Patterns of Distant Metastases in Patients With Triple-Negative Breast Cancer — A Population-Based Study

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Abstract

Background

Currently, the prognosis of triple-negative breast cancer (TNBC) patients remained poor mainly due to resistance, recurrence, metastasis and severe side effects. The study provided systematic insights into the patterns of TNBC distant metastases (DM), as well as investigating the related elements for the prognosis prediction of TNBC patients on the basis of on large sample.

Methods

We screened eligible patients with triple-negative breast cancer from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. Besides, we analyzed differences in baseline characteristics among patients with diverse modes of metastasis. Meanwhile, we calculated proportional mortality ratio (PMR) and the expression of proportional trends in different patients. Subsequently, Kaplan-Meier (KM) analysis was employed to investigate the survival outcomes. Finally, the predictive and prognostic factors of DM were identified.

Results

In this study, we included 24,822 TNBC patients, including 1,026 DM patients and 23,796 non-DM patients. At the time of initial diagnosis, 4.1% of patients had DM, and 36.9% had multiple metastases. According to the study, the most common sites of metastasis in DM patients were bone (251 cases) and lung (244 cases), while the least common organ of metastasis was brain (37 cases). Age, tumor grade, T, N and marital status were deemed as risk elements of DM. T stage, insurance status, marital status, surgery treatment, chemotherapy, number of metastatic sites and metastatic sites also effect the diagnosis of DM significantly.

Conclusion

Our study showed that the most common site of metastasis in TNBC patients with DM was bone and the least common site was brain. Different modes of metastasis have different survival and prognostic characteristics. Thus, our research may have important implications for the clinical practice of TNBC patients in the future.

Introduction

Breast cancer (BC) remained the most severe public health problem that endangers women's lives and health in the world [1, 2], accounting for 10.4% of all cancers. Although there are still regional differences between different countries, breast cancer is still the leading cause of death among women aged 20-

50[3]. BC is a heterogeneous disease. In view of genetic, epigenetic and transcriptome changes, its histological and biological characteristics are different. 95% of BC is adenocarcinoma, starting as a local disease [4]. Invasive/metastatic BC can be divided into nonspecific type (NST) cancer (60-75%) and special type (20%- 25%) [5]. In the aspect of biological characteristics, three kinds of molecular biomarkers (estrogen receptor (ER), progesterone receptor (PR) and HER2) are detected by molecular biological methods for the molecular type of BC [6–8], including estrogen receptor positive (ER+) type or progesterone receptor positive (PR+) type, human epidermal receptor 2 positive (HER2+) type and triple-negative BC (TNBC) [9, 10].

The incidence of TNBC in BC is about 10-15%, but it is one of the most aggressive subtypes [11]. TNBC distant metastasis (DM) refers to the metastasis of BC outside the ipsilateral breast, chest wall and regional lymph nodes, which is the main cause of death (COD) of BC. 6-10% of cases have metastasis at the time of diagnosis, and nearly 30% will relapse or metastasize [12]. About 25% of TNBC patients still have local recurrence and DM after active treatment. There are many metastases of BC such as brain, lung, liver, etc [13]. At present, there are few effective methods for the treatment of metastatic TNBC, resulting in poor prognosis of patients with metastatic TNBC. Therefore, it is urgent to further study the prediction and prognostic factors of DM in TNBC [14–17]. But, the shortcomings of previous studies are mostly single-center studies with small sample size and incomplete long-term follow-up information.

Therefore, we used SEER database to establish prognostic models for TNBC patients with different metastasis modes to further explore the risk factors affecting distant metastasis of tumor.

Methods And Materials

Database

We employed the the “SEER*Stat 8.3.8” software (Version 8.3.6; NCI) to download the data from the SEER registry. The SEER database detailed information about cancer patients in the USA. In our study, we signed the data agreement and used the 10977-Nov2019 database. In addition, the Institutional Review Board allowed us to proper use of this public database.

Patient identification

The TNBC patients with positive pathology were retrospectively extracted from SEER 18 registry. All patients were diagnosed between 2010 and 2015 because data DM data were recorded from 2010. Inclusion criteria: (1) patients diagnosed with TNBC (C50.0-C50.6, C50.8-C50.9; AYA site recode/WHO 2008= 8.4 Carcinoma of the breast), (2) BC was the first primary malignancy of each patient, (3) patients with complete data of long-term follow-up. Exclusion criteria: (1) patients with bilateral tumors or unknown tumor laterality, (2) patients with unknown data on marital status, insurance status, household income, the administration of surgery, T stage, N stage, race, and tumor grade, (3) unknown metastatic status, (4) data were from autopsy or death certificate only.

Data extraction

For each patient, essential clinical characteristics and long-term survival outcomes were extracted using the “Case Listing Session”. Variables including race, age, year of diagnosis, tumor grade, laterality, AJCC 7th T stage, N stage, the administration of surgery/ chemotherapy and radiotherapy, DM status, survival months, COD, insurance status, metastatic status, vital status and, household income were identified. Based on DM status, all patients were categorized into DM group and without DM group. Moreover, those in DM group were further subdivided based on the metastatic status.

