Risk factors and prognostic factors for inflammatory breast cancer with bone metastasis: A population-based study

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Research article

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Abstract

Background: Inflammatory breast cancer (IBC) is a rare type of breast cancer with poor prognosis. IBC patients with bone metastasis (BM) often suffer from many complications. This study was to identify risk factors with strong capability of predicting high BM risk for IBC patients and find prognostic factors of IBC patients

Methods: The Surveillance, Epidemiology and End Results (SEER) database was used to collect the clinicopathological and survival information of IBC patients. 966 IBC patients diagnosed between 2010 and 2015 were to study the risk factors for developing BM by using Multivariable logistic regression. 194 and 176 patients were to analyze independent prognostic factors for overall survival (OS) and cancer specific survival (CSS) of IBC patients with BM by performing Cox proportional hazard model.

Results: Of the 966 IBC patients, 194 (20.1%) patients were with BM. IBC patients of unmarried, double breast tumor, N1 stage, N3 stage, and liver metastases had higher risk of BM, while those of uninsured status and triple negative breast cancer (TNBC) were less likely to have BM. The survival analysis showed that TNBC subtype and liver metastases were independently significantly associated with poorer OS and CSS of BM patients, while chemotherapy could serve as an independent prognostic factor for better OS and CSS of BM patients.

Conclusions: The risk factors for developing BM could provide potential guidelines for screening BM in IBC patients. The independent prognostic factors for survival outcome of IBC patients with BM could help doctors precisely treat those patients.

Background

Breast cancer is one of the most frequently diagnosed cancer types and has ranked second for the leading cause for cancer-associated death in women (1). Among a variety of subtypes of breast cancer, inflammatory breast cancer (IBC) makes up 1%-6% of breast carcinoma, which is a rare but aggressive subtype of breast cancer (BC) (2). Because of the distinct biological and clinical characteristics, IBC is always treated as mastitis. This delays the correct diagnosis and treatment time of those IBC patients. Though IBC is a relatively rare BC subtype, the survival outcome of IBC patients is much poorer than other subtypes of BC (3). Besides, the progression of IBC is quite rapid. After the tumor infiltrating dermal lymphatics, clinically featured skin changes rapidly present in patients' breast. Due to these factors, it is important to accurately diagnose and rapidly treat the fatal IBC.

Like many other cancer types, the treatment methods of IBC mainly contain surgery, radiation therapy, and chemotherapy (4, 5). However, this does not promise a good overall survival rate for the IBC patients. This is mainly because of the existence of metastasis and high risk of recurrence (6). Bone metastasis (BM) is a common type of metastasis for IBC patients (7). IBC patients with skeletal spread have a poor quality of life because of the unbearable bone pain and other complications like spinal cord compression and pathologic fracture (8). Many IBC patients are unwilling to seeing doctors until they have the

symptoms of BM. Hence, IBC patients always diagnose with BM when they have already had severe skeletal-related events (SREs). Therefore, it is important to find reliable clinical risk factors to screen BM for IBC patients. In clinical conditions, factors utilized to indicate BM mainly include hypercalcemia and alkaline phosphatase (9). However, there has been no investigation studying factors with strong capability of predicting high BM risk for IBC patients. Besides, the study for prognostic factors of IBC patients with BM also needs more investigation.

In this study, the Surveillance, Epidemiology, and End Results (SEER) database was used to study the risk factors for developing BM in IBC patients. To further understand outcomes of IBC patients with BM, we also assessed the survival outcome and independent prognostic factors for IBC patients with BM between 2010 and 2015.

Methods

Patients

The SEER database was utilized to establish the study cohort. The SEER program owns population-based data, which covers about 30% of the population in the US (10, 11). It mainly included the information of cancer patients' incidence, clinicopathological factors, survival outcomes, as well as treatment methods.

Patients initially diagnosed with IBC between 2010 and 2015 were included. IBC was diagnosed on the basis of International Classification of Disease for Oncology, 3rd edition (8530/3). Those who were under 18 years old, without positive histology, with unknown survival time, and with unavailable BM status were excluded from the study cohort. A total of 966 IBC patients were included to analyze the risk factors for developing BM. After excluding those without BM, 194 BM patients were left to study prognostic factors for overall survival (OS) of IBC patients with BM. Then, those dead from other reasons were excluded. 176 patients were used to investigate prognostic factors for cancer specific survival (CSS) of IBC patients with BM. The procedure of the study cohort selection was exhibited in Fig. 1.

