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−) BC, a median age of 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, 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. \(^5\) 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 metachronal 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, lympathic vessel infiltration, and skin infiltration. Other clinical characteristics including laterality, delivery, hysterecomy, fatty liver, liver cyst, hepatic hemangioma, diabetes, blood subtypes, anti-HBAg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), \(\gamma\)-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
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)      | 33324 (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)      | 29099 (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)        | 2046 (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**               |               |                  |                   |
| I                        | 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-ampifed             | 177 (14.5)    | 415 (9.8)        | 2405 (7.8)        |
| TN                       | 267 (21.9)    | 1123 (26.4)      | 3664 (11.9)       |
| **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)      |

(continued)
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.

| Characteristics                      | Cox univariate analysis (LM) | Cox multivariate analysis (LM) | Cox univariate analysis (Death) | Cox multivariate analysis (Death) |
|--------------------------------------|-----------------------------|--------------------------------|--------------------------------|---------------------------------|
|                                      | HR  | 95% CI  | p-value | HR  | 95% CI  | p-value | HR  | 95% CI  | p-value | HR  | 95% CI  | p-value |
| Age, years                           |     |         |         |     |         |         |     |         |         |     |         |         |
| ≤59                                   | 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  | 1.42 | [1.19–1.70] | <.001  | 1.42 | [1.19–1.70] | <.001  | 1.42 | [1.19–1.70] | <.001  |
| 60–75                                 | 1.33 | [1.24–1.43] | <.001  | 1.09 | [1.00–1.18] | 0.039  |
| Menopausal status                     |     |         |         |     |         |         |     |         |         |     |         |         |
| Post-                                 |     |         |         |     |         |         |     |         |         |     |         |         |
| Pre-                                  | 1.06 | [0.94–1.20] | .339   |     |         |         |     |         |         |     |         |         |
| Peri-                                 | 1.49 | [1.21–1.82] | <.001  |     |         |         |     |         |         |     |         |         |
| Unknown                               | 0.75 | [0.59–0.96] | .020   |     |         |         |     |         |         |     |         |         |
| Unilateral oophorectomy (yes vs no)  | 1.44 | [1.12–1.85] | .005   |     |         |         |     |         |         |     |         |         |
| Pregnancy (yes vs no)                 | 3.52 | [2.50–4.95] | <.001  |     |         |         |     |         |         |     |         |         |
| HBAg (yes vs no)                      | 2.03 | [1.62–2.54] | <.001  |     |         |         |     |         |         |     |         |         |
| Region of residence (SE vs NW)        | 1.59 | [1.35–1.88] | <.001  |     |         |         |     |         |         |     |         |         |
| Pathological type                     |     |         |         |     |         |         |     |         |         |     |         |         |
| IDC                                   | 1.28 | [0.99–1.64] | .060   | 1.37 | [1.01–1.85] | .044   |     |         |         |     |         |         |
| IDC +                                 | 1.76 | [1.30–2.38] | <.001  | 1.37 | [1.01–1.85] | .044   |     |         |         |     |         |         |
| Others                                | 1.06 | [0.95–1.18] | .330   | 1.27 | [1.17–1.39] | <.001  |
| Tumor size                            |     |         |         |     |         |         |     |         |         |     |         |         |
| ≤2 cm                                 |     |         |         |     |         |         |     |         |         |     |         |         |
| 2.1–5.0 cm                            | 2.27 | [1.97–2.60] | <.001  | 1.68 | [1.41–2.00] | <.001  | 1.27 | [1.18–1.37] | <.001  |
| ≥5.1 cm                               | 4.81 | [3.99–5.81] | <.001  | 1.92 | [1.50–2.46] | <.001  | 1.71 | [1.52–1.93] | <.001  |
| Lymph node                            |     |         |         |     |         |         |     |         |         |     |         |         |
| 0                                     |     |         |         |     |         |         |     |         |         |     |         |         |
| 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] | <.001  |
| 4–9                                   | 2.99 | [2.12–4.22] | <.001  | 2.45 | [2.24–2.68] | <.001  | 2.72 | [2.25–2.39] | <.001  | 1.95 | [1.77–2.15] | <.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] | <.001  |
| Clavicular lymph node (yes vs no)     | 2.26 | [1.74–3.18] | <.001  | 1.66 | [1.37–2.02] | <.001  | 1.37 | [1.09–1.71] | .060   |     |         |         |
| 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                             |     |         |         |     |         |         |     |         |         |     |         |         |
| 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] | <.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] | <.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] | <.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] | <.001  |
| Histological grade                    |     |         |         |     |         |         |     |         |         |     |         |         |
| I                                     |     |         |         |     |         |         |     |         |         |     |         |         |
| 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)

