	0(0.00)	1(0.32)	4(1.60)	13(0.38)	
Marital status						0.771
Single	620(28.89)	189(28.13)	89(28.16)	73(29.20)	971(28.69)	
Married	1049(48.88)	342(50.89)	150(47.47)	113(45.20)	1654(48.88)	
Other [b]	377(17.57)	111(16.52)	64(20.25)	47(18.80)	599(17.70)	
Unknown	100(4.66)	30(4.46)	13(4.11)	17(6.80)	160(4.73)	
Insurance						0.490
Insured	104(4.85)	42(6.25)	17(5.38)	11(4.40)	174(5.14)	
Uninsured	2027(94.45)	623(92.71)	297(93.99)	235(94.00)	3182(94.03)	
Unknown	15(0.70)	7(1.04)	2(0.63)	4(1.60)	28(0.83)	
Grade						<0.001

I	247(11.51)	21(3.13)	4(1.27)	2(0.80)	274(8.10)	
II	1017(47.39)	244(36.31)	64(20.25)	67(26.80)	1392(41.13)	
III or IV	619(28.84)	334(49.70)	230(72.78)	149(59.60)	1332(39.36)	
Unknown	263(12.26)	73(10.86)	18(5.70)	32(12.80)	32(12.80)	
Histology						<0.001
Ductal	1571(73.21)	559(83.18)	277(87.66)	216(86.40)	2623(77.51)	
Lobular	353(16.45)	28(4.17)	13(4.11)	6(2.40)	400(11.82)	
Others	222(10.34)	85(12.65)	26(8.23)	28(11.20)	361(10.67)	
Laterality						0.153
Right	1054(49.11)	330(49.11)	156(49.37)	102(40.80)	1642(48.52)	
Left	1070(49.86)	337(50.15)	155(49.05)	146(58.40)	1708(50.47)	
Bilateral, single primary	5(0.23)	4(0.60)	2(0.63)	1(0.40)	12(0.35)	
Unknown	17(0.79)	1(0.15)	3(0.95)	1(0.40)	22(0.65)	
Lung metastases						<0.001
No	1643(76.56)	452(67.26)	216(68.35)	158(63.20)	2469(72.96)	
Yes	449(20.92)	205(30.51)	96(30.38)	89(35.60)	839(24.79)	
Unknown	54(2.52)	15(2.23)	4(1.27)	3(1.20)	76(2.25)	
Liver metastases						<0.001
No	1691(78.80)	418(62.20)	208(65.82)	132(52.80)	2449(72.37)	
Yes	423(19.71)	244(36.31)	101(31.96)	155(46.00)	883(26.09)	
Unknown	32(1.49)	10(1.49)	7(2.22)	3(1.20)	52(1.54)	
Brain metastases						<0.001
No	1992(92.82)	595(88.54)	263(83.23)	214(85.60)	3064(90.54)	
Yes	107(4.99)	62(9.23)	44(13.92)	31(12.40)	244(7.21)	
Unknown	47(2.19)	15(2.23)	9(2.85)	5(2.00)	76(2.25)	
Only bone metastases						<0.001
No	748(34.86)	360(53.57)	170(53.80)	168(67.20)	1446(42.73)	
Yes	1326(61.79)	300(44.64)	140(44.30)	80(32.00)	1846(54.55)	

Unknown	72(3.36)	12(1.79)	6(1.90)	2(0.80)	21(2.72)	
Surgery						0.971
No	1541(71.81)	489(72.77)	225(71.20)	180(72.00)	2435(71.96)	
Yes	588(27.40)	179(26.64)	88(27.85)	68(27.20)	923(27.28)	
Unknown	17(0.79)	4(0.60)	3(0.95)	2(0.80)	26(0.77)	
Breast cancer - specific death						<0.001
No	1502(69.99)	504(75.00)	140(44.30)	165(66.00)	2311(68.29)	
Yes	644(30.01)	168(25.00)	176(55.70)	85(34.00)	1073(31.71)	
Status						<0.001
Alive	1350(62.91)	474(70.54)	92(29.11)	153(61.20)	2069(61.14)	
Dead	796(37.09)	198(29.46)	224(70.89)	97(38.80)	1315(38.86)	

Other [a] (American Indian/AK Native, Asian/Pacific Islander)
Other [b] (Divorced/Widowed/Separated)
Unknown patients are excluded from the comparative analysis.