Clinicopathological variables

A total of 17 variables were included in this investigation: race (white, black, other, unknown), marital status (married, unmarried, unknown), age (< 40, 40–59, 60–79, ≥ 80), sex (female, male), insurance status (Uninsured, Medicaid, Other insured, unknown), laterality (left, right, double), breast subtype [HR+/HER2+, HR+/HER2-, HR-/HER2+, triple negative breast cancer (TNBC), unknown], N stage (N0, N1, N2, N3, unknown), tumor size (< 2 cm, 2-4.9 cm, ≥ 5 cm, unknown), grade (I-II, III-IV, unknown), whether with other tumors (one primary tumor, more than one tumor), brain metastases (no, yes, unknown), liver metastases (no, yes, unknown), lung metastases (no, yes, unknown), surgery of primary site (no, yes, unknown), radiation therapy (no, yes, unknown), and chemotherapy (no, yes, unknown).

Statistical analysis

All of the data in this study were downloaded from SEER*Stat Software version 8.3.5. SPSS Version 23.0 software (IBM Corporation, Armonk, NY, USA) were utilized to analyze the data. The risk factors for BM of IBC was found by performing Multivariable logistic regression. Survival analysis for OS and CSS was conducted by using Kaplan–Meier analysis (log-rank test). Cox proportional hazard model was used to assess independent prognostic factors OS and CSS for IBC patients with BM. A p-value < 0.05 < 0.05 indicated statistical significance.

Results

Clinical characteristics of patients with bone metastases

The study cohort had 966 IBC patients, including 194 (20.1%) patients with BM and 772 (79.9%) patients without BM. Among the 194 BM patients, there were 148 (76.3%) white patients, 34 (17.5%) black patients, and 12 (6.2%) patients of other races. Of the BM patients, 71 (36.6%) were married and 112 (57.7%) were unmarried. Most of the BM patients were aged between 40 and 59 years old (N = 91, 46.9%) and were insured (N = 186, 95.9%). Besides, among BM patients, there were 98 (50.5%) patients of IBC in the left breast, 86 (44.3%) patients of IBC in the right breast, and 10 (5.2%) patients of IBC in the double breast. As for breast type, there were 38 (19.6%) HR+/HER2 + patients, 77 (39.7%) HR+/HER2- patients, 30 (15.5%) HR-/HER2 + patients, and 28 (14.4%) TNBC patients. The majority of BM patients was N1 stage (N = 85, 43.8%) and owned larger than 5 cm tumor (N = 101, 52.1%). In addition, there were 40 (20.6%) BM patients of grade I-II and 97 (50.0%) BM patients of grade III-IV. There were 13 (6.7%) BM patients with brain metastases, 54 (27.8%) BM patients with liver metastases, and 62 (32.0%) BM patients with lung metastases. Most (N = 138, 71.1%) of BM patients received chemotherapy but only 60 (30.9%) BM patients received surgery of primary site (Table 1).

Table 1
Multivariable logistic regression for analyzing the demographic and related clinical characteristics for developing bone metastases in patients diagnosed with initial primary IBC.

Characteristics	With BM	Without BM		OR (95%CI)	P value
	Number	%	Number	%	
Race					
White	148	76.3	608	78.8	1	-
Black	34	17.5	102	13.2	1.048 (0.616–1.785)	0.862
Other	12	6.2	59	7.6	0.926 (0.440–1.950)	0.841
Unknown	0	0.0	3	0.4	NA	NA
Marital status						
Married	71	36.6	364	47.2	1	-
Unmarried	112	57.7	368	47.7	1.539 (1.018–2.326)	0.041
Unknown	11	5.7	40	5.2	1.321 (0.538–3.244)	0.543
Age						
< 40	18	9.3	80	10.4	1	-
40–59	91	46.9	345	44.7	0.891 (0.461–1.724)	0.733
60–79	70	36.1	276	35.8	0.807 (0.404–1.612)	0.544
≥ 80	15	7.7	71	9.2	1.102 (0.454–2.679)	0.830
Sex						
Male	0	0.0	2	0.3	1	-
Female	194	100.0	770	99.7	NA	NA
Insurance status						
Medicaid	59	30.4	179	23.2	1	-
Other insured	127	65.5	535	69.3	0.803 (0.516–1.250)	0.331
Uninsured	5	2.6	39	5.1	0.261 (0.077–0.888)	0.032
Unknown	3	1.5	19	2.5	0.251 (0.036–1.740)	0.162
Laterality						
Left	98	50.5	393	50.9	1	-
Right	86	44.3	370	47.9	0.935 (0.638–1.370)	0.731

