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A Nomogram for Predicting Liver Metastasis of Lymph-Node Positive Luminal B HER2 Negative Subtype Breast Cancer by Analyzing the Clinicopathological Characteristics of Patients with Breast Cancer

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Abstract

Background: Luminal B-like human epidermal growth factor receptor 2 negative (Luminal B [HER2−]) is the most common molecular subtype of breast cancer (BC). Since the relationship between Luminal B (HER2−) BC and liver metastasis (LM) is poorly defined, this retrospective study aimed to develop an LM risk nomogram for patients with lymph node-related (N + Luminal B [HER2−]) BC. **Methods:** Data were obtained for patients initially diagnosed with BC from the Tianjin Medical University Cancer Institute and Hospital. There were 30,975 Chinese female patients with stage I–III BC and follow-up confirming 1217 subsequent patients with LM, and 427 patients with N + Luminal B (HER2−). The LM risk was assessed using Cox proportional hazards regression, histogram, Venn diagram, and Kaplan–Meier survival analysis, with further analysis for patients with N + Luminal B (HER2−) BC. A nomogram was established based on the N + Luminal B (HER2−) BC data, which was validated using calibration plots. **Results:** The median age of 427 patients with N + Luminal B (HER2−) liver metastasis of breast cancer (BCLM) was 49 years. The largest number of patients with BCLM was diagnosed between the second to the 6th year, the longest interval from initial BC diagnosis to subsequent LM was 145 months. The patients with LM as the first site of distant metastasis which is associated with better survival were analyzed by Kaplan–Meier. The nomogram was constructed for the risk of LM that included age, menstrual status, unilateral oophorectomy, pregnancy, hepatitis B antigen, region of residence, tumor size, lymph node, clavicular lymph nodes, progesterone receptor, and lymph vessel invasion. **Conclusion:** We described the clinicopathological characteristics of patients with stage I–III BC, and constructed a nomogram for calculating personalized LM probabilities for patients with N + Luminal B (HER2−), which could guide future prolonged or early extensive treatment decisions.

Keywords

nomogram, lymph node positive, luminal B(HER2−), breast cancer, liver metastasis, Chinese female patient

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Introduction

Breast cancer (BC) is the most common malignant tumor and the second leading cause of cancer death in women worldwide,[1] with approximately one-third million new cases annually (as recorded in 2022). It has been recently recognized that liver metastasis (LM) may also develop in the later stages of BC progression in approximately 5–12% of the patients treated for non-metastatic BC.[2–4] LM is the poorer prognosis of metastatic BC (MBC). A vast number of molecular subtypes of BC exist with Luminal B-like human epidermal growth factor receptor 2 negative (Luminal B [HER2−]), which accounts for more than half the cases of BC,[5] has a longer recurrence-free and metastasis-free survival rate.[6] Owing to the heterogeneity in their clinical behavior,[7,8] development of a special population occurs as patients evolve from BC to LM; thus, special clinicopathological characteristics can be seen within this special internal environment.[9,10]

The clinical features of the relationship between BC and LM are poorly defined; thus, defining the high-risk clinicopathological characteristics for individuals and determining the possible treatment options may provide a reference for the inclusion criteria of new clinical trials directed toward patients with high risk of LM. A nomogram, which provides an individualized assessment of risk, is an easy-to-use tool that can be useful to patients and doctors for predicting risk, and for individualized treatment planning decisions for patients and their families, follow-up, and prognosis.[11,12]

The current treatment and prognosis vary according to the patient prognostic factors, including hormone receptor (HR), HER2, age at diagnosis, tumor size (T), and lymph node status (N), as well as certain molecular markers.[13–15] Traditionally, adjuvant chemotherapy and endocrine therapy (ET) or radiotherapy were considered the main postoperative treatment regimens for patients with Luminal B (HER2−) BC, which had a lower pathological complete response rate.[16,17] During the coronavirus disease-2019 (COVID-19) pandemic, transportation between cities and provinces was temporarily shut to prevent the spread of the virus, resulting in increased waiting time for some of those patients requiring surgery, adjuvant chemotherapy, or radiotherapy. In order to prevent delayed treatment, patients with high-risk Luminal B (HER2−) BC can be assisted at home with extensive ET. Therefore, the current model employed in our study is the first nomogram to be developed using a sample comprising study N + Luminal B (HER2−) BC patients across China, to assess the risk of clinicopathological characteristics. If effective preventive treatment was provided during the COVID-19 pandemic, the reduced rate of LM would serve as a highlight in the contemporary era.

Patients and Methods

In this retrospective study, data were collected between May 2005 and April 2015 at the Tianjin Medical University Cancer Institute and Hospital (TMUCIH, Tianjin, China), which included 38,185 patients with newly diagnosed stage I–III BC and 105 patients with de novo liver metastasis of breast cancer (BCLM). December 2020 was considered as the follow-up cutoff date. The final N + Luminal B (HER2−) dataset contained 7782 patients. All the BCLM cases were confirmed by histology or imageology (tomography-computed and/or magnetic resonance imaging). Patients with non-LM pathological subtypes were dropped from the dataset and with a very low probability of LM were excluded. Other exclusion criteria included patients with occult BC, male patients with BC, age ≥ 76 years, synchronous or metachronous bilateral BC, patients lost to follow-up, and unknown immunohistochemistry. The dataset included 30,975 patients for analysis. The study flow chart was shown in Figure 1. This study was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital (approval number bc2022128). All patients provided written informed consent prior to treatment.

The following parameters were obtained for each patient including age, menopausal status, unilateral oophorectomy, pregnancy/lactation period, hepatitis B antigen (HBAg), region of residence, pathological subtypes, tumor size, lymph node stage, clavicular lymph node metastasis, lesions, immunohistochemistry (IHC) subtypes, histological grade, TNM stage, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, nipple areola infiltration, pectoralis infiltration, lymphatic vessel infiltration, and skin infiltration. Other clinical characteristics including laterality, delivery, hysterectomy, fatty liver, liver cyst, hepatic hemangioma, diabetes, blood subtypes, anti-HBAg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), triglyceride (TG), total cholesterol (TCH), LM/follow-up time in months (continuous), and LM and survival status (with or without liver metastases, alive or dead). The high-risk clinicopathological characteristics were evaluated among the sufficient number of patients with N + Luminal B (HER2−) BCLM, and further perform a comparative analysis from the time of initial BC diagnosis to LM or death of the patient with liver metastasis special survival (LMSS). In addition, the prediction model dataset contained 7782 patients with N + Luminal B (HER2−) subtype BC. In order to maximize the usefulness of the model, the variables used in the multivariable model were employed to develop a linear predictive nomogram.

Statistical Analysis

Cox proportional hazard regression models were used to assess liver metastasis-free survival (LMFS) in the univariable and multivariable models, which were used to analyze the relationship between LM and the clinicopathological characteristics for all the patients with BC and N + Luminal B (HER2−) BC. No significant variables ($p > .05$) were excluded unless they demonstrated considerable clinical significance. Bar charts and Venn diagrams were used for displaying the data for subsequent MBC. LMSS was calculated for patients with N + Luminal B