Survival analysis

A median follow-up of 17 months (range, 1–60 months), 1315 deaths were reported (60.53% in the HR+/HER2- group, 15.06% in the HR+/HER2+ group, 17.03% in the HR-/HER2- group and 7.38% in the HR-/HER2+ group).

Median OS for the entire population was 38 months (95%CI: 35.89–40.11 months), and 33.9% of the patients (95% CI, 30.6–37.2%) were alive at 60 months. Analysis of OS according to tumour subtype showed significant differences with stage IV patients with bone metastases, the five-year survival rate was 32.7% for HR+/HER2-, 48.8% for HR+/HER2+, 8.6% for HR-/HER2- and 36.1% for HR-/HER2+. Stage IV Patients with bone metastases of HR-/HER2- breast cancer experiencing the shortest survival (median OS: 11 months; 95% CI: 9.9–12.1 months), whereas stage IV patients with HR+/HER2+ breast cancer experiencing the longest survival, median OS was 52 months (95% CI was not estimable; P<0.001).

The impact of the presence of metastases at each individual site on OS is shown in Fig.2. Stage IV patients with lung metastases survival (median OS: 23 months; 95% CI: 19.98–26.02 months) had significantly shorter than stage IV patients with no lung metastases (median OS: 42 months; 95% CI: 39.77–44.23 months; P<0.001; Fig. 2a). Stage IV patients with liver metastases survival (median OS: 22 months; 95% CI: 19.10–24.86 months) had significantly shorter than no liver metastases (median OS: 44 months; 95% CI: 41.14–46.86 months; P<0.001; Fig. 2b). Stage IV patients with brain metastases survival (median OS: 14 months;

95% CI: 11.08–40.10 months) had significantly shorter than no brain metastases (median OS: 40 months; 95% CI: 37.80–42.20 months; *P*<0.001; Fig. 2c). A similar finding was seen for with only bone metastases (median OS: 46 months; 95% CI: 42.56–49.44 months) than metastases to the bone and other sites (median OS: 24 months; 95% CI: 24.61–26.38 months *P*<0.001; Fig. 2d).

Unadjusted models for the overall patient population were consistent with log-rank analysis (except laterality) and revealed that patients who were older, black race, single, uninsured, duct histology, III or IV Grade, primary bilateral breast cancer, triple-negative subtype, Visceral metastases and those who did not receive surgery to the primary tumour had shorter OS (Table 2).

Multivariate Cox analyses confirmed that age of 55-59 (vs. age of 40-44, HR=1.270, 95%CI: 1.032-1.562), black race (vs. white race, HR=1.317, 95%CI: 1.127-1.540), grade in III or IV (vs. grade in, HR=1.960, 95%CI: 1.491-2.577), HR-/HER2- (vs. HR+/HER2-, HR=2.808, 95%CI: 2.169-3.634), lung metastases (vs. no, HR=1.378 , 95%CI: 1.188-1.598), live metastases (vs. no, HR=2.085, 95%CI: 1.795-2.422), brain metastases (vs. no, HR=1.930, 95%CI: 1.542-2.248) are independent risk factors of prognosis; married status (vs. single, HR=0.819, 95%CI: 0.707-0.949), insurance (vs. no, HR=0.587, 95%CI: 0.459-0.751) and surgery (vs. no, HR=0.504, 95%CI: 0.431-0.590), are independent protection factors of prognosis. There is interaction between HR+/HER2+ subtype and multi-metastases (bone +Visceral metastases, HR=0.694, 95%CI: 0.485-0.992) on prognosis. Histology, primary laterality, interaction between race and substype did not reach significance with this test. Multivariate Cox model is shown in Table 3.

Table 2 Univariate Analysis of Prognostic Factors				
Characteristics	Median OS	*P* value	HR	95%CI for HR
Age at diagnosis		<0.001		
40-44 years	42		Reference	
45-49 years	41		1.013	0.829-1.237
50-54 years	39		1.103	0.915-1.329
55-59 years	32		1.364	1.139-1.634
Race		<0.001		
White	41		Reference	
Black	28		1.498	1.315-1.707
Other [a]	38		1.003	0.824-1.220
Marital status		<0.001		
Single	32		Reference	
Married	42		0.723	0.638-0.819
Other [b]	35		0.903	0.772-1.057
Insurance		<0.001		
Uninsured	26		Reference	
Insured	38		0.633	0.513-0.781
Grade		<0.001		
I	48		Reference	
II	44		1.214	0.953-1.547
III or IV	28		2.071	1.634-2.625
Histology		0.003		
Ductal	36		Reference	
Lobular	44		0.748	0.624-0.897
Others	40		0.856	0.713-1.028
Laterality		0.084		
Right	38		Reference	
Left	38		1.058	0.949-1.179
Bilateral, single primary	13		2.254	1.008-5.039