Characteristics	With BM	Without BM			OR (95%CI)	P value
	Number	%	Number	%		
Double	10	5.2	9	1.2	3.779 (1.237–11.548)	0.020
Breast subtype						
HR+/HER2+	38	19.6	127	16.5	1	-
HR+/HER2-	77	39.7	240	31.1	1.513 (0.885–2.588)	0.130
HR-/HER2+	30	15.5	131	17.0	0.663 (0.343–1.278)	0.220
TNBC	28	14.4	203	26.3	0.422 (0.220–0.811)	0.010
Unknown	21	10.8	71	9.2	0.864 (0.390–1.915)	0.719
N stage						
N0	21	10.8	149	19.3	1	-
N1	85	43.8	311	40.3	1.896 (1.022–3.517)	0.042
N2	29	14.9	125	16.2	1.864 (0.920–3.774)	0.084
N3	40	20.6	157	20.3	1.981 (1.003–3.914)	0.049
Unknown	19	9.8	30	3.9	2.172 (0.840–5.621)	0.110
Tumor size						
< 2 cm	14	7.2	64	8.3	1	-
2-4.9 cm	31	16.0	149	19.3	0.898 (0.404–1.999)	0.793
≥ 5 cm	101	52.1	385	49.9	0.903 (0.445–1.833)	0.777
Unknown	48	24.7	174	22.5	1.297 (0.601–2.799)	0.507
Grade						
I-II	40	20.6	178	23.1	1	-
III-IV	97	50.0	383	49.6	1.331 (0.817–2.168)	0.251
Unknown	57	29.4	211	27.3	1.151 (0.657–2.014)	0.623
Whether with other tumors						
One primary tumor	160	82.5	577	74.7	1	-
More than one tumor	34	17.5	195	25.3	0.712 (0.444–1.141)	0.157

Characteristics	With BM	Without BM			OR (95%CI)	P value
	Number	%	Number	%		
Brain metastases						
No	175	90.2	759	98.3	1	-
Yes	13	6.7	13	1.7	1.885 (0.653–5.436)	0.241
Unknown	6	3.1	0	0.0	NA	NA
Liver metastases						
No	135	69.6	744	96.4	1	-
Yes	54	27.8	26	3.4	9.868 (5.532–17.604)	< 0.001
Unknown	5	2.6	2	0.3	2.767 (0.321–23.827)	0.354
Lung metastases						
No	127	65.5	722	93.5	1	-
Yes	62	32.0	48	6.2	5.682 (3.449–9.360)	0
Unknown	5	2.6	2	0.3	2.798 (0.333–23.492)	0.343
Surgery of primary site					NA	NA
No	131	67.5	245	31.7	NA	NA
Yes	60	30.9	523	67.7	NA	NA
Unknown	3	1.5	4	0.5	NA	NA
Radiation therapy					NA	NA
No	122	62.9	409	53.0	NA	NA
Yes	72	37.1	363	47.0	NA	NA
Chemotherapy					NA	NA
No	56	28.9	122	15.8	NA	NA
Yes	138	71.1	650	84.2	NA	NA

Abbreviations: Inflammatory breast cancer (IBC); Bone metastasis (BM); CI (confidence interval); OR (odds ratio)

Risk factors for occurrence of bone metastases

We next investigated risk factors for developing BM in IBC patients. As shown in Table 1, IBC patients of unmarried [OR (odds ratio) = 1.539, 95% CI (confidence interval) = 1.018–2.326, P = 0.041], double breast tumor (OR = 3.779, 95% CI = 1.237–11.548, P < 0.020), N1 stage (OR = 1.896, 95% CI = 1.022–3.517, P < 0.042), N3 stage (OR = 1.981, 95% CI = 1.003–3.914, P < 0.049), and liver metastases (OR = 9.868, 95% CI = 5.532–17.604, P < 0.001) had higher risk of BM. Compared with those with Medicaid, IBC patients of uninsured status were less likely to have BM (OR = 0.261, 95% CI = 0.077–0.888, P = 0.032). Besides, TNBC patients had lower risk of BM compared with HR+/HER2 + patients (OR = 0.422, 95% CI = 0.220–0.811, P = 0.010).