For further analyses, age at diagnosis was divided into < 45, 45 - 69 and $\geq$ 70 years old, the race was classified into White, Black and Other. Furthermore, the pathological grade was divided into four levels: high, moderately, poorly and undifferentiated. Median household income was calculated to define high- and low-level household income.

Identification of prognostic characteristics

KM curves were used to explore the overall survive of DM or the metastatic site in TNBC patients. We analyzed COD in different groups of patients who died during long-term follow-up. Uni- and multivariable cox analyses were constructed to explore the risk factors of DM in TNBC patients. Finally, COX analyses were developed to find prognostic factors of OS and CSS.

Statistical analysis

In our study, data were mainly presented by n (%). Chi-square test was used for comparison between categorical variables. The fundamental analyses were completed on the basis of SPSS 23.0 software (SPSS Inc) and R software (Version 3.4.1). All analytical processes were two-sided, and $P < 0.05$ was deemed to have statistical significance.

Results

Characteristics of baseline and prognosis

Figure 1 presented the selection flow chart of this study. Table 1 indicated that our study ultimately identified 24,822 patients with TNBC, including 1,026 DM patients and 23,796 patients without DM. In general, most of the patients were aged 45-69 years old (61.44%), white (71.60%), early lesion (T1: 42.00%, N0: 63.79%), and tumor-directed surgery (92.56%). Compared with none-DM patients, those DM patients had older age ($P = 0.003$), higher probability of black ($P < 0.001$), later stage of diseases ($P < 0.001$), lower median household income ($P = 0.002$), lower married rate ($P < 0.001$) and lower insurance rate ($P < 0.001$). In addition, the rate of surgery and radiotherapy was significantly higher ($P < 0.001$) in patients without DM. But, there was no statistical difference in diagnosis year, laterality and chemotherapy

Table 1
Baseline characteristics of included patients (with DM vs. without DM).

	Total	Without DM	With DM	P Value
N	24,822	23,796	1,026	
Age				0.003
< 45	4,563	4,407	156	
45-69	15,250	1,4620	630	
≥ 70	5,009	4,769	240	
Race				<0.001
White	17,773	17,078	695	
Black	5,148	4,877	271	
Other	1,901	1,841	60	
Year of Diagnosis				0.714
2010	3,972	3,813	159	
2011	4,109	3,942	167	
2012	4,080	3,927	153	
2013	4,083	3,904	179	
2014	4,200	4,020	180	
2015	4,378	4,190	188	
Laterality				0.968
Left	12,783	12,254	529	
Right	12,039	11,542	497	
Grade ¹				<0.001
Grade I	490	479	11	
Grade II	4,150	3,983	167	
Grade III	19,992	19,162	830	

Data were n (%), unless otherwise specified.

DM=distant metastasis; ¹Grade I = Well differentiated; Grade II = Moderately differentiated; Grade III = Poorly differentiated; Grade IV = Undifferentiated. ²Median household income: defined by earnings above the median of the median household income in this sample.

	Total	Without DM	With DM	P Value
Grade IV	190	172	18	
T stage				<0.001
T1	10,424	10,340	84	
T2	10,528	10,229	299	
T3	2,240	2,026	214	
T4	1,630	1,201	429	
N stage				<0.001
N0	15,834	15,618	216	
N1	6,192	5,713	479	
N2	1,567	1,442	125	
N3	1,229	1,023	206	
Surgery				<0.001
No	1,847	1,271	576	
Yes	22,975	22,525	450	
Chemotherapy				0.736
No/Unknown	5,795	5,551	244	
Yes	19,027	18,245	782	
Radiotherapy				<0.001
No/Unknown	13,170	11,587	688	
Yes	11,652	12,209	338	
Median household income ²				0.002
Low	13,170	12,576	594	
High	11,652	11,220	432	
Marital status				<0.001

Data were n (%), unless otherwise specified.

DM=distant metastasis; ¹Grade I = Well differentiated; Grade II = Moderately differentiated; Grade III = Poorly differentiated; Grade IV = Undifferentiated. ²Median household income: defined by earnings above the median of the median household income in this sample.

	Total	Without DM	With DM	P Value
Never Married	4,519	4,275	244	
Married	14,012	13,561	451	
Previous married	6,291	5,960	331	
Insurance status				<0.001
Uninsured	602	550	52	
Insured	24,220	23,246	974	
Data were n (%), unless otherwise specified.				
DM=distant metastasis; ¹ Grade I = Well differentiated; Grade II = Moderately differentiated; Grade III = Poorly differentiated; Grade IV = Undifferentiated. ² Median household income: defined by earnings above the median of the median household income in this sample.				