Tumour subtype		<0.001		
HR+/HER2-	39		Reference	
HR+/HER2+	52		0.747	0.640-0.873
HR-/HER2-	11		3.571	3.071-4.152
HR-/HER2+	35		1.132	0.917-1.397
Bone+Lung metastases		<0.001		
No	42		Reference	
Yes	23		1.888	1.679-2.123
Bone+Liver metastases		<0.001		
No	44		Reference	
Yes	22		2.182	1.950-2.443
Bone+Brain metastases		<0.001		
No	40		Reference	
Yes	14		2.674	2.245-3.184
Only bone metastases		<0.001		
No	46		Reference	
Yes	24		2.29	2.04-2.559
Surgery		<0.001		
No	32		Reference	
Yes	52		0.496	0.433-0.568
Other [a] (American Indian/AK Native, Asian/Pacific Islander) Other [b] (Divorced/Widowed/Separated)				

Table 3 Multivariate Analysis of Prognostic Factors			
Characteristics	*P* value	HR	95%CI for HR
Age at diagnosis			
40-44 years		Reference	
45-49 years	0.542	0.932	0.741-1.170
50-54 years	0.878	1.017	0.821-1.260
55-59 years	0.024	1.270	1.032-1.562
Race			
White		Reference	
Black	0.001	1.317	1.127-1.540
Other [a]	0.128	1.192	0.951-1.495
Marital status			
Single		Reference	
Married	0.008	0.819	0.707-0.949
Other [b]	0.130	0.871	0.728-1.042
Insurance(yes vs no)	<0.001	0.587	0.459-0.751
Histology			
Ductal		Reference	
Lobular	0.744	1.041	0.820-1.321
Others	0.356	1.105	0.894-1.365
Laterality			
Right		Reference	
Left	0.506	1.043	0.921-1.182
Bilateral, single primary	0.177	2.21	0.894-1.365
Grade			
I		Reference	
II	0.309	1.147	0.881-1.492
III or IV	<0.001	1.960	1.491-2.577
Tumour subtype			

HR+/HER2-		Reference	
HR+/HER2+	0.002	0.631	0.474-0.839
HR-/HER2-	<0.001	2.808	2.169-3.634
HR-/HER2+	0.258	0.716	0.401-1.277
Site of metastases			
Lung(yes vs no)	0.020	1.378	1.188-1.598
Live(yes vs no)	<0.001	2.085	1.795-2.422
Brain(yes vs no)	<0.001	1.903	1.542-2.248
Surgery(yes vs no)	<0.001	0.504	0.431-0.590
HR+/HER2- * multi-metastases		Reference	
HR+/HER2+ * multi-metastases	0.045	0.694	0.485-0.992
HR-/HER2- * multi-metastases	0.717	0.941	0.675-1.310
HR-/HER2+ * multi-metastases	0.564	0.828	0.437-1.572
Next step			
White*HR+/HER2-		Reference	
Black*HR+/HER2+	0.366	0.821	0.536-1.258
Other a*HR+/HER2+	0.652	0.862	0.453-1.641
Black*HR-/HER2-	0.323	0.817	0.546-1.220
Other a*HR-/HER2-	0.299	1.508	0.695-3.271
Black*HR-/HER2+	0.696	0.881	0.466-1.664
Other a*HR-/HER2+	0.368	0.701	0.323-1.521
Other [a] (American Indian/AK Native, Asian/Pacific Islander) Other [b] (Divorced/Widowed/Separated)			

Discussion

Bones metastases are the most common distant metastatic site in breast cancer, severe complications, low quality of life and poor prognosis in patients, the rate of survival significantly decreased are often associated with the occurrence of bone metastases [16]. Our study analyzed recently available data on the subtype in stage IV patients bone metastatic breast cancer patients from the SEER registries, in an attempt to analysis differences in the effects of the breast cancer subtype and other factors on the patient prognosis.