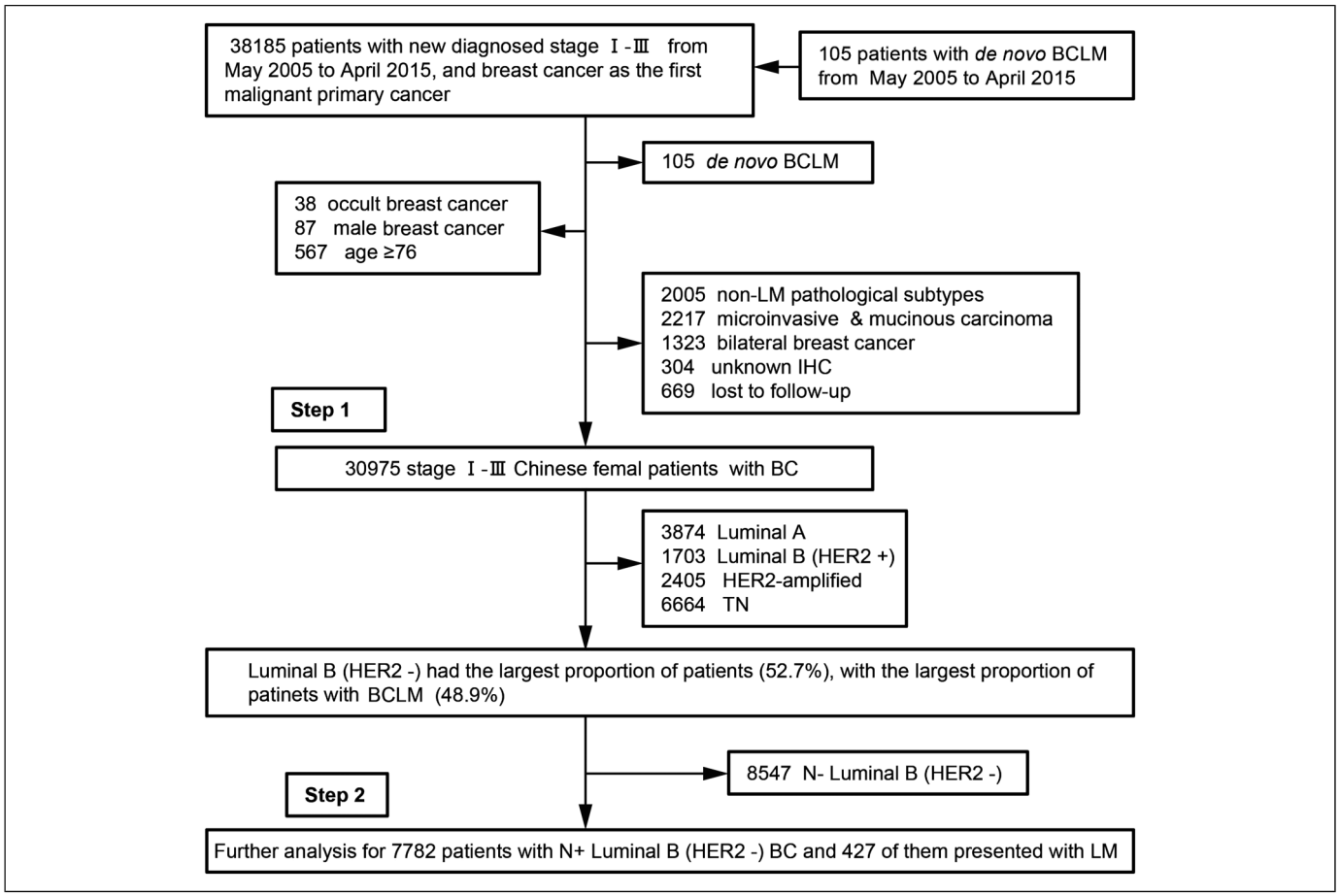

Figure 1. The flow chart of the patient selection process. BCLM, liver metastasis of breast cancer; IHC, immunohistochemistry; Luminal A, Luminal A-like; Luminal B (HER2 −), Luminal B-like human epidermal growth factor receptor 2 negative; Luminal B (HER2 +), Luminal B-like human epidermal growth factor receptor 2 positive; N−, lymph node negative; N + , lymph node positive; TN, triple negative.

(HER2−) using the Kaplan–Meier method, and the differences were evaluated using the log-rank test. All the analyses were performed using SPSS 22.0 (SPSS 22, IBM, NY, USA). A two-sided p-value of <.05 was considered statistically significant.

After these variables were eliminated, a final nomogram with the greatest predictive accuracy for individual assessment of risk in patients with N + Luminal B (HER2−) BC was created. The Concordance index (C-index), calibration plots, and receiver operating characteristic (ROC) curve of the final model were visually verified by constructing a nomogram for 24-, 48-, and 60-month prediction; LM probabilities for patients with N + Luminal B (HER2−) BC were estimated using the rms package of R version 4.0.3 (http://www.r-project.org). The study was according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[18]

Results

A total of 1467 patients with BCLM included 105 stage IV patients with *de novo* LM and 1362 patients with subsequent BCLM; the rate of LM was 3.57% (1362/38,185) till the cut-off follow-up date. According to the pathological subtypes of all the patients with BC to select the pathological subtypes of LM, we analyzed the pathological subtypes of patients with BCLM and restricted our analysis to the eight subtypes and well-defined histologic types (Supplementary Table 1). According to IHC subtypes analysis, the patients with Luminal B (HER2−) BCLM had the highest composition ratio both in the patients with subsequent BCLM and de novo BCLM (50.03%, 734/1467; Supplementary Table 2).

All the Patients with BC

Analyzed the 30,975 patients with a median age of 51 years (range 18-75) at BC diagnosis; the median follow-up for LM-free survival was 96 months (range 3-175 months). The clinicopathological characteristics of 30,975 patients were studied and shown (Table 1, Supplementary Table 3), including 1217 patients (3.9%) with LM. Luminal B (HER2−) had the largest proportion of patients (52.7%), with the largest proportion of patients with BCLM (48.9%, 595/1217), however, which had a lower LM rate (3.6%) compared to

Table 1. Baseline Characteristics of All the Patients with BC.

Characteristics	LM $N=1217$ (%)	Death $N=4251$ (%)	Total $N=30,975$ (%)
Age, years			
≤39	247 (20.3)	602 (14.2)	3949 (12.7)
40–59	795 (65.3)	2643 (62.2)	20741 (67.0)
60–75	175 (14.4)	1006 (23.6)	6285 (20.3)
Menopausal status			
Post-	483 (39.7)	2051 (48.2)	12857 (41.5)
Pre-	539 (44.3)	1629 (38.3)	13324 (43.0)
Peri-	116 (9.5)	304 (7.2)	2090 (6.7)
Unknown	79 (6.5)	267 (6.3)	2704 (8.7)
Unilateral oophorectomy			
No	1154 (94.8)	4084 (96.1)	29835 (96.3)
Yes	63 (5.2)	167 (3.9)	1140 (3.7)
Pregnancy†			
No	265 (88.6)	670 (90.4)	5188 (94.8)
Yes	34 (11.4)	71 (9.6)	285 (5.2)
HBAg			
Negative	1137 (93.4)	4047 (95.2)	29909 (96.6)
Positive	80 (6.6)	204 (4.8)	1066 (3.4)
Region of residence			
NW	158 (13.0)	623 (14.7)	6027 (19.5)
SE	1059 (87.0)	3628 (85.3)	24948 (80.5)
Pathological subtype			
IDC	1032 (84.8)	3542 (83.3)	26573 (85.8)
IDC +	121 (9.9)	374 (8.8)	2355 (7.6)
Others	64 (5.3)	335 (7.9)	2047 (6.6)
Tumor size			
≤2cm	266 (21.9)	1148 (27.0)	12497 (40.3)
2.1–5.0cm	767 (63.0)	2527 (59.4)	16377 (52.9)
≥5.1	184 (15.1)	576 (13.5)	2101 (6.8)
Lymph node			
0	300 (24.7)	1507 (35.5)	16476 (53.2)
1–3	328 (26.9)	1060 (24.9)	7822 (25.3)
4–9	213 (17.5)	684 (16.1)	3476 (11.2)
≥10	376 (30.9)	1009 (23.5)	3201 (10.3)
Clavicular lymph node♮			
Negative	797 (94.8)	3137 (96.8)	27269 (98.2)
Positive	44 (5.2)	105 (3.2)	505 (1.8)
Lesion			
1	1181 (97.0)	4151 (97.6)	30306 (97.8)
≥2	36 (3.0)	100 (2.4)	669 (2.2)
IHC subtype			
Luminal A	57 (4.7)	212 (5.0)	3874 (12.5)
Luminal B (HER2−)	595 (48.9)	2214 (52.1)	16329 (52.7)
Luminal B (HER2+)	121 (9.9)	287 (6.7)	1703 (5.5)
HER2-amplified	177 (14.5)	415 (9.8)	2405 (7.8)
TN	267 (21.9)	1123 (26.4)	6664 (21.5)
Histological grade			
I	31 (2.5)	189 (4.4)	1838 (5.9)
II	868 (71.3)	2951 (69.4)	21833 (70.5)
III	197 (16.2)	659 (15.5)	4916 (15.9)
Unknown	121 (9.9)	452 (10.6)	2388 (7.7)
Stage			
I	128 (10.5)	660 (15.5)	8543 (27.6)
II	465 (38.2)	1789 (42.1)	15074 (48.7)
III	624 (51.3)	1802 (42.4)	7358 (11.9)
ER			
Positive	773 (63.5)	2711 (63.8)	21907 (70.7)
Negative	444 (36.5)	1540 (36.2)	9068 (29.3)
PR			
Positive	550 (45.2)	1790 (42.1)	16763 (54.1)
Negative	667 (54.8)	2461 (57.9)	14212 (46.9)
HER2			
Positive	300 (24.7)	704 (16.6)	4108 (13.3)
Negative	917 (75.3)	3547 (83.4)	26867 (86.7)
Nipple areola invasion			
Positive	257 (21.1)	766 (18.0)	3335 (10.8)
Negative	960 (78.9)	3485 (82.0)	27640 (89.2)
Pectorales invasion			
Positive	24 (2.0)	76 (1.8)	193 (0.6)
Negative	1193 (98.0)	4175 (98.2)	30782 (99.4)
Lymph vessel invasion			
Positive	281 (23.1)	877 (20.6)	3062 (9.9)
Negative	936 (76.9)	3374 (79.4)	27,913 (90.1)
Skin invasion			
Positive	56 (4.6)	226 (5.3)	685 (2.2)
Negative	1161 (95.4)	4025 (94.7)	30,290 (97.8)

BC, breast cancer; ER, estrogen receptor; HBAg, hepatitis B antigen; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; IDC +, 10% to 90% of the invasive ductal carcinoma component; IHC, immunohistochemistry; Luminal A, Luminal A-like; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; Luminal B (HER2+), Luminal B-like human epidermal growth factor receptor 2 positive; LM, liver metastasis; NW, northwest China; PR, progesterone receptor; SE, southeast China; TN, triple negative.