The most common sites of metastasis in DM patients were bone (24.46%) and lung (23.78%), while the least common organ of metastasis was brain (3.61%). Besides, we found that nearly 36.94% patients had two or more metastases (Table 2). Compared with patients with multiple organ metastases, patients with single organ metastases were more likely to undergo surgery and less likely to receive radiotherapy. (52.86% vs. 28.50%, $P < 0.001$; 30.6% vs. 36.9%, $P = 0.037$). But, no statistically significant differences were found in comparison with other variables. Eventually, the patients were chopped up into four groups (simple brain, simple bone, simple liver, and simple lung), and the comparison between groups was shown in Table S1. Compared with other sites, patients with lung metastasis later stage of diseases while patients with brain metastasis underwent radiotherapy more frequently ($P = 0.021$, $P < 0.001$).

Table 2
Baseline characteristics of patients with DM, stratified by the number of metastatic sites

	1 site	>1 site	P value
N	647	379	
Age			0.151
< 45	97	59	
45-69	386	244	
≥ 70	164	76	
Race			0.466
White	432	263	
Black	179	92	
Other	36	24	
Year of Diagnosis			0.128
2010	110	49	
2011	101	66	
2012	105	48	
2013	103	76	
2014	107	73	
2015	121	67	
Laterality			0.223
Left	343	186	
Right	304	193	
Grade ¹			0.998
Grade I	7	4	
Grade II	105	62	
Grade III	524	306	

Data were n (%), unless otherwise specified. DM=distant metastasis; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

	1 site	>1 site	P value
Grade IV	11	7	
T stage			0.007
T1	58	26	
T2	205	94	
T3	139	75	
T4	245	184	
N stage			0.389
N0	146	70	
N1	295	184	
N2	81	44	
N3	125	81	
Surgery			<0.001
No	305	271	
Yes	342	108	
Chemotherapy			0.530
No/Unknown	158	86	
Yes	489	293	
Radiotherapy			0.037
No/Unknown	449	239	
Yes	198	140	
Median household income ²			0.852
Low	376	218	
High	271	161	
Marital status			0.636
Never Married	148	96	

Data were n (%), unless otherwise specified. DM=distant metastasis; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

	1 site	>1 site	P value
Married	290	161	
Previous married	209	122	
Insurance status			0.088
Uninsured	27	25	
Insured	620	354	
Data were n (%), unless otherwise specified. DM=distant metastasis; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.			

Proportional Death Rate

The results of subgroup analyses are shown in Figure 3. Compared with the non-DM group, the mortality rate from BC in DM group was significantly increased (77.57–94.75%), while the mortality rate from other causes (21.15%-4.68%) and the mortality rate from unknown causes (1.28%-0.57%) were significantly decreased (Figure 2A). In other words, once BC patients had DM, They have a greater chance of dying from their disease. This trend became more pronounced with the increase of metastatic sites (Figure 2B). It is worth noting that DM in brain causes all the deaths (Figure 2C).

Survival Results

As shown in Figure 3A, B, Non-dm patients had a better survival advantage (OS and CSS) than DM patients. Besides, patients with a single metastasis had a better survival advantage (OS and CSS) than patients with multiple metastases.patient (Figure 3C, D) In patients with multiple metastases, patients with two metastases had better OS and CSS than patients with more than two metastases (Figure 3E, F). What is more, the greater the number of metastases in DM patients, the worse the survival advantage (OS and CSS) (Figure 3G, H). Patients with brain metastasis or liver metastases had the worst OS and CSS of all metastatic sites (Figure 4A, B). Figure 4C-4F indicated the survival analyses of patients with two and three metastatic sites. However, in patients with two or three metastatic sites, there were no statistically significant differences in OS and CSS between different metastatic types. Table 3 showed that older TNBC patients, higher T, and higher N were at higher risk for DM, stage T, insurance status, number of managed surgery, chemotherapy, government metastatic style, and important factors affecting the operating system of DM patients (Table 4), and stage T, insurance status, surgical management, number of metastatic lesions, and marital status were significantly correlated with CSS (Table 5). Besides, the multivariate COX analysis indicated that T stage, insurance status, chemotherapy management, surgical method and metastatic site were obvious factors affecting OS in patients with a single metastatic site.

(Table 6). T stage, insurance status, surgical method, chemotherapy method, and site of metastasis were correlated with CSS (Table 7).

Table 3
Uni- and multivariate logistic regression analyses of risk factors for patients with DM

Variable	Univariate			Multivariate		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Age			0.004			0.001
< 45	Reference			Reference		
45-69	1.217	1.018-1.455	0.031	1.430	1.183-1.730	<0.001
≥ 70	1.422	1.157-1.746	0.001	1.582	1.254-1.997	<0.001
Race			<0.001			0.111
White	Reference			Reference		
Black	1.365	1.182-1.577	<0.001	1.057	0.899-1.242	0.502
Other	0.801	0.613-1.047	0.104	0.761	0.572-1.011	0.060
Grade ¹			0.001			0.037
Grade I	Reference					
Grade II	1.826	0.985-3.385	0.056	1.058	0.549-2.037	0.867
Grade III	1.886	1.033-3.443	0.039	0.851	0.449-1.612	0.620
Grade IV	4.557	2.110-9.843	<0.001	1.426	0.619-3.289	0.405
Laterality			0.968			
Left	Reference					
Right	0.997	0.880-1.130	0.968			
T stage			<0.001			<0.001
T1	Reference					
T2	3.598	2.820-4.591	<0.001	2.829	2.205-3.631	<0.001
T3	13.002	10.057-16.809	<0.001	7.916	6.043-10.370	<0.001
T4	43.970	34.541-55.973	<0.001	21.616	16.643-28.077	<0.001