Analysis of prognostic factors for OS of patients with bone metastases

In the survival analysis, we found that marital status (Fig. 2A), liver metastases (Fig. 2B), breast subtype (Fig. 2C), age (Fig. 2D), chemotherapy (Fig. 2E), and surgery of primary site (Fig. 2F) were significantly associated with BM patients' OS. Besides, patients of married status (24 months), 40–59 years old (28 months), HR+/HER2+ (45 months), no liver metastases (21 months), receiving surgery of primary site (29 months), and receiving chemotherapy (25 months) had longer overall survival time (Table 2). The Multivariable prognostic analysis found TNBC subtype [HR (hazard ratio) = 3.991, 95% CI = 2.065–7.714, P < 0.001] and liver metastases (HR = 1.863, 95% CI = 1.232–2.819, P = 0.003) were independently significantly associated with poorer OS of BM patients, while chemotherapy (HR = 0.517, 95% CI = 0.332–0.805, P = 0.003) could serve as an independent prognostic factor for better OS of BM patients.

Table 2
Multivariable Cox regression for the OS among primary IBC patients with BM (diagnosed 2010–2015)

Characteristics	Median survival months	OS		
		HR	95%CI	P value
Marital status				
Married	24	1	-	-
Unmarried	20	0.999	0.693–1.441	0.996
Unknown	9	2.690	1.279–5.661	0.009
Age				
< 40	25	1	-	-
40–59	28	0.805	0.435–1.491	0.491
60–79	16	1.032	0.549–1.942	0.921
≥ 80	8	2.158	0.936–4.977	0.071
Breast subtype				
HR+/HER2+	45	1	-	-
HR+/HER2-	20	1.411	0.785–2.538	0.25
HR-/HER2+	21	1.336	0.692–2.579	0.388
TNBC	9	3.991	2.065–7.714	< 0.001
Unknown	9	2.345	1.172–4.692	0.016
Liver metastases				
No	21	1	-	-
Yes	12	1.863	1.232–2.819	0.003
Unknown	21	0.772	0.267–2.232	0.633
Surgery of primary site				
No	17	1	-	-
Yes	29	0.693	0.453–1.060	0.091
Unknown	NA	0.611	0.083–4.514	0.629
Chemotherapy				
No	9	1	-	-

Characteristics	Median survival months	OS		
		HR	95%CI	P value
Yes	25	0.517	0.332–0.805	0.003

Abbreviations: Overall survival (OS); Inflammatory breast cancer (IBC); Bone metastasis (BM); CI (confidence interval); HR (hazard ratio).

Analysis of prognostic factors for CSS of patients with bone metastases

The survival analysis for CSS showed that marital status (Fig. 3A), liver metastases (Fig. 3B), breast subtype (Fig. 3C), age (Fig. 3D), chemotherapy (Fig. 3E), and surgery of primary site (Fig. 3F) were significantly associated with BM patients' CSS. In addition, patients of married status (25 months), 40–59 years old (29 months), HR+/HER2+ (45 months), no liver metastases (22 months), receiving surgery of primary site (29 months), and receiving chemotherapy (25 months) had longer cancer specific survival time (Table 3). The multivariable Cox model exhibited that TNBC subtype [HR = 4.531, 95% CI = 2.184–9.401, P < 0.001] and liver metastases (HR = 1.907, 95% CI = 1.226–2.965, P = 0.004) were independent prognostic factors for poorer CSS of BM patients, while chemotherapy (HR = 0.472, 95% CI = 0.294–0.757, P = 0.002) was independently related to better OS of BM patients.