†: only age≤ 41 patients were included. ♮: only axillary lymph node ≤ 9 patients were included.

HER2-amplified (7.4%), Luminal B (HER2+) (7.1%), and TN (4.0%).

Figure 2a displayed the number of all the 1217 patients with BCLM according to the year at diagnosis. The largest number of all the patients with LM according to the year at diagnosis was in the 2nd year (19.6%, 238/1217). Luminal A had the lowest number of patients with BCLM (57, 4.7%). The higher ratio of patients with LM was shown that Luminal B (HER2−) in the 2nd year to the 6th year at diagnosis, even lasting for a long time, and the longest interval from initial BC diagnosis to subsequent LM was beyond 12 years, Luminal B (HER2+) in the first 5 years, patients with HER2− amplified in the first 3 years, and TN was occurring earlier in the first 2 years, respectively.

In the univariate and multivariate analyses, age at initial diagnosis, menstrual status, unilateral oophorectomy, pregnancy period, HBAg, region of residence, pathological subtype, T, N, clavicular lymph node, IHC subtype, histological grade, stage, ER status, HER2 status, nipple areola infiltration, lymphatic vessel infiltration, and delivery, hepatic hemangioma, anti-HBAg independently correlated with the LM during the follow-up period (Table 2, Supplementary Table 4).

The Patients with N + Luminal B (HER2−) BC

There was no significant difference in comparing the patients with Luminal A and those with N− Luminal B (HER2−) based on LM probability (LM%: 1.5% vs 2.0%; $p=.091$; Table 3). According to the analysis, the clinicopathological characteristics of patients with N + Luminal B (HER2−) were

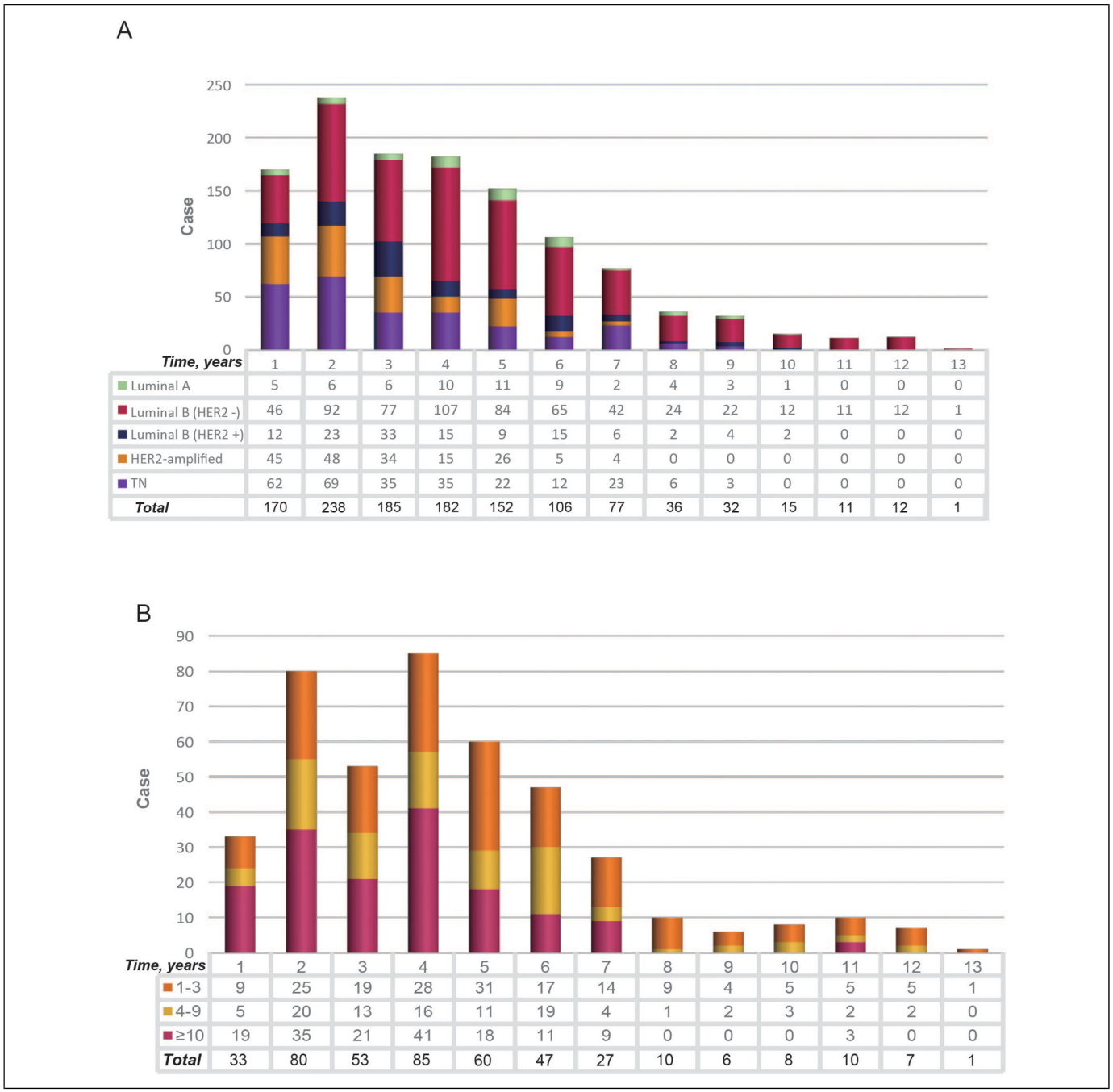

Figure 2. The number of patients with LM according to the year at diagnosis. Bar chart for all the patients with BC (A) and N + Luminal B (HER2−) BC (B). BC, breast cancer; LM, liver metastasis; Luminal A, Luminal A-like; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; Luminal B (HER2 +), Luminal B-like human epidermal growth factor receptor 2 positive; N + , lymph node positive; TN, triple negative.

shown in Table 4 and Supplementary Table 5. The median follow-up of 7782 patients with N + Luminal B (HER2−) was 94 months (range, 4-174 months), the median age was 51 years (range 22-75) and 427 of them (5.5%) presented with LM. Figure 2b displayed the number of all the 427 patients with N + Luminal B (HER2−) BCLM according to the year of diagnosis. The largest number of patients with LM according to the year at diagnosis was in the 2nd year to the 6th year at diagnosis. Patients with N ≥ 10 were prone to LM occurring in the first 5 years (134, 85.4%).

The differences in the risk of LM are based on the distribution of the metastases sites. The characteristics of the patients with MBC according to the distribution of the metastases sites are displayed in Figure 3. A total of 3364 patients with MBC, and 1173 patients with N + Luminal B (HER2−) MBC showed bone, lung, liver, brain, and distant lymph node (DN)

Table 2. Cox Univariate and Multivariate Analysis for LM and Death in all the Patients with BC.