Bone metastasis is most abundant among the HR+ subtype, the distribution of our study stage IV patients tumour subtype is similar to other studies in the published literature [12, 19, 20]. Our studies have identified the subgroups of stage IV patients with HR+/HER2- breast cancer is the most prone to bone metastasis, secondly is HR+/HER2+ breast cancer. HR-/HER2- has a particular propensity to metastasize to the brain and lung, brain metastasis is more common than for the other subtype, and the bone metastasis is relatively less likely to occur, this is consistent with previous research [21]. This may be due to different molecular subtype of breast cancer lead to different metastasis sites due to their special molecular biological characteristics.

The median OS for the entire cohort was 38 months of the patients, this is similar with Kuchuk's study that from 294 electronic records of metastatic breast cancer patients were reviewed, they found the median OS from bone metastasis diagnosis is 40 months in bone metastasis patients [22]. The median OS is 46 months for stage IV patients with only bone metastases, those with bone and other sites metastases is 24 months in our study is similar to the survival reported by previous authors in recent years [8]. Study of 815 patients with denovo or recurrent metastatic breast cancer and identified that patients with visceral metastases as well as those with multiple metastatic sites had worse OS, findings consistent with our results [23]. The five year survival rate is 33.9% which is similar with previous studies that shown 24–39% of patients alive in five year after diagnosis of bone metastases [5]. It may be due to the fact that the subjects of this study are menopausal women, the age of the previous subjects is unlimited, the proportion of elderly patients is large and the prognosis is poor, and with the improving of treatment methods in recent years, the prognosis of the patients has been improved.

Our study shown the five-year survival rate of HR+/HER2+ stage IV patients is the highest, reached 5.6 times of HR-/HER2- patients. Stage IV Patients with HR+/HER2+ breast cancer had the longest median survival period. However, our study have shown that the incidence of bone metastasis in HR-/HER2- breast cancer was low, but stage IV patients with HR-/HER2- tumour had the worst prognosis. And OS in stage IV patients with HR-/HER2- breast cancer were significantly lower than those in stage IV patients with other molecular subtype, with the shortest median survival time. The large difference in prognosis observed across all tumour subtype confirms that breast cancer is a heterogeneous disease, even in the specific group of patients with bone metastases. The improvements in OS seen in HER2+ patients could be explained in part by the efficacy of HER2-targeted agents. In Dawood's large-scale, randomized study , there were 2019 women with metastatic breast cancer that showed HER2+ patients who received trastuzumab had improved prognosis compared with HER2- patients [24]. However, the HR-/HER2- is an invasion subtype, with the characteristics of rapid progress, strong aggressiveness, high degree of malignancy, easy occurrence of distant metastasis, rapid relapse [25-27]. Therefore, Our study includes tumour subtype as a prognostic factor and provides evidence of a clear association of age, race, marital status, insurance, tumour grade, histology, subtype, and visceral metastases in bone metastasis patients with OS. This was similar with previous study. The Denmark data were population-based health registries, included all women in diagnosed during 1999–2011 with regional or stage II/III breast cancer, showed predictors of recurrence, metastases, and mortality included age, hormone receptor status, and stage at diagnosis [28]. Ahn's study showed ER- negative and bone metastasis combined with visceral metastasis is a risk factor for OS [8]. Iqbal J's study showed US women diagnosed with invasive breast cancer, the survival varied by race and ethnicity, black women are more likely to die due to breast cancer within 7 years compared with non-Hispanic white or Asian women [29]. Previous study observed that

Hispanics and Non-Hispanic Blacks were more likely to have ER-positive and PR-negative tumors compared to Non-Hispanic Whites [30]. However, in our study we found no interaction between subtype and race .

The protective effect of marriage for survival, that can be explained by patients can gained better economic resources and greater social support in marriage [31]. Although some factors have been found in previous studies, no covariates have been adjusted for other factors, or fewer covariates have been adjusted. We used a Cox proportional regression model by adjusting for all the factors and demonstrated the tumour subtype were prognosis factors. Therefore, in clinical and nursing work, doctors and nurses can carry out different treatment and nursing work for different patients according to age, race, marital status, insurance, tumour grade, histology, subtype, and visceral metastases. In addition, we found that there was interaction between subtype and multiple visceral metastasis, this suggests that we should pay attention to the risk of visceral metastasis in patients with different subtype. Future studies are recommended to explore the mechanism of molecular subtype and metastasis site, but also explore the influence of their interaction on the outcome and management of patients.