Table 3
Multivariable Cox regression for the CSS among primary IBC patients with BM (diagnosed 2010–2015)

Characteristics	Median survival months	CSS		
		HR	95%CI	P value
Marital status				
Married	25	1	-	-
Unmarried	20	0.968	0.656–1.429	0.87
Unknown	9	2.675	1.252–5.712	0.011
Age				
< 40	25	1	-	-
40–59	29	0.793	0.418–1.505	0.478
60–79	15	1.028	0.531–1.990	0.934
≥ 80	8	1.946	0.793–4.773	0.146
Breast Subtype				
HR+/HER2+	45	1	-	-
HR+/HER2-	20	1.559	0.814–2.983	0.18
HR-/HER2+	21	1.575	0.776–3.197	0.209
TNBC	9	4.531	2.184–9.401	< 0.001
Unknown	11	2.369	1.1-5.102	0.028
Liver metastases				
No	22	1	-	
Yes	13	1.907	1.226–2.965	0.004
Unknown	21	0.814	0.279–2.372	0.705
Surgery of Primary Site				
No	18	1	-	-
Yes	29	0.699	0.446–1.094	0.117
Unknown	NA	0.662	0.089–4.929	0.687
Chemotherapy				
No	9	1	-	-

Characteristics	Median survival months	CSS		
		HR	95%CI	P value
Yes	25	0.472	0.294–0.757	0.002

Abbreviations: Cancer specific survival (CSS); Inflammatory breast cancer (IBC); Bone metastasis (BM); CI (confidence interval); HR (hazard ratio).

Discussion

On the basis of SEER database, our study found that 20.1% of IBC patients had BM. Hence, it is important to find risk factors of developing BM in IBC patients and the prognostic factors of IBC patients with BM. In the previous study, Zheng Wang et al. found BM could be independent prognostic factor for IBC patients (12). However, there has been no investigation focusing on the cohort of IBC patients with BM. Those BM patients who suffered from the pain often had poor physical status. Therefore, it is vital to find risk factors that can promote BM in IBC patients and prognostic factors that can independently predict the prognosis of IBC patients with BM.

In our study, we found that IBC patients of unmarried, double breast tumor, N3 stage, and liver metastases were more likely to develop BM. Therefore, physicians need to pay great attention to IBC patients with those risk factors for the high risk of BM. Besides, a routine bone scanning is highly advised for IBC patients with these risk factors. Interestingly, our study showed that those with Medicaid had higher risk of BM than those uninsured patients. We inferred that this might be the reason that those with Medicaid have more chance of having a thorough check of their body than those uninsured patients. Thus, IBC patients with Medicaid were easier to detect BM than uninsured IBC patients. Besides, our study found TNBC patients had lower risk of BM compared with HR+/HER2 + patients in the IBC cohort. TNBC is a highly aggressive subtype of breast tumor that is with high rate of metastasis and poor survival outcome (13). However, in IBC patients, the property of bone invasion of TNBC subtype seems to weakened. This might be due to the different molecular and biological mechanisms between IBC and non-IBC patients, which needs further investigations in the future.

Besides, we also investigated prognostic factors for IBC patients with BM. Our study showed that TNBC subtype and liver metastases could serve as independent prognostic factors for poorer OS and CSS of BM patients, and chemotherapy was independently significantly associated with better OS and CSS of IBC patients with BM. On the basis of these prognostic factors, physicians were able to effectively make a survival estimation for IBC patients with BM in clinical conditions. In addition, these prognostic factors can also serve as clinical guidelines for doctors. Our study indicated that despite the factor that patients of TNBC had lower risk of BM compared with HR+/HER2 + patients, those with TNBC had worse survival outcome than those with HR+/HER2 + in BM patients. More importantly, we found chemotherapy was the most suitable treatment methods for IBC patients with BM. A previous study showed that patients of stage IV IBC had an improved survival outcome after receiving surgery of the primary tumor (14).

However, there has been no study evaluating the treatment methods of IBC patients with BM. Therefore, this study is the first one that reports chemotherapy rather than radiation therapy or surgery of primary site could significantly improve the OS and CSS of IBC patients with BM. In addition, this study showed that BM patients suffering from liver metastasis exhibited a worse survival outcome, whereas brain metastases and lung metastases had no influences on BM patients' prognosis. Therefore, oncologist should pay great attention to liver metastases of IBC patients with BM, considering the poor prognosis of BM patients with liver metastases.

Despite of astonishing discoveries of the study, some limitations existed in this investigation. First, part of the unknown data was excluded. Besides, some useful clinicopathological factors were not included in the SEER database. In addition, considering this is a retrospective study, inherent bias is unavoidable.

Conclusions

In conclusion, this study identified risk factors for developing BM including unmarried status, double breast tumor, N3 stage, and liver metastases, while IBC patients with Medicaid and TNBC were less likely to develop BM. We also identified prognostic factors including TNBC subtype, liver metastases, and chemotherapy could serve as independent prognostic factors for OS and CSS of IBC patients with BM.