	Cox univariate analysis						Cox multivariate analysis					
	LM			Death			LM			Death		
Characteristics	HR	95% CI	*p-value*	HR	95% CI	*p-value*	HR	95% CI	*p-value*	HR	95% CI	*p value*
Age, years												
≤39	2.25	[1.86–2.74]	<.001	1.12	[1.02–1.23]	.017	2.21	[1.80–2.72]	<.001	1.12	[1.02–1.23]	0.017
40–59	1.35	[1.15–1.59]	<.001	1			1.42	[1.19–1.70]	<.001	1		
60–75	1			1.33	[1.24–1.43]	<.001	1			1.09	[1.00–1.18]	0.039
Menopausal status												
Post-	1			1			1			1		
Pre-	1.06	[0.94–1.20]	.339	0.74	[0.69–0.79]	<.001	-	-	-	0.87	[0.80–0.93]	<0.001
Peri-	1.49	[1.21–1.82]	<.001	0.91	[0.80–1.02]	.110	1.37	[1.12–1.69]	.002	-	-	-
Unknown	0.75	[0.59–0.96]	.020	0.45	[0.40–0.51]	<.001	-	-	-	-	-	-
Unilateral oophorectomy (yes vs no)	1.44	[1.12–1.85]	.005	1.10	[0.94–1.28]	.248	1.29	[1.00–1.67]	.049	-	-	-
Pregnancy[†] (yes vs no)	3.52	[2.50–4.95]	<.001	2.48	[1.96–3.13]	<.001	2.35	[1.66–3.32]	<.001	1.65	[1.30–2.09]	<0.001
HBAg (yes vs no)	2.03	[1.62–2.54]	<.001	1.45	[1.26–1.67]	<.001	1.86	[1.47–2.34]	<.001	1.44	[1.25–1.67]	<0.001
Region of residence (SE vs NW)	1.59	[1.35–1.88]	<.001	1.26	[1.16–1.37]	<.001	1.73	[1.46–2.05]	<.001	1.27	[1.17–1.39]	<0.001
Pathological type												
IDC	1.28	[0.99–1.64]	.060	1			-	-	-	1		
IDC +	1.76	[1.30–2.38]	<.001	1.37	[1.23–1.52]	<.001	1.37	[1.01–1.85]	.044	-	-	-
Others	1			1.06	[0.95–1.18]	.330	1			-	-	-
Tumor size												
≤2 cm	1			1			1			1		
2.1–5.0 cm	2.27	[1.97–2.60]	<.001	1.71	[1.60–1.83]	<.001	1.68	[1.41–2.00]	<.001	1.27	[1.18–1.37]	<0.001
≥5.1 cm	4.81	[3.99–5.81]	<.001	3.79	[3.42–4.18]	<.001	1.92	[1.50–2.46]	<.001	1.71	[1.52–1.93]	<0.001
Lymph node												
0	1			1			1			1		
1–3	2.20	[1.82–2.67]	<.001	1.55	[1.44–1.68]	<.001	2.13	[1.81–2.49]	<.001	1.42	[1.31–1.54]	<0.001
4–9	2.99	[2.12–4.22]	<.001	2.45	[2.24–2.68]	<.001	2.72	[2.25-3.29]	<.001	1.95	[1.77–2.15]	<0.001
≥10	5.91	[4.21–8.29]	<.001	4.55	[4.20–4.93]	<.001	5.41	[4.50–6.49]	<.001	3.10	[2.82–3.42]	<0.001
Clavicular lymph node[’] (yes vs no)	2.36	[1.74–3.18]	<.001	1.66	[1.37–2.02]	<.001	1.37	[1.09–1.71]	.006	-	-	-
Lesion (≥2 vs 1)	1.40	[1.01–1.95]	.045	1.21	[0.99–1.47]	.061	1.34	[0.96–1.87]	.085	1.20	[0.99–1.47]	0.069
IHC subtype												
Luminal A	1			1			1			1		
Luminal B (HER2−)	2.50	[1.91–3.28]	<.001	2.02	[1.75–2.33]	<.001	2.17	[1.65–2.85]	<.001	2.01	[1.74–2.31]	<0.001
Luminal B (HER2+)	5.17	[3.77–7.08]	<.001	2.91	[2.43–3.47]	<.001	3.82	[2.78–5.24]	<.001	2.61	[2.18–3.12]	<0.001
HER2-amplified	5.43	[4.03–7.32]	<.001	3.18	[2.69–3.75]	<.001	4.18	[3.09–5.66]	<.001	2.82	[2.38–3.33]	<0.001
TN	2.83	[2.13–3.77]	<.001	2.77	[2.39–3.20]	<.001	2.68	[2.00–3.57]	<.001	2.83	[2.44–3.29]	<0.001
Histological grade												
I	1			1			1			1		
II	2.52	[1.76–3.60]	<.001	1.48	[1.28–1.71]	<.001	1.53	[1.07–2.20]	.021	-	-	-
III	2.61	[1.79–3.82]	<.001	1.60	[1.36–1.89]	<.001	-	-	-	-	-	-
Unknown	3.33	[2.24–4.94]	<.001	2.15	[1.82–2.55]	<.001	-	-	-	-	-	-

(continued)

Table 2. (continued)

	Cox univariate analysis						Cox multivariate analysis					
	LM			Death			LM			Death		
Characteristics	HR	95% CI	*p-value*	HR	95% CI	*p-value*	HR	95% CI	*p-value*	HR	95% CI	*p value*
Stage												
I	1			1			1			1		
II	2.08	[1.71–2.54]	<.001	1.53	[1.40–1.67]	<.001	1.92	[1.58–2.34]	<.001	1.41	[1.29–1.54]	<0.001
III	6.38	[5.27–7.72]	<.001	3.77	[3.45–4.12]	<.001	4.81	[3.92–5.91]	<.001	2.87	[2.60–3.17]	<0.001
ER (negative vs positive)	1.44	[1.28–1.62]	<.001	1.49	[1.40–1.59]	<.001	1.33	[1.13–1.57]	.001	1.21	[1.11–1.31]	<0.001
PR (negativevs positive)	1.46	[1.31–1.64]	<.001	1.60	[1.51–1.70]	<.001	-	-	-	1.34	[1.23–1.45]	0.001
HER2 (positive vs negative)	2.27	[2.00–2.59]	<.001	1.49	[1.37–1.61]	<.001	1.75	[1.52–2.00]	<.001	1.12	[1.03–1.22]	0.012
Nipple areola invasion (yes vs no)	2.33	[2.03–2.68]	<.001	2.08	[1.92–2.25]	<.001	1.28	[1.10–1.49]	.002	1.15	[1.06–1.26]	0.001
Pectorales invasion (yes vs no)	3.70	[2.47–5.54]	<.001	3.60	[2.87–4.51]	<.001	-	-	-	1.87	[1.48–2.36]	<0.001
Lymph vessel invasion (yes vs no)	2.98	[2.61–3.40]	<.001	2.78	[2.58–3.00]	<.001	1.22	[1.04–1.43]	.014	1.27	[1.16–1.38]	<0.001
Skin invasion (yes vs no)	2.57	[1.96–3.36]	<.001	3.19	[2.79–3.64]	<.001	-	-	-	1.44	[1.25 −1.66]	<0.001

BC, breast cancer; CI, confidence interval; ER, estrogen receptor; HBAg, hepatitis B antigen; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDC, invasive ductal carcinoma; IDC + , 10–90% of the invasive ductal carcinoma component; IHC, immunohistochemistry; Luminal A, Luminal A-like; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; Luminal B (HER2 +), Luminal B-like human epidermal growth factor receptor 2 positive; LM, liver metastasis; NW, northwest China; PR, progesterone receptor; SE, southeast China; TN, triple negative.
†: only age≤ 41 patients were included. ‡: only axillary lymph node ≤ 9 patients were included.

metastases that meant non-locoregional recurrence during follow-up.

In the univariate analysis, the significant independent characteristics for LM probability including age at initial diagnosis, menstrual status, unilateral oophorectomy, pregnancy period, HBAg, region of residence, tumor size, lymph node, clavicular lymph node, stage, PR status, nipple areola invasion, lymphatic vessel invasion, and skin invasion, while in the multivariate analysis, only nipple areola invasion and skin invasion among all the characteristics that were not independently correlated with the LM during the follow-up period (Table 5, Supplementary Table 6). These variables were further used to construct the nomogram.

A total of 389 (91.1%) of 427 patients died during the follow-up, the median follow-up of the 427 patients with BCLM was 7 months (range 0-123 months). The mean LMSS was 15.4 months (95% confidence interval [CI]: 13.1–17.7 months). We divided the patients with the N + Luminal B (HER2−) subtype BCLM into three subgroups: first liver metastases (FLM) subgroup (95, 22.2%) with LM as the first site of distant metastasis, the lowest mortality was 73.7%, subsequent liver metastases (SLM) subgroup (169, 39.6%) with LM, in which the liver was not the first site of distant metastasis, the mortality was 94.7%, and multisites including liver metastases (MLM) subgroup (163, 38.2%) with simultaneous multisite metastases including the liver. The Kaplan–Meier curves for N + Luminal B (HER2 −) showed a significant difference ($p < .001$). There were 147 patients who had died within 3 months, including 130 patients (88.4%) with SLM or MLM. A total of 38 patients with secondary BCLM were still alive, which included 25, 9, and 4 patients in the FLM, SLM, and MLM subgroups respectively (Figure 4).