DM: distant metastasis; OR: odds ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample;

Variable	Univariate		Multivariate			
N stage			<0.001		<0.001	
N0	Reference					
N1	6.062	5.148-7.139	<0.001	3.197	2.682-3.811	<0.001
N2	6.268	4.996-7.863	<0.001	2.372	1.855-3.032	<0.001
N3	14.560	11.908-17.803	<0.001	4.304	3.435-5.393	<0.001
Insurance status			<0.001		0.219	
Insured	Reference					
Uninsured	0.443	0.331-0.593	<0.001	0.817	0.592-1.128	0.219
Marital status			<0.001		0.005	
Never Married	Reference					
Married	0.583	0.497-0.683	<0.001	0.851	0.712-1.017	0.076
Previous married	0.973	0.821-1.153	0.753	1.110	0.914-1.349	0.294
Household income ²			0.002		0.094	
Low	Reference					
High	0.815	0.718-0.925	0.002	0.889	0.775-1.020	0.094
DM: distant metastasis; OR: odds ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample;						

Table 4

Univariate and Multivariate Cox regression analyses of prognostic factors for OS in patients with DM

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age			0.002			0.269
< 45	Reference			Reference		
45-69	1.059	0.875-1.281	0.556	1.086	0.892-1.323	0.411
≥ 70	1.386	1.113-1.724	0.003	1.213	0.954-1.542	0.115
Race			0.770			
White	Reference					
Black	1.029	0.884-1.199	0.711			
Other	0.919	0.6850-1.234	0.575			
Grade ¹			0.741			
Grade I	Reference					
Grade II	1.050	0.553-1.994	0.880			
Grade III	0.952	0.510-1.778	0.877			
Grade IV	0.904	0.410-1.992	0.801			
Laterality			0.494			
Left	Reference					
Right	1.047	0.917-1.196	0.494			
T stage			<0.001			0.016
T1	Reference			Reference		
T2	1.015	0.779-1.324	0.911	1.136	0.868-1.487	0.353
T3	1.040	0.789-1.370	0.781	1.146	0.865-1.519	0.341

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

Variable	Univariate			Multivariate		
T4	1.376	1.065-1.777	0.014	1.387	1.068-1.802	0.014
N stage			0.545			
N0	Reference					
N1	1.098	0.919-1.313	0.303			
N2	1.127	0.887-1.431	0.329			
N3	1.162	0.942-1.434	0.160			
Insurance status			<0.001			0.003
Uninsured	Reference			Reference		
Insured	0.575	0.431-0.768	<0.001	0.644	0.479-0.865	0.003
Marital status			<0.001			0.039
Never Married	Reference			Reference		
Married	0.764	0.646-0.903	0.002	0.808	0.680-0.961	0.016
Previous married	1.023	0.858-1.219	0.799	0.925	0.763-1.120	
Median household income ²			0.625			
Low	Reference					
High	0.967	0.846-1.106	0.625			
Surgery			<0.001			<0.001
No	Reference			Reference		
Yes	0.510	0.445-0.585	<0.001	0.586	0.507-0.678	<0.001
Chemotherapy			<0.001			<0.001
No/Unknown	Reference			Reference		
Yes	0.372	0.319-0.434	<0.001	0.373	0.316-0.440	<0.001
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Variable	Univariate			Multivariate		
Radiotherapy	0.012			0.868		
No/Unknown	Reference			Reference		
Yes	0.833	0.723-0.960	0.012	0.987	0.850-1.147	0.868
Number of metastatic sites	<0.001			<0.001		
1 site	Reference					
2 sites	1.595	1.371-1.856	<0.001	1.463	1.249-1.713	<0.001
> 2 sites	2.323	1.857-2.906	<0.001	2.255	1.768-2.845	<0.001
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Table 5

Univariate and Multivariate Cox regression analyses of prognostic factors for CSS in patients with DM

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age			0.010			0.446
< 45	Reference			Reference		
45-69	1.038	0.855-1.261	0.703	1.062	0.869-1.298	0.557
≥ 70	1.321	1.056-1.654	0.015	1.166	0.911-1.492	0.222
Race			0.831			
White	Reference					
Black	1.025	0.876-1.199	0.760			
Other	0.929	0.688-1.255	0.633			
Grade ¹			0.757			
Grade I	Reference					
Grade II	0.993	0.522-1.888	0.983			
Grade III	0.900	0.482-1.681	0.741			
Grade IV	0.902	0.409-1.988	0.798			
Laterality			0.365			
Left	Reference					
Right	1.065	0.929-1.220	0.365			
T stage			<0.001			0.014
T1	Reference			Reference		
T2	1.018	0.773-1.341	0.898	1.143	0.864-1.511	0.349
T3	1.096	0.824-1.456	0.529	1.207	0.904-1.612	0.203