Abbreviations

Inflammatory breast cancer (IBC); Bone metastasis (BM); The Surveillance, Epidemiology and End Results (SEER); Overall survival (OS); Cancer specific survival (CSS); Triple negative breast cancer (TNBC); Skeletal-related events (SREs); OR (odds ratio); CI (confidence interval); HR (hazard ratio)

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available either online or from the corresponding author on reasonable request.

Competing interests

The authors have stated that they have no conflict of interest.

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Authors' contributions

SF designed the study. SF collected the data and performed the data analysis. SF wrote the manuscript. . All authors read and approved the final manuscript.

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Figures

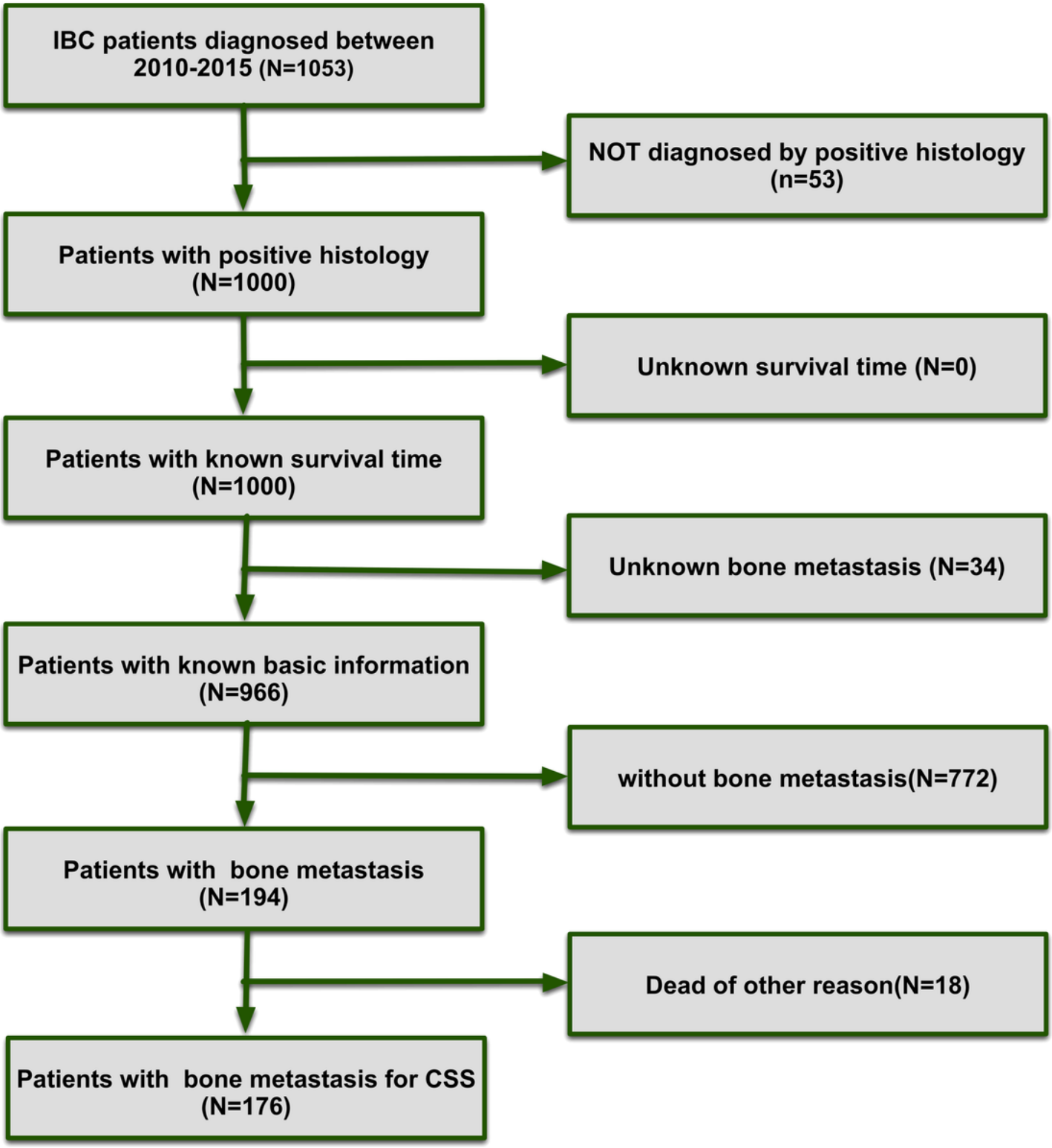

Figure 1

Flowchart for selecting IBC patients with BM.