Nomogram for the Patients with N + Luminal B (HER2−) BC

The significant variables in the multivariable analysis were integrated into the nomogram scoring system. A nomogram to estimate the 24-, 48-, and 60-month LM probabilities was constructed using the N + Luminal B (HER2−) BC data (Figure 5). The C-index value of the nomogram was 0.714 (95% CI, 0.690–0.738). The nomogram presenting the weights and points of the BCLM risk prediction score could be used to assess a person's probability of developing subsequent LM over a 5-year period.

The calibration curves were used to evaluate the predicted LM probability and the validity of the nomogram. The estimated versus observed LM probability calibration curve was evenly distributed on both sides of the diagonal, indicating that the predicted value approximated the observed value within the 95% CI (Figure 6a–C). The ROC curve was constructed for the 24-, 48-, and 60-month LM probability, and the area under the curve was 0.744, 0.752, and 0.738, respectively (Figure 6d–F). The calibration curves demonstrated that

Table 3. The Patients with Luminal A Were Compared with Those with N− Luminal B (HER2−) for LM Probability and Probability of Death on Cox Univariate Analysis

	LM					Death				
Subtype	*N*	Probability	HR	95% CI	*p-value*	*N*	Mortality	HR	95% CI	*p-value*
Luminal A	57	1.5%	1			212	5.5%	1		
N− Luminal B (HER2−)	168	2.0%	1.30	[0.96–1.75]	.091	872	9.7%	1.19	[1.02–1.39]	.032

CI, confidence interval; HR, hazard ratio; Luminal A, Luminal A-like; Luminal B (HER2 -), Luminal B-like human epidermal growth factor receptor 2 negative; LM, liver metastasis; N−, lymph node negative.

the predictive outcome corresponded well with the actual 24-, 48-, and 60-month LM probability.

Discussion

Certain heterogeneity may exist with different clinical outcomes of BC owing to the varying histopathological and molecular features.[19,20] Even though the mechanism of BCLM is unclear, in some clinicopathological studies, the interval time of the confirmed diagnosis of BCLM varied, thus, molecular subtypes may be important factors resulting in BCLM.[21] LM is considered a poor prognosis subgroup of MBC.

For the multivariate analysis, the age, menstrual, unilateral oophorectomy, pregnancy, HBAg (+), region of residence, pathological types, T, N, clavicle lymph nodes, IHC subtypes, histological grade, stage, ER, HER2, nipple-areola invasion, lymphatic vessel invasion, and liver hemangioma were associated with BCLM. We suggest these factors to be independent risk factors for BCLM, rather than secondary findings associated with the clinicopathological parameters. Moreover, those parameters have advantages with respect to convenience, easy access, and low cost. In previous studies, when Luminal B (HER2−) was considered as a better prognosis for various types of LMSS,[22,23] these data suggest that ET may be the basis for prolonging LMSS in the overall course of the treatment. N+ was identified as a negative prognostic factor,[24] and patients with high-risk clinicopathological characteristics at the time of diagnosis of BC were associated with the worst prognosis.

In this study, we reviewed the characteristics of the metastatic sites of patients with MBC in order to provide insights into the prognosis and other clinical variables that may contribute to clinical treatment options. To our knowledge, this is the largest sample of Chinese patients with MBC in the literature classifying the various sites of metastasis through retrospective analysis. Liang *et al* have previously described the features of BCLM as features of targeted metastasis rather than random.[25] Our study confirmed these findings, wherein 1.97% of the patients with N− Luminal B (HER2−) developed LM, and found that patients with N+ Luminal B (HER2−) with the rate of LM was 5.5%, and frequent LM in parallel with metastases in bone compared to the total number of patients in the study. These clinicopathological characteristics were identified enable to establish a nomogram as an LM risk assessment for patients with N+ Luminal B (HER2−), Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are beneficial for patients of MBC with bone and visceral metastases,[26] moreover, considering the current COVID-19 pandemic, high-risk patients who cannot be admitted to the hospital for undergoing chemotherapy can be administered adjuvant extensive ET first.

For Luminal B (HER2−), the highest number of patients with subsequent LM was observed from the 2nd to 4th year after BC diagnosis, and a small peak confirmed diagnosis of LM after 5 years, which could occur even after the 10th year, regardless of other sites metastases. Our goal was to analyze the time of occurrence of LM which should prolong ET to 10 years or early extended interventions was necessary. This time interval was not associated with the unique preference of Luminal B (HER2−) tumors for LM.[27,28] According to previous studies, patients with N− HR+ require only 5 years of ET.[29] Recently, mechanisms of BC metastasis and gene mutations promoting the potential of drug resistance have been identified in ET.[5] In addition, analysis of Luminal B (HER2 −)-related intensive ET shows that the selection of individual patients is key for benefit from ET when opting for extensive ET.[30] Although there is little evidence to analyze the time of occurrence of LM in patients with Luminal B (HER2−), these phenomena may be related to age, comorbidities, economic status, and individual genetic mutations.[8] It is important to note that these BCLM studies lack detailed data on the clinicopathological features in a large number of Chinese patients, therefore, the critical window for screening people at high risk of LM has not been identified in patients with BC. A major advantage of our study is the use of large data on the unique clinicopathological characteristics of BC in Chinese women.

Notably, based on the collected data from northwest China, these patients include those with better economic status, medical insurance, and educational level, and mostly belonging to the higher-income population, while the data from southeast China, which is densely populated, showed both rich and poor patient distribution with a higher proportion of patients with hepatitis B,[31] which may lead to a low probability of LM in northwest China. Currently, a model based on treatment and prevention of complications has been considered an important strategy in medical practice to identify those most likely to benefit from treatment interventions and cure liver disease, the patients in our study were more likely to have variant potential etiology of LM with the residence of northwest-southeast

Table 4. Baseline Characteristics of the Patients with N + Luminal B (HER2−) BC

Characteristics	LM $N = 427$ (%)	Death $N = 1342$ (%)	Total $N = 7782$ (%)
Age, years			
≤39	87 (20.4)	193 (14.4)	1024 (13.2)
40–59	279 (65.3)	834 (62.1)	5158 (66.3)
60–75	61 (14.3)	315 (23.5)	1600 (20.5)
Menopausal status			
Post-	180 (42.2)	657 (48.9)	3241 (41.6)
Pre-	175 (40.9)	480 (35.8)	3246 (41.7)
Peri-	48 (11.2)	122 (9.1)	577 (7.4)
Unknown	24 (5.6)	83 (6.2)	718 (9.2)
Unilateral oophorectomy			
No	391 (91.6)	1268 (94.5)	7478 (96.1)
Yes	36 (8.4)	74 (5.5)	304 (3.9)
Pregnancy†			
No	34 (73.9)	85 (78.7)	368 (82.0)
Yes	12 (26.1)	23 (21.3)	81 (18.0)
HBAg			
Negative	396 (92.7)	1274 (94.9)	7515 (96.6)
Positive	31 (7.3)	68 (5.1)	267 (3.4)
Region of residence			
NW	38 (8.9)	163 (12.1)	1583 (20.3)
SE	389 (91.1)	1179 (87.9)	6199 (79.7)
Pathological subtype			
IDC	360 (84.3)	1098 (81.8)	6477 (83.2)
IDC +	47 (11.0)	145 (10.8)	850 (10.9)
Others	20 (4.7)	99 (7.4)	455 (5.8)
Tumor size			
≤2cm	77 (18.0)	248 (18.5)	2159 (27.7)
2.1–5.0cm	280 (65.6)	876 (65.3)	4783 (61.5)
≥5.1	70 (16.4)	218 (16.2)	840 (10.8)
Lymph node			
1–3	172 (40.3)	535 (39.9)	4274 (54.9)
4–9	98 (22.9)	342 (25.5)	1837 (23.6)
≥10	157 (36.8)	465 (34.6)	1671 (21.5)
Clavicular lymph node♮			
No	248 (91.9)	824 (94.0)	5854(95.8)
Yes	22 (8.1)	53 (6.0)	257 (4.2)
Lesion			
1	418 (97.9)	1311 (97.7)	7632 (98.1)
≥2	9 (2.1)	31 (2.3)	150 (1.9)
Histological grade			
I	10 (2.3)	42 (3.1)	290 (3.7)
II	338 (79.2)	1011 (75.3)	6016 (77.3)
III	37 (8.7)	141 (10.5)	818 (10.5)
Unknown	42 (9.8)	148 (11.0)	658 (8.5)
Stage			
II	160 (37.5)	489 (36.4)	3996 (51.3)
III	267 (62.5)	853 (63.6)	3786 (48.7)
PR			
Positive	319 (74.7)	949 (70.7)	6221 (79.9)
Negative	108 (25.3)	393 (29.3)	1561 (20.1)
Nipple areola invasion			
Positive	83 (19.4)	299 (22.3)	1191 (15.3)
Negative	344 (80.6)	1043 (77.7)	6591 (84.7)
Pectorales invasion			
Positive	9 (2.1)	43 (3.2)	99 (1.3)
Negative	418 (97.9)	1299 (96.8)	7683 (98.7)
Lymph vessel invasion			
Positive	139 (32.6)	453 (33.8)	1647 (21.2)
Negative	288 (67.4)	889 (66.2)	6135 (78.8)
Skin invasion			
Positive	23 (5.4)	96 (7.2)	285 (3.7)
Negative	404 (94.6)	1246 (92.8)	7497 (96.3)