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

Variable	Univariate			Multivariate		
T4	1.407	1.080-1.835	0.012	1.421	1.084-1.864	0.011
N stage			0.271			
N0	Reference					
N1	1.137	0.944-1.369	0.175			
N2	1.151	0.898-1.475	0.267			
N3	1.241	1.000-1.540	0.050			
Insurance status			<0.001			0.002
Uninsured	Reference			Reference		
Insured	0.552	0.412-0.739	<0.001	0.619	0.459-0.835	0.002
Marital status			<0.001			0.047
Never Married	Reference			Reference		
Married	0.761	0.641-0.904	0.002	0.814	0.682-0.972	0.023
Previous married	1.017	0.8560-1.218	0.850	0.941	0.772-1.146	0.544
Median household income ²			0.546			
Low	Reference					
High	0.958	0.836-1.100	0.546			
Surgery			<0.001			<0.001
No	Reference			Reference		
Yes	0.508	0.442-0.585	<0.001	0.585	0.504-0.680	<0.001
Chemotherapy			<0.001			<0.001
No/Unknown	Reference			Reference		
Yes	0.388	0.331-0.456	<0.001	0.384	0.323-0.457	<0.001
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Variable	Univariate			Multivariate		
Radiotherapy	0.034			0.947		
No/Unknown	Reference			Reference		
Yes	0.855	0.740-0.988	0.034	1.005	0.862-1.172	0.947
Number of metastatic sites	<0.001			<0.001		
1 site	Reference			Reference		
2 sites	1.627	1.392-1.900	<0.001	1.479	1.257-1.740	<0.001
> 2 sites	2.447	1.949-3.071	<0.001	2.359	1.863-2.987	<0.001
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Table 6

Univariate and Multivariate Cox regression analyses of prognostic factors for OS in patients with DM

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age			0.015			0.529
< 45						
45-69	1.007	0.786-1.289	0.959	1.022	0.791-1.319	0.870
≥ 70	1.341	1.017-1.770	0.038	1.157	0.847-1.581	0.358
Race			0.964			
White						
Black	0.974	0.802-1.183	0.788			
Other	0.987	0.680-1.433	0.945			
Grade ¹			0.889			
Grade I						
Grade II	1.036	0.453-2.371	0.933			
Grade III	0.983	0.439-2.201	0.967			
Grade IV	0.795	0.283-2.234	0.663			
Laterality			0.491			
Left						
Right	0.942	0.794-1.117	0.491			
T stage			0.016			0.011
T1						
T2	1.069	0.768-1.486	0.694	1.290	0.919-1.812	0.141
T3	1.061	0.750-1.500	0.738	1.246	0.873-1.778	0.226
T4	1.406	1.017-1.943	0.039	1.630	1.166-2.281	0.004
N stage			0.540			
N0						

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

Variable	Univariate		Multivariate			
N1	1.131	0.901-1.420	0.287			
N2	1.228	0.909-1.658	0.180			
N3	1.165	0.890-1.525	0.266			
Insurance status			0.003			0.004
Uninsured						
Insured	0.539	0.360-0.806	0.003	1.630	1.166-2.281	0.004
Marital status			0.015			0.146
Never Married						
Married	0.833	0.670-1.036	0.100	0.815	0.651-1.021	0.076
Previous married	1.109	0.882-1.394	0.378	0.946	0.732-1.224	0.674
Median household income ²			0.740			
Low						
High	1.030	0.867-1.223	0.740			
Surgery			<0.001			<0.001
No						
Yes	0.527	0.444-0.626	<0.001	0.545	0.454-0.654	<0.001
Chemotherapy			<0.001			<0.001
No/Unknown						
Yes	0.386	0.317-0.470	<0.001	0.411	0.331-0.511	<0.001
Radiotherapy			0.004			0.437
No/Unknown						
Yes	0.758	0.628-0.914	0.004	0.921	0.748-1.133	0.437
Metastatic sites			0.013			<0.001
Bone						
Brain	1.687	1.166-2.441	0.006	1.676	1.145-2.453	0.008

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

Variable	Univariate			Multivariate		
Liver	1.276	1.003-1.624	0.047	1.334	1.043-1.707	0.022
Lung	1.034	0.849-1.260	0.740	0.861	0.700-1.058	0.155
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Table 7

Univariate and Multivariate Cox regression analyses of prognostic factors for CSS in patients with DM

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age			0.025			0.508
< 45	Reference			Reference		
45-69	0.970	0.754-1.247	0.811	0.980	0.755-1.271	0.877
≥ 70	1.289	0.971-1.710	0.079	1.126	0.819-1.550	0.464
Race			0.933			
White	Reference					
Black	0.964	0.789-1.179	0.722			
Other	1.010	0.691-1.477	0.957			
Grade ¹			0.958			
Grade I	Reference					
Grade II	0.955	0.416-2.190	0.913			
Grade III	0.932	0.416-2.088	0.864			
Grade IV	0.792	0.282-2.228	0.659			
Laterality			0.590			
Left	Reference					
Right	0.953	0.799-1.136	0.590			
T stage			0.013			0.013
T1	Reference			Reference		

OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ²Median household income: defined by earnings above the median of the median household income in this sample.