We acknowledge that the study has some limitations. SEER database could not know the expression status of ki-67, the ki-67 index value is a prognostic factor in primary breast cancer and is a proliferation marker that also distinguishes between luminal A and luminal B breast cancer [32]. Breast cancer is generally divided into luminal A and luminal B, according to HR\HER2 status and ki-67 in the course of clinical diagnosis and treatment [33]. This may contribute to some disparities between our investigation and clinical applications. We do not have information with regards to radiotherapy or systemic treatments of this cohort, which may contribute to some of the differences observed in survival according to prognostic variables. Addition,the pathological data could not be centrally reviewed and were collected from different local pathology laboratories.

Conclusions

In conclusion, our results revealed a relatively good prognosis of bone metastasis in stage IV patients, the median OS was 38 months, 33.9% of stage IV patients were alive at five years. Subtype is a significant prognostic factor, the prognosis of stage IV patients with HR-/HER2- subtype is the worst, median OS only 11 months. Except tumour subtype, race, marital status, insurance, grade, site of metastases, surgery are independent predictors of OS. There was interaction between subtype and multiple visceral metastasis.

Abbreviations

OS: overall survival;

BCSS: time from the breast cancer diagnosis to death due to breast cancer

ER: estrogen receptor

PR: progesterone receptor

HR-: ER- and PR-;

HR+: ER+ or\and PR+

HR: hazard ratio

HER2: human epidermal growth factor receptor-2

CI : confidence interval

ICD-O-3 : International Classification of Diseases for Oncology, 3rd Edition;

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed for the current study will be available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LX and LJ conceived the study design and analytical concept. LX conducted the data acquisition, performed statistical analyses and drafted the manuscript. All authors contributed to the interpretation of results and the critical revision of the manuscript. All authors participated in the revision of the manuscript and approved the final manuscript.

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Figures

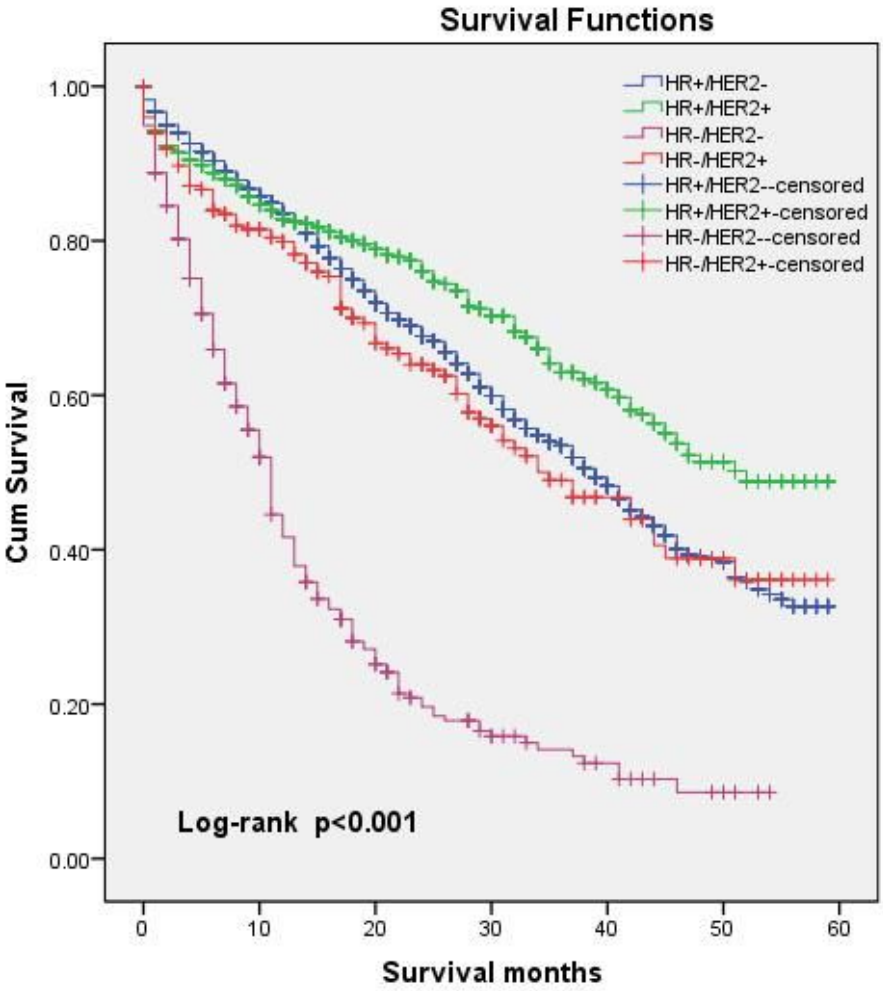

Figure 1

Kaplan–Meier curve for overall survival according to tumour subtype.