BC, breast cancer; HBAg, hepatitis B antigen; IDC, invasive ductal carcinoma; IDC +, 10–90% of the invasive ductal carcinoma component; IHC, immunohistochemistry; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; LM, liver metastasis; N +, lymph node positive; NW, northwest China; PR, progesterone receptor; SE, southeast China. †: only age≤ 34 patients were included. ♮: only axillary lymph node ≤ 9 patients were included.

differences in China[31,32] since concurrent liver-related disease could attribute to the LM.[33–35] Recent guidelines describe PR-tumors as having a unique molecular signature and therefore, possess a particular therapeutic response to ET compared with PR + BC.[24] Our study also showed that the PR status correlated with the LM. Even though a small number of patients were present with PR-BC in this study, they had a significantly higher risk of LM compared to the patients with PR + BC.

Based on the sequence of metastases sites considering LM, for the first time, we displayed the impact of the sequence of the sites of metastases as a survival probability function in patients with N + Luminal B (HER2−) BCLM. The median LMSS of Luminal B (HER2−) BC is higher than other molecular subtypes.[6,23] We found that LMSS is similar among patients with SLM and MLM, however, SLM was more severe at LMSS compared to MLM.[36] For MLM, routine medical examination fails to distinguish the sequence of sites of metastases in the patients. Higher mortality, which is associated with higher drug resistance, has been linked to LM-free survival.[26,27] A survival analysis plot could enable clinicians to clearly visualize the prognosis of patients with BCLM and aid in precise treatment decisions. In addition, conventional therapies are prone to failure in these high-risk patients, thus, LM prediction of the high-risk populations is urgently warranted. Although it is plausible that the risk of death may increase with the number of metastatic sites, herein, we quantified the cumulative effect of increasing sequential LM with the burden of other sites on the LMSS.

Nomograms have been previously developed for BCLM, few models are based on subsequent BCLM, while more survival prediction models exist on patients with *de novo* BCLM using SEER data.[11,21] Most of the prediction models were based on the prediction of overall survival (OS) and LMSS for patients with *de novo* BCLM,[23,37–39] and the prediction accuracy was higher than that of the seventh version American Joint Committee on Cancer (AJCC)-TNM staging system.[12,23] Li *et al* created a risk evaluation tool to predict the OS of patients with MBC using a nomogram prediction

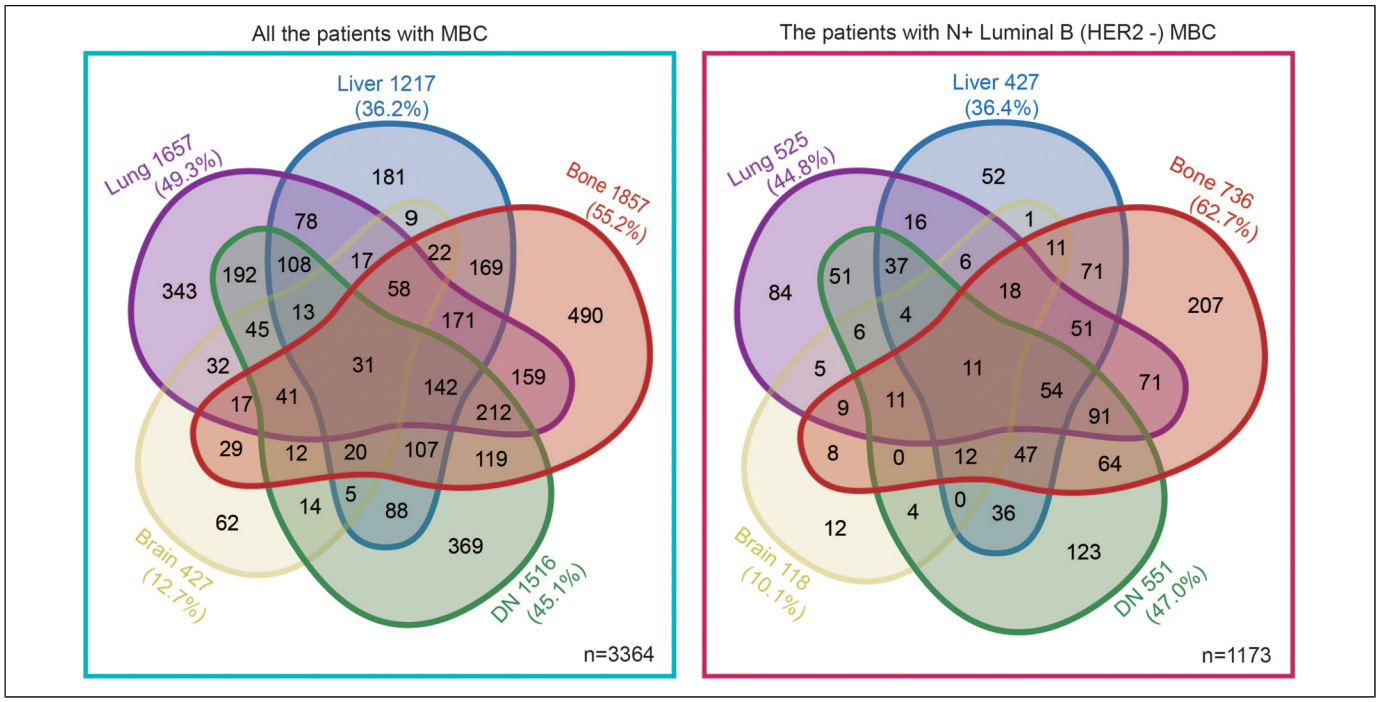

Figure 3. Distribution of the metastases sites among the patients with MBC. DN, distant lymph node metastases; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; MBC, metastatic breast cancer; N+, lymph node positive.