Variable	Univariate			Multivariate		
T2	1.085	0.768-1.532	0.644	1.280	0.898-1.825	0.172
T3	1.144	0.799-1.638	0.463	1.314	0.910-1.900	0.146
T4	1.471	1.048-2.062	0.025	1.657	1.168-2.351	0.005
N stage			0.272			
N0	Reference					
N1	1.211	0.954-1.537	0.116			
N2	1.259	0.918-1.727	0.153			
N3	1.297	0.981-1.715	0.068			
Insurance status			<0.001			0.001
Uninsured	Reference			Reference		
Insured	0.442	0.293-0.668	<0.001	0.471	0.307-0.724	0.001
Marital status			0.026			0.256
Never Married	Reference			Reference		
Married	0.839	0.670-1.050	0.125	0.846	0.669-1.069	0.160
Previous married	1.103	0.871-1.398	0.416	0.976	0.748-1.275	0.861
Median household income ³			0.784			
Low	Reference					
High	1.025	0.858-1.224	0.784			
Surgery			<0.001			<0.001
No	Reference			Reference		
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Variable	Univariate			Multivariate		
Yes	0.540	0.452-0.645	<0.001	0.558	0.462-0.673	<0.001
Chemotherapy	<0.001			<0.001		
No/Unknown	Reference			Reference		
Yes	0.403	0.328-0.494	<0.001	0.435	0.347-0.545	<0.001
Radiotherapy	0.009			0.496		
No/Unknown	Reference			Reference		
Yes	0.773	0.637-0.937	0.009	0.929	0.750-1.149	0.496
Metastatic sites	0.011			0.001		
Bone	Reference			Reference		
Brain	1.819	1.255-2.637	0.002	1.809	1.233-2.656	0.002
Liver	1.237	0.960-1.593	0.100	1.281	0.989-1.660	0.061
Lung	1.084	0.885-1.329	0.435	0.899	0.728-1.111	0.325
OS: overall survival; DM: distant metastasis; HR: hazard ratio; CI: confidence interval; ¹ Grade I=Well differentiated; Grade II=Moderately differentiated; Grade III=Poorly differentiated; Grade IV=Undifferentiated; ² Median household income: defined by earnings above the median of the median household income in this sample.						

Discussion

In the manuscript, we discovered that 4.13% of TNBC patients had DM at the time of diagnosis. Among DM patients, 3.07% had multiple metastases. The most metastatic sites were bone (24.46%, 251/1026) followed by lung (23.78%, 244/1026). Multivariate cox analysis indicated that age, high tumor grade, T, N and marital status were significant risk elements for DM. It is consistent with previous studies of other tumors [18–20]. In addition, T stage, insurance status, marital status, surgery treatment, chemotherapy, location and number of metastases were confirmed to be associated with the diagnosis of DM patients. Moreover, only TNBC was included in this study, which is more convincing to think that this data is the only representative of TNBC. Last but not least, with the rapid improvement in the understanding and diagnosis of the disease, earlier TNBC or smaller breast lumps will be detected in clinical practice.

There have also been previous studies on distant metastasis in BC patients. A retrospective study collected and analyzed information from 2033 BC patients from 2012 to 2014 and showed that high

tumor grade, T, and N were significant risk factors for DM [21]. Another study identified 1173 BC liver metastases from the SEER database. Classification, marital status, surgery, radiotherapy, chemotherapy, tumor size and tumor subtypes were identified as risk factors for liver metastases from BC [22]. These conclusions are similar to our results. But only a few studies have focused on the triple negative subtype and combined metastatic pattern based on a larger sample size. In our study, 36.94% (379/1,026) of metastatic patients had multiple metastases. In addition, compared with patients with a single metastasis, patients with multiple metastases had a poorer survival advantage, and the more metastases there were, the worse the prognosis was (Table 4, 5). Furthermore, diverse combination of metastatic sites represented different prognosis.

Our results indicated that patients with DM have a significantly poor prognosis. Besides, the greater the number of metastases, the worse the prognosis. Hence, we further to identify the risk factors of DM and metastasis in patients with prognostic factors is very essential. In primary bladder cancer, high pathological grade, N and T were positively correlated with bone metastasis [20]. Another meta-analysis showed that poor tumor differentiation was related to the risk of metastasis in cutaneous squamous cell carcinoma [23]. In DM patients, the results of multi-COX analysis indicated that tumor grade, age at first diagnosis, T, N, marital status and surgical treatment were the significant influence affecting the OS. This is in line with what many previous studies have confirmed. In a BC study based on Asian female patients, age, grade, TNM stage, and chemotherapy have been shown to be associated with BC long-term survival [24]. Another SEER database study found that race, age, grade, molecular subtype, surgery, brain and liver metastases were independently associated with BC specific survival [25].