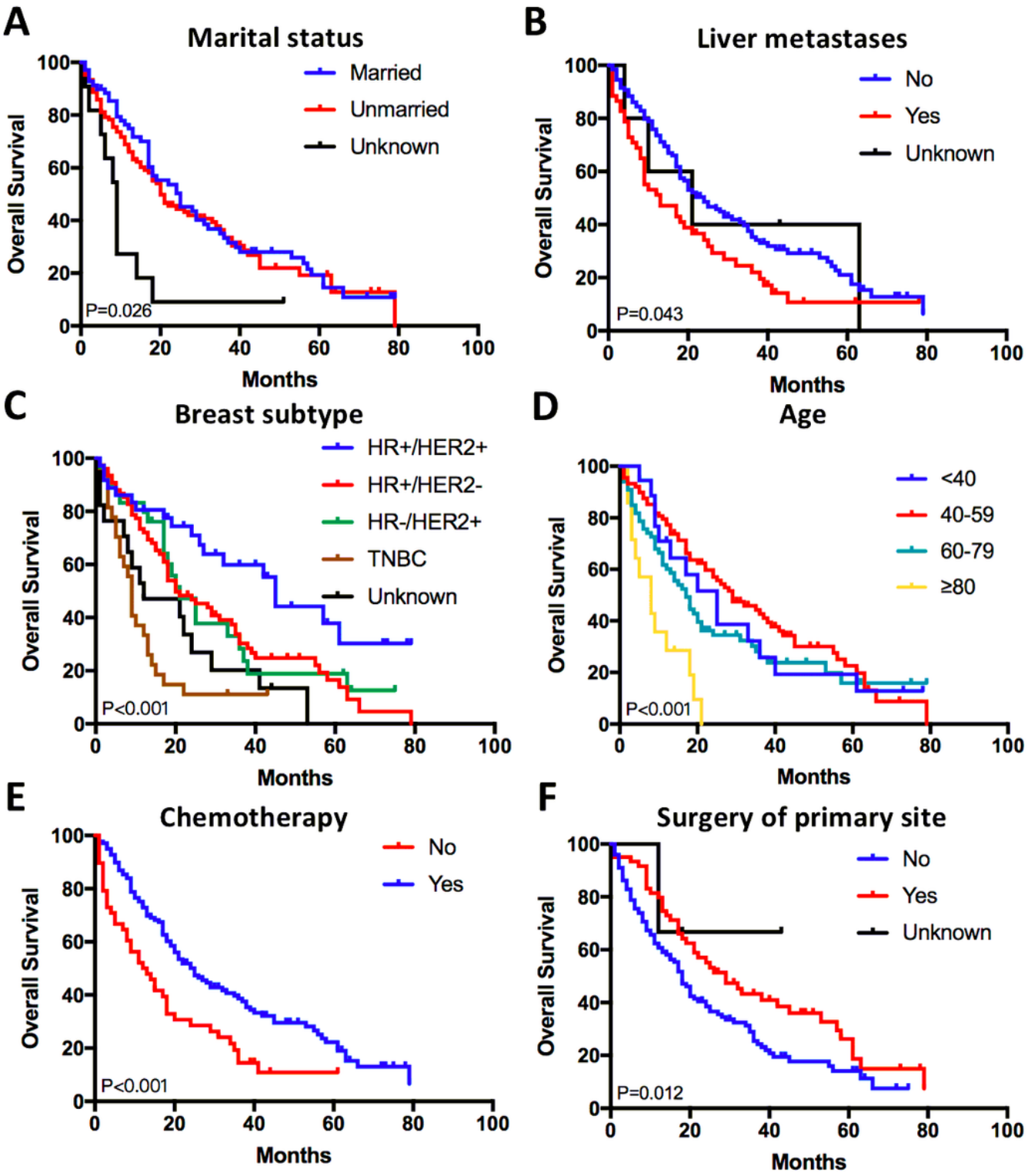

Figure 2

Kaplan-Meier analysis of overall survival in IBC patients with BM according to marital status (A), liver metastasis (B), breast subtype (C), age (D), chemotherapy (E), surgery of primary site (F).