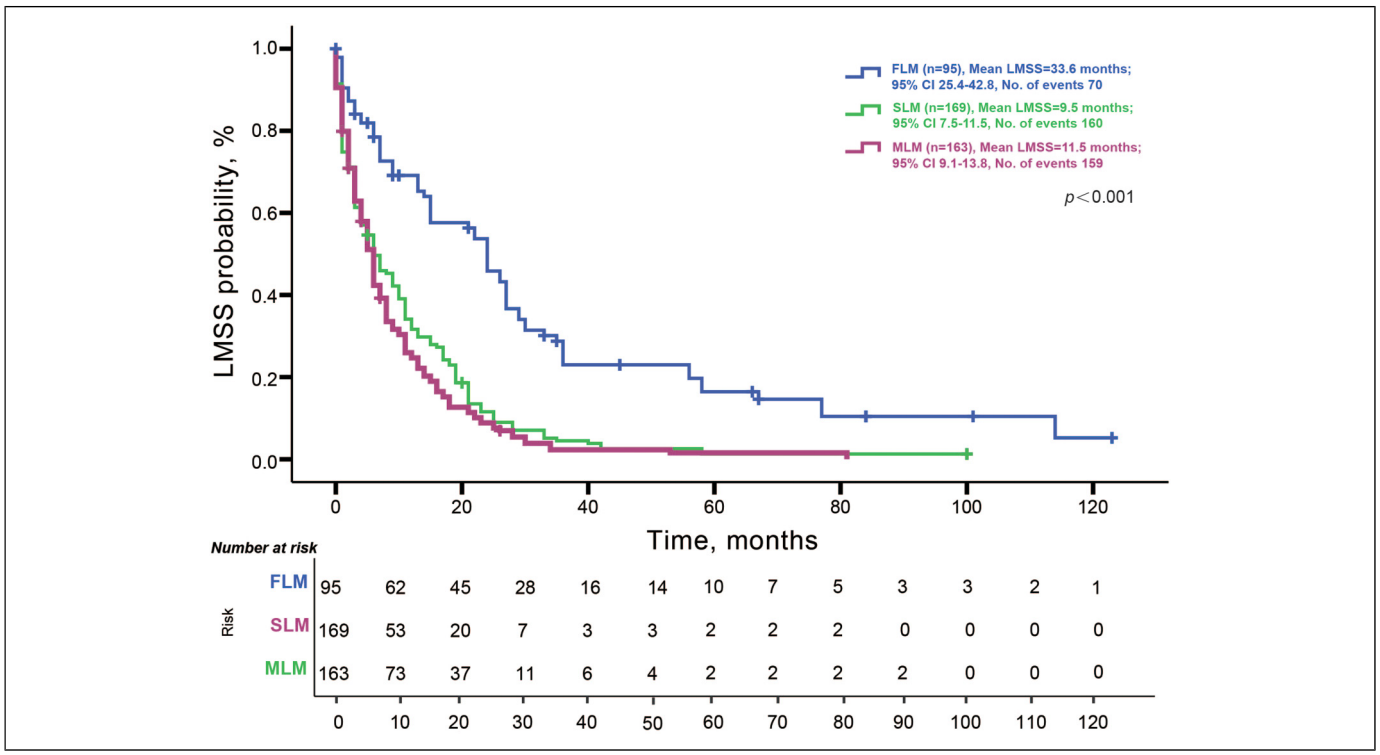

Figure 4. Kaplan–Meier curves showed that the LMSS for the patients with N+Luminal B (HER2−) BC ($p < .001$). BC, breast cancer; CI, confidence interval; FLM, liver metastasis as the first site of distant metastasis; LMSS, liver metastasis special survival; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; MBC, metastatic breast cancer; MLM, simultaneous multisite metastases including liver; No, number; N+, lymph node positive; SLM, subsequent liver metastases subgroup with LM, in which the liver was not the first site of distant metastasis.

Table 5. Cox Univariate and Multivariate Analysis for LM and Death in the Patients with N + Luminal B (HER2−) BC

	Cox univariate analysis						Cox multivariable analysis					
	LM			Death			LM			Death		
Characteristics	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age, years												
≤39	2.23	[1.61–3.10]	<.001	0.90	[0.75–1.07]	.226	2.30	[1.61–3.27]	<.001	-	-	-
40–59	1.39	[1.06–1.84]	.019	0.79	[0.69–0.89]	<.001	1.61	[1.19–2.17]	.002	-	-	-
60–75	1			1			1			1		
Menopausal status												
Post-	1.06	[0.86–1.30]	.599	1.43	[1.27–1.61]	<.001	-	-	-	1.28	[1.11–1.46]	<.001
Pre-	1			1			1			1		
Peri-	1.60	[1.16–2.20]	.004	1.45	[1.19–1.77]	<.001	1.59	[1.15–2.20]	.005	1.42	[1.15–1.74]	.001
Unknown	0.59	[0.38–0.90]	.014	0.63	[0.50–0.79]	<.001	-	-	-	-	-	-
Unilateral oophorectomy (yes vs no)	2.38	[1.69–3.35]	<.001	1.48	[1.17–1.87]	.001	1.83	[1.91–2.07]	<.001	1.29	[1.02–1.64]	.037
Pregnancy† (yes vs no)	3.35	[1.88–5.94]	<.001	2.39	[1.58–3.61]	<.001	1.91	[1.03–3.55]	.004	2.00	[1.28–3.10]	.002
HBAg (yes vs no)	2.30	[1.60–3.32]	<.001	1.58	[1.24–2.02]	<.001	1.99	[1.37–2.90]	<.001	1.62	[1.26–2.08]	<.001
Region of residence (SE vs NW)	2.59	[1.86–3.61]	<.001	1.71	[1.45–2.02]	<.001	2.91	[2.08–4.07]	<.001	1.83	[1.55–2.16]	<.001
Pathological type												
IDC	1.28	[0.82–2.01]	.279	0.86	[0.70–1.05]	.138	-	-	-	-	-	-
IDC +	1.34	[0.79–2.26]	.273	0.97	[0.75–1.25]	.801	-	-	-	-	-	-
Others	1			1			1			1		
Tumor size												
≤2cm	1			1			1			1		
2.1–5.0cm	1.70	[1.32–2.19]	<.001	1.65	[1.44–1.90]	<.001	1.41	[1.09–1.83]	.009	0.32	[1.14–1.53]	<.001
≥5.1cm	2.73	[1.97–3.77]	<.001	2.85	[2.37–3.42]	<.001	1.83	[1.27–2.64]	.001	1.60	[1.30–1.98]	<.001
Lymph node												
1–3	1			1			1			1		
4–9	1.37	[1.07–1.75]	.013	1.55	[1.35–1.77]	<.001	1.10	[0.84–1.43]	.049	1.28	[1.12–1.48]	.001
≥10	2.66	[2.14–3.30]	<.001	2.63	[2.32–2.98]	<.001	2.02	[1.58–2.58]	<.001	1.90	[1.65–2.19]	<.001
Clavicular lymph node♮ (yes vs no)	1.60	[1.04–2.46]	.031	1.26	[0.95–1.65]	.104	1.75	[1.11–2.75]	.016	-	-	-
Lesion (≥2 vs 1)	1.15	[0.59–2.23]	.677	1.34	[0.94–1.91]	.110	-	-	-	-	-	-
Histological grade												
I	1			1			1			1		
II	1.82	[0.97–3.41]	.062	1.40	[1.03–1.90]	.034	-	-	-	-	-	-
III	1.48	[0.74–2.98]	.271	1.45	[1.02–2.04]	.036	-	-	-	-	-	-
Unknown	2.16	[1.08–4.30]	.029	1.95	[1.38–2.75]	<.001	-	-	-	-	-	-
Stage (IIIvs II)	1.90	[1.56–2.31]	<.001	2.03	[1.82–2.27]	<.001	1.56	[1.23–1.93]	<.001	1.61	[1.42–1.82]	<.001
PR (negative vs positive)	1.35	[1.08–1.68]	.007	1.55	[1.37–1.74]	<.001	1.33	[1.06–1.65]	.012	1.52	[1.35–1.72]	<.001
Nipple areola invasion (yes vs no)	1.37	[1.08–1.74]	.010	1.69	[1.49–1.93]	<.001	-	-	-	1.13	[0.98–1.30]	.083
Pectorales invasion (yes vs no)	1.91	[0.99–3.70]	.054	3.07	[2.27–4.16]	<.001	-	-	-	1.87	[1.36–2.57]	<.001
Lymph vessel invasion (yes vs no)	1.88	[1.54–2.30]	<.001	2.05	[1.83–2.30]	<.001	1.43	[1.14–1.79]	.002	1.43	[1.25–1.62]	<.001
Skin invasion (yes vs no)	1.83	[1.20–2.79]	.005	2.68	[2.17–3.30]	<.001	-	-	-	1.44	[1.15–1.81]	.002

BC, breast cancer; CI, confidence interval; HBAg, hepatitis B antigen; HR, hazard ratio; IDC, invasive ductal carcinoma; IDC +, 10–90% of the invasive ductal carcinoma component; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; LM, liver metastasis; NW, northwest China; PR, progesterone receptor; SE, southeast China.

†: only age≤ 34 patients were included. ♮: only axillary lymph node ≤ 9 patients were included.