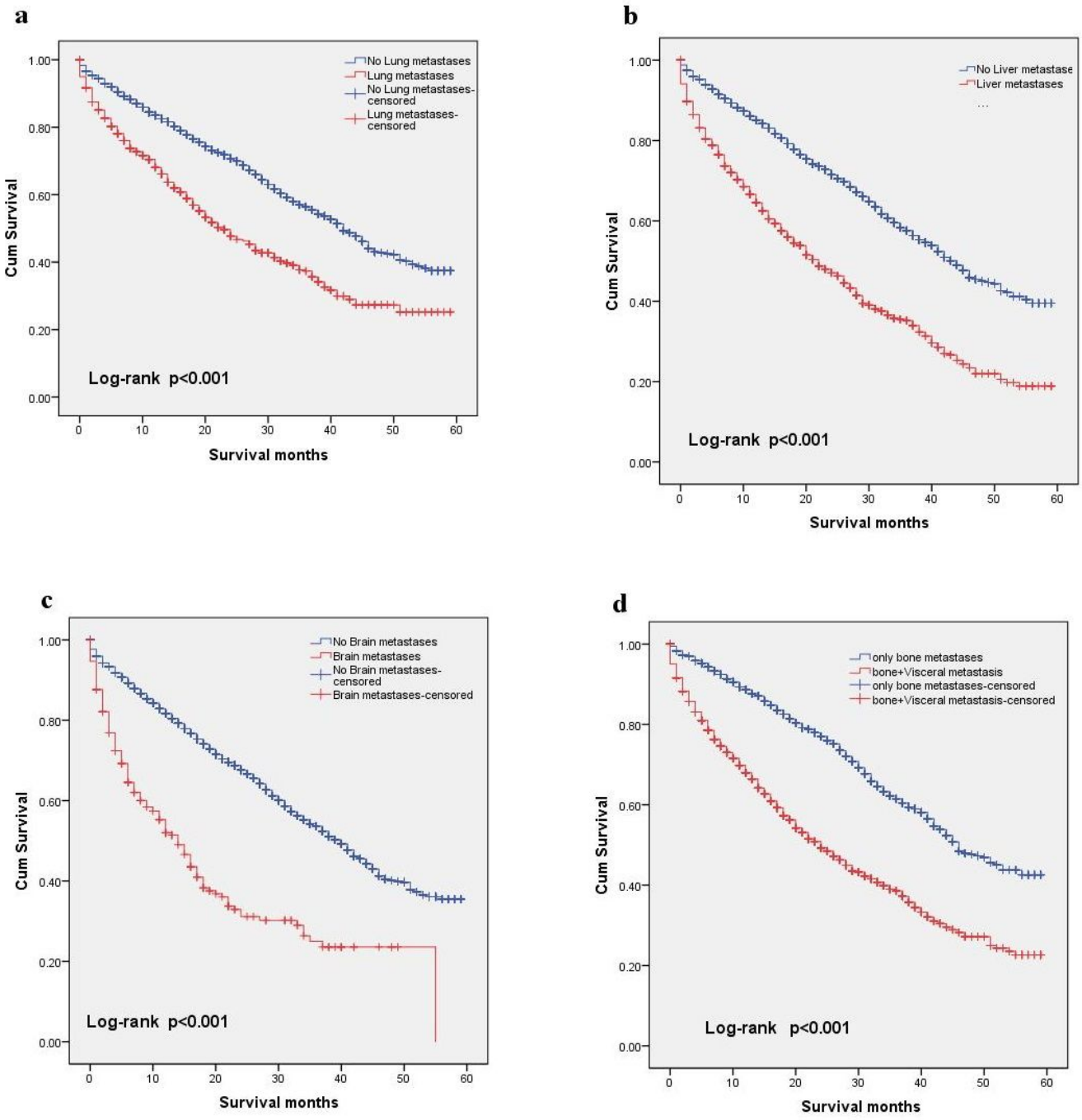

Figure 2

Kaplan–Meier curves for overall survival according to metastases site.

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- tables.xls