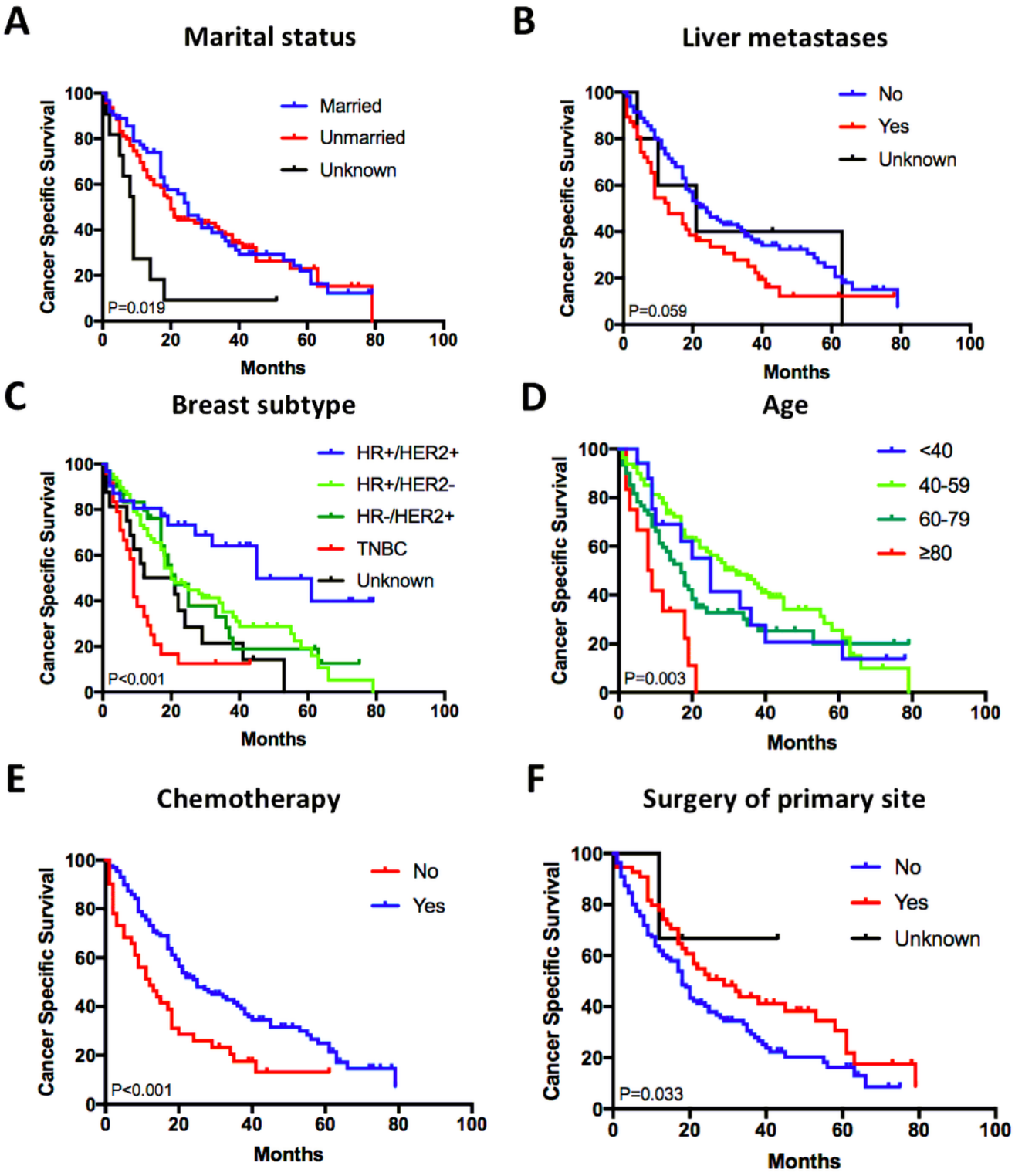

Figure 3

Kaplan-Meier analysis of cancer specific survival in IBC patients with BM according to marital status (A), liver metastasis (B), breast subtype (C), age (D), chemotherapy (E), surgery of primary site (F).