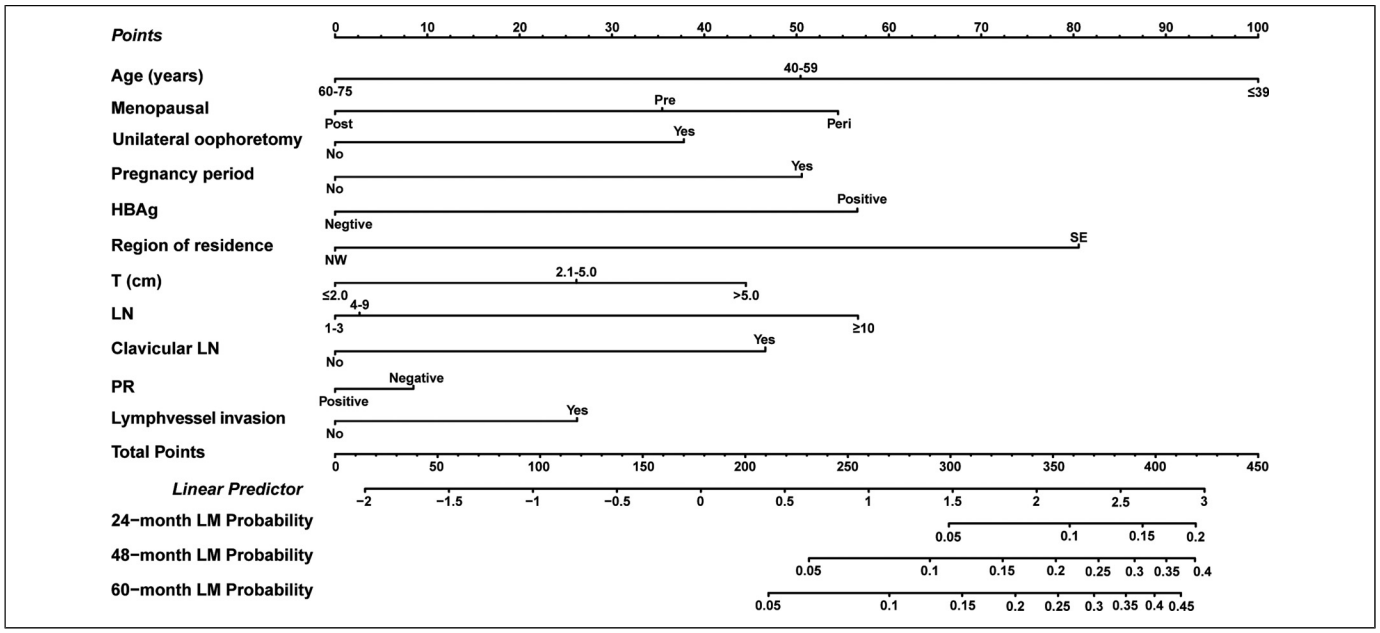

Figure 5. Nomogram to estimate the 24-, 48-, and 60-month LM probabilities for patients with N + Luminal B (HER2−) BC. BC, breast cancer; HBAg, hepatitis B antigen; LM, liver metastasis; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; N, lymph node status; N + , lymph node positive; NW, northwest China; PR, progesterone receptor; SE, southeast China; T, tumor size.

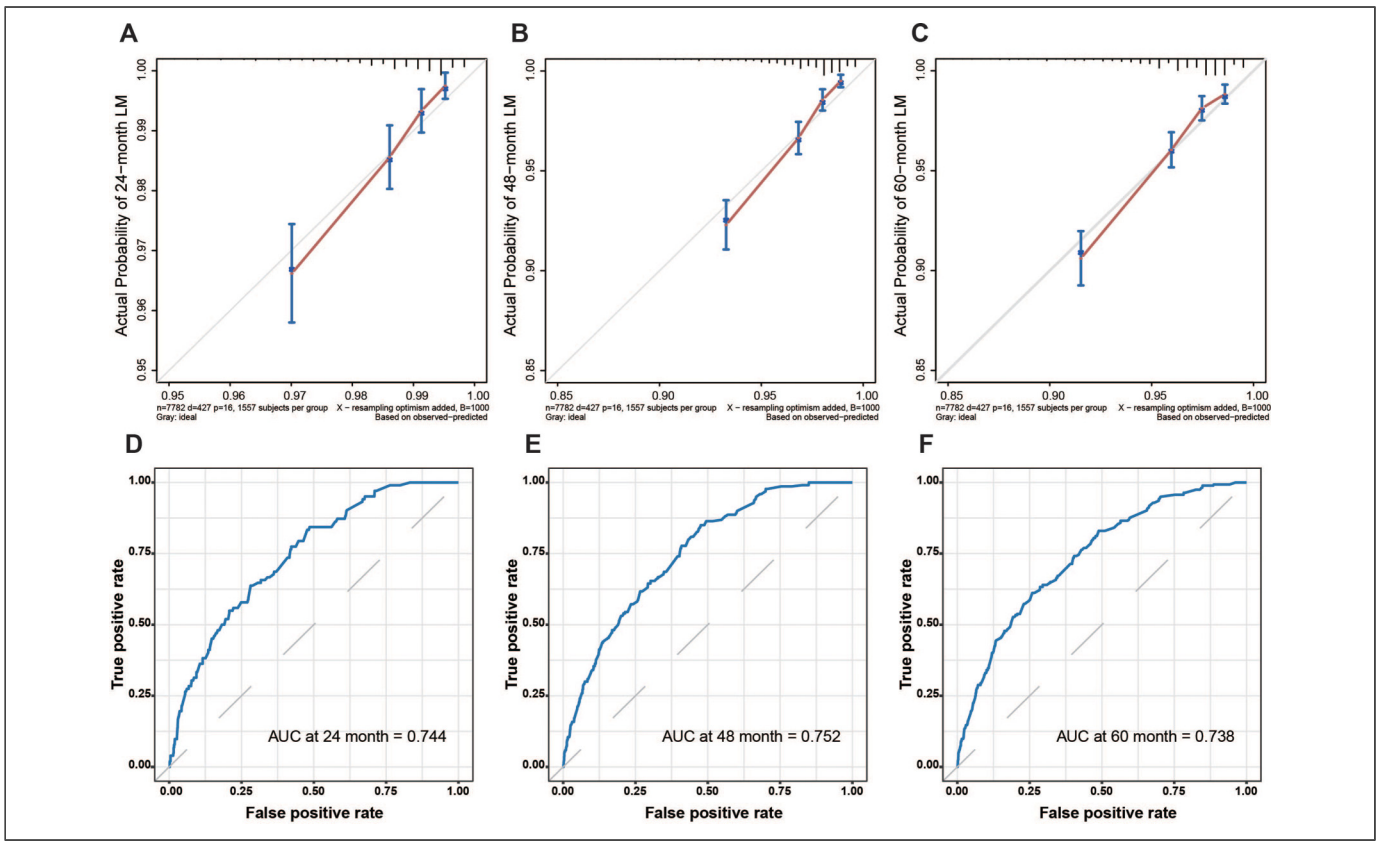

Figure 6. (A–C) Calibration curves for predicting the 24-, 48-, and 60-month LM probability for the patients with N + Luminal B (HER2−) BC. (D–F) Predictive efficacy of the 24-, 48-, and 60-month LM probability nomogram by ROC curve analysis for the patients with N + Luminal B (HER2−) BC. AUC, area under the curve; BC, breast cancer; LM, liver metastasis; Luminal B (HER2−), Luminal B-like human epidermal growth factor receptor 2 negative; N + , lymph node positive; ROC, receiver operating characteristic.

model for the prognosis of LM similar to brain metastases.[40] This study considered the clinicopathological characteristics as actual data on the potential risk of LM in female patients with N + Luminal B (HER2−) BC in China. We believe that the nomogram can be used for the diagnosis and treatment by clinicians with limited experience for prompt identification of high-risk patients and for the prediction of disease progression and subsequent treatment options following initial diagnosis. Moreover, the requirement for extensive or prolonged ET would be more beneficial in these patients with N + Luminal B (HER2−),[41,42] thus, reducing treatment delays during the COVID-19 pandemic, when hospitalization for surgery or chemotherapy is temporarily unavailable, thereby achieving better treatment outcomes.

In this study, our predictive model demonstrated that these 11 parameters affected the risk factors for LM, and the C-index of the model was 0.714. Moreover, upon performing sensitivity calibration plot analysis using the collected data, the model performance did not change, thus, our model could be considered reliable. However, further studies are warranted to evaluate the feasibility and effectiveness of the current LM-based risk assessment tools based on clinicopathological characteristics, improvement of the BCLM risk factors, and overall potential for BCLM prevention when incorporated in tertiary treatment strategies, especially as a pre-screening tool for high-risk patients.

Additional predictors, including chemotherapy, ET, and genetic variables, should be further explored for improving the precise prevention of BCLM in future studies. Additionally, we derived a feasible and accurate assessment method comprising a nomogram considering simultaneous LM risk prediction, which could be useful for individualized prediction. The potential limitations of our study are worth discussing. First, since many patients among those lost to follow-up die of LM, the number of patients with LM was low. Second, very few patients in this study were treated with Tamoxifen and/or an aromatase inhibitor for 10 years. Moreover, patients with axillary accessory BC occurring with unilateral or bilateral BC were included in bilateral BC who were excluded.[43] Although, our predictive model could be useful for considering extensive treatment strategies, further well-designed clinical studies are warranted for its validation.

In conclusion, we explored the relationship between the clinicopathological characteristics of patients with BCLM, and developed a prediction model for patients with N + Luminal B (HER2−) BC for LM prediction. Extended ET targeting could be the best choice for high-risk patients with N + Luminal B (HER2−) BC.

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Declaration of Conflicting Interests

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Ethics Approval

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Supplemental Material

Supplemental material for this article is available online.

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