However, there remain several limitations in our study that should not be ignored. First, we failed to get more information from SEER database, including lymphatic or vascular invasion, multifocality, the sequence and specific arrangement of multiple metastases and even molecular biomarkers. Secondly, the database lacked several important clinical information, including LDH, hemoglobin, neutrophil count, platelet count, etc. If we include these, we can improve the comprehensiveness of analysis and conclusion. Furthermore, limitations include a lack of information on rare subtypes of TNBC that may alter treatment, such as metaplasia, adenoid cystic, and acrosine subtypes. Last but not least, the main population for this study is Americans, and whether the results applied to other populations was questionable.

Conclusion

About 4.13% of TNBC patients had DM at the time of initial diagnosis, and 36.94% of them had multiple metastases. Compared with non-DM patients, DM patients represented worse prognosis. Meanwhile, the survival was significantly reduced while the number of metastases increasing. In addition, the predictors and prognostic factors of DM were also studied with the expectation of providing potential value for clinical guidance.

Declarations

Acknowledgements

We confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

Author Contributions

Zhao Yunian designed the study. Gao Yang wrote the manuscript. Gu Kang, Bian Chuanzhen and Yan Ping analyzed the data. All authors read and approved the final manuscript.

Competing Interests

The authors declare no conflict of interests.

References

1. Beyer K, Zhou Y, Laud P, McGinley E, Yen T, Jankowski C, Rademacher N, Namin S, Kwarteng J, Beltrán Ponce S, Nattinger A. Mortgage Lending Bias and Breast Cancer Survival Among Older Women in the United States. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2021:JCO2100112.
2. Mayer I, Zhao F, Arteaga C, Symmans W, Park B, Burnette B, Tevaarwerk A, Garcia S, Smith K, Makower D, Block M, Morley K, Jani C, Mescher C, Dewani S, Tawfik B, Flaum L, Mayer E, Sikov W, Rodler E, Wagner L, DeMichele A, Sparano J, Wolff A, Miller K. Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2021:JCO2100976.
3. Gao C, Polley E, Hart S, Huang H, Hu C, Gnanaolivu R, Lilyquist J, Boddicker N, Na J, Ambrosone C, Auer P, Bernstein L, Burnside E, Eliassen A, Gaudet M, Haiman C, Hunter D, Jacobs E, John E, Lindström S, Ma H, Neuhausen S, Newcomb P, O'Brien K, Olson J, Ong I, Patel A, Palmer J, Sandler D, Tamimi R, Taylor J, Teras L, Trentham-Dietz A, Vachon C, Weinberg C, Yao S, Weitzel J, Goldgar D, Domchek S, Nathanson K, Couch F, Kraft P. Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2021:JCO2001992.
4. Bandera E, Qin B, Lin Y, Zeinomar N, Xu B, Chanumolu D, Llanos A, Omene C, Pawlish K, Ambrosone C, Demissie K, Hong C. Association of Body Mass Index, Central Obesity, and Body Composition With Mortality Among Black Breast Cancer Survivors. *JAMA oncology*. 2021.
5. Weigelt B, Reis-Filho J. Histological and molecular types of breast cancer: is there a unifying taxonomy? *Nature reviews Clinical oncology*. 2009;6(12):718-730.
6. Siegel R, Miller K, Jemal A. Cancer statistics, 2019. *CA: a cancer journal for clinicians*. 2019;69(1):7-34.
7. DeSantis C, Ma J, Gaudet M, Newman L, Miller K, Goding Sauer A, Jemal A, Siegel R. Breast cancer statistics, 2019. *CA: a cancer journal for clinicians*. 2019;69(6):438-451.

8. DeSantis C, Miller K, Goding Sauer A, Jemal A, Siegel R. Cancer statistics for African Americans, 2019. *CA: a cancer journal for clinicians*. 2019;69(3):211-233.
9. Liedtke C, Mazouni C, Hess K, André F, Tordai A, Mejia J, Symmans W, Gonzalez-Angulo A, Hennessy B, Green M, Cristofanilli M, Hortobagyi G, Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2008;26(8):1275-1281.
10. Lehmann B, Bauer J, Chen X, Sanders M, Chakravarthy A, Shyr Y, PiTENpol J. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *The Journal of clinical investigation*. 2011;121(7):2750-2767.
11. Pérez-García J, Soberino J, Racca F, Gion M, Stradella A, Cortés J. Atezolizumab in the treatment of metastatic triple-negative breast cancer. *Expert opinion on biological therapy*. 2020;20(9):981-989.
12. Anwar M, Chen Q, Ouyang D, Wang S, Xie N, Ouyang Q, Fan P, Qian L, Chen G, Zhou E, Guo L, Gu X, Ding B, Yang X, Liu L, Deng C, Xiao Z, Li J, Wang Y, Zeng S, Hu J, Zhou W, Qiu B, Wang Z, Weng J, Liu M, Li Y, Tang T, Wang J, Zhang H, Dai B, Tang W, Wu T, Xiao M, Li X, Liu H, Li L, Yi W. Pyrotinib treatment in patients with HER2-positive metastatic breast cancer and brain metastasis: exploratory final analysis of real-world, multicenter data. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2021.
13. Chiou A, Liu C, Moreno-Jiménez I, Tang T, Wagermaier W, Dean M, Fischbach C, Fratzl P. Breast cancer-secreted factors perturb murine bone growth in regions prone to metastasis. *Science advances*. 2021;7(12).
14. Weigelt B, Peterse J, van 't Veer L. Breast cancer metastasis: markers and models. *Nature reviews Cancer*. 2005;5(8):591-602.
15. Correia A, Guimaraes J, Auf der Maur P, De Silva D, Trefny M, Okamoto R, Bruno S, Schmidt A, Mertz K, Volkmann K, Terracciano L, Zippelius A, Vetter M, Kurzeder C, Weber W, Bentires-Alj M. Hepatic stellate cells suppress NK cell-sustained breast cancer dormancy. *Nature*. 2021.
16. Tsilimigras D, Brodt P, Clavien P, Muschel R, D'Angelica M, Endo I, Parks R, Doyle M, de Santibañes E, Pawlik T. Liver metastases. *Nature reviews Disease primers*. 2021;7(1):27.
17. Chen Y, Jiang T, Zhang H, Gou X, Han C, Wang J, Chen A, Ma J, Liu J, Chen Z, Jing X, Lei H, Wang Z, Bao Y, Baqri M, Zhu Y, Bindra R, Hansen J, Dou J, Huang C, Zhou J. LRR31 inhibits DNA repair and sensitizes breast cancer brain metastasis to radiation therapy. *Nature cell biology*. 2020;22(10):1276-1285.
18. Zhang Y, Guo Y, Zhou X, Wang X, Wang X. Prognosis for different patterns of distant metastases in patients with uterine cervical cancer: a population-based analysis. *Journal of Cancer*. 2020;11(6):1532-1541.
19. Wang Z, Chen M, Pan J, Wang X, Chen X, Shen K. Pattern of distant metastases in inflammatory breast cancer - A large-cohort retrospective study. *Journal of Cancer*. 2020;11(2):292-300.
20. Zhang C, Liu L, Tao F, Guo X, Feng G, Chen F, Xu Y, Li L, Han X, Baklaushev V, Bryukhovetskiy A, Wang X, Wang G. Bone Metastases Pattern in Newly Diagnosed Metastatic Bladder Cancer: A Population-

Based Study. *Journal of Cancer*. 2018;9(24):4706-4711.

21. Pan H, Wang H, Qian M, Mao X, Shi G, Ma G, Yu M, Xie H, Ling L, Ding Q, Zhang K, Wang S, Zhou W. Comparison of Survival Outcomes Among Patients With Breast Cancer With Distant vs Ipsilateral Supraclavicular Lymph Node Metastases. *JAMA network open*. 2021;4(3):e211809.
22. Xiong Y, Shi X, Hu Q, Wu X, Long E, Bian Y. A Nomogram for Predicting Survival in Patients With Breast Cancer Liver Metastasis: A Population-Based Study. *Frontiers in oncology*. 2021;11:600768.
23. Thompson A, Kelley B, Prokop L, Murad M, Baum C. Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis. *JAMA dermatology*. 2016;152(4):419-428.
24. Fan R, Chen Y, Nechuta S, Cai H, Gu K, Shi L, Bao P, Shyr Y, Shu X, Ye F. Prediction models for breast cancer prognosis among Asian women. *Cancer*. 2021;127(11):1758-1769.
25. Zheng Y, Wang X, Fan L, Shao Z. Breast Cancer-Specific Mortality in Small-Sized Tumor with Stage IV Breast Cancer: A Population-Based Study. *The oncologist*. 2021;26(2):e241-e250.

Figures

Figure 1

Flowchart of patient selection.

Figure 2

PMRs of TNBC patients. (A) PMRs of TNBC patients with DM and without DM; (B) PMRs of TNBC patients with different numbers of metastatic sites; (C) PMRs of TNBC patients with different metastatic organ.

Figure 3

Kaplan–Meier curves of OS in TNBC patients according to metastatic status: with or without DM (A), 1 site versus >1 sites (C), 2 sites versus >2 sites (E), the number of metastatic sites (G), Kaplan–Meier curves of CSS in TNBC patients according to metastatic status: with or without DM (B), 1 site versus >1 sites (D), 2 sites versus >2 sites (F), the number of metastatic sites (H).

Figure 4

Kaplan–Meier curves of OS in TNBC patients according to metastatic status: with single site (A), with two sites (C), with three sites (E). Kaplan–Meier curves of CSS in TNBC patients according to metastatic status: with single site (B), with two sites (D), with three sites (F).

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