| Characteristics                        | Cox univariate analysis | Cox multivariate analysis |
|-----------------------------------------|-------------------------|--------------------------|
|                                         | LM Death                | Death                    | LM Death                | Death |
|                                         | HR 95% CI p-value       | HR 95% CI p-value        | HR 95% CI p-value       | HR 95% CI p-value |
| Stage                                   | I                       | II                       | III                      |                  |
| LM Death                                | 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 |
| ER (negative vs positive)               | 1.44 [1.28–1.62] <.001  | 1.49 [1.40–1.59] <.001   | 1.33 [1.13–1.57] <0.001  | 1.21 [1.11–1.31] <0.001 |
| PR (negative vs positive)               | 1.46 [1.31–1.64] <.001  | 1.60 [1.51–1.70] <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   | -                      | -                      |
| Pectorales invasion (yes vs no)         | 3.70 [2.47–5.54] <.001  | 3.60 [2.87–4.51] <.001   | 1.28 [1.10–1.49] <.002   | 1.15 [1.06–1.26] 0.001 |
| Lymph vessel invasion (yes vs no)       | 2.98 [2.61–3.40] <.001  | 2.78 [2.58–3.00] <.001   | -                      | -                      |
| Skin invasion (yes vs no)               | 2.57 [1.96–3.56] <.001  | 3.19 [2.79–3.64] <.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.
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 as 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 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

| Subtype | LM | Death |
|---------|----|-------|
| LM 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.
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)     |

(continued)
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.
| Characteristics                        | Cox univariate analysis | Cox multivariable analysis |
|---------------------------------------|-------------------------|---------------------------|
|                                       | LM | Death | p-value | HR  | 95% CI | p-value | HR  | 95% CI | p-value |
| Age, years                            |    |       |         |     |        |         |     |        |         |
| ≤39                                   | 2.23 [1.61–3.10]        | 0.90 [0.75–1.07]         | .001 | 2.30 [1.61–3.27] | <.001 | -    | -    | -       |
| 40–59                                 | 1.39 [1.06–1.84]        | 0.79 [0.69–0.89]         | <.001 | 1.61 [1.19–2.17] | .002 | 1.43 [1.25–1.62] | <.001 |
| 60–75                                 | 1  | 1     |         |     | 1      | -       |     | 1      |         |
| Menopausal status                     |    |       |         |     |        |         |     |        |         |
| Post-                                 | 1.06 [0.86–1.30]        | 1.43 [1.27–1.61]         | <.001 | -  | -    |         | -    | -    |         |
| Pre-                                  | 1  | 1     |         |     | 1      | -       |     | 1      |         |
| Unknown                               | 0.59 [0.38–0.90]        | 0.63 [0.50–0.79]         | <.001 | 1.59 [1.15–2.20] | .005 | 1.42 [1.15–1.74] | .001 |
| Unilateral oophorectomy (yes vs no)   | 2.38 [1.69–3.35]        | 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]        | 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]        | 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]        | 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]        | 0.86 [0.70–1.05]         | .138 | -    | -    |         | -    | -    |         |
| IDC +                                 | 1.34 [0.79–2.26]        | 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]        | 1.65 [1.44–1.90]         | <.001 | 1.41 [1.09–1.83] | .009 | 1.60 [1.39–1.98] | <.001 |
| ≥5.1cm                                | 2.73 [1.97–3.77]        | 2.85 [2.37–3.42]         | <.001 | 1.83 [1.27–2.64] | .001 | 1.74 [1.72–1.78] | <.001 |
| Lymph node                            |    |       |         |     |        |         |     |        |         |
| 1–3                                   | 1  | 1     |         |     | 1      | -       |     | 1      |         |
| 4–9                                   | 1.37 [1.07–1.75]        | 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]        | 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]        | 1.26 [0.95–1.65]         | .104 | 1.75 [1.11–2.75] | .016 | -    | -    |         |
| Lesion (≥2 vs 1)                      | 1.15 [0.59–2.23]        | 1.34 [0.94–1.91]         | .110 | -    | -    |         | -    | -    |         |
| Histological grade                    |    |       |         |     |        |         |     |        |         |
| I                                     | 1  | 1     |         |     | 1      | -       |     | 1      |         |
| II                                    | 1.82 [0.97–3.41]        | 1.40 [1.03–1.90]         | .034 | -    | -    |         | -    | -    |         |
| III                                   | 1.48 [0.74–2.98]        | 1.45 [1.02–2.04]         | .036 | -    | -    |         | -    | -    |         |
| Unknown                               | 2.16 [1.08–4.30]        | 1.95 [1.38–2.75]         | <.001 | -    | -    |         | -    | -    |         |
| Stage (III vs II)                     | 1.90 [1.56–2.31]        | 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]        | 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]        | 1.69 [1.49–1.93]         | <.001 | -    | -    |         | -    | -    |         |
| Pectorales invasion (yes vs no)       | 1.91 [0.99–3.70]        | 3.07 [2.27–4.16]         | <.001 | -    | -    |         | -    | -    |         |
| Lymph vessel invasion (yes vs no)     | 1.88 [1.54–2.30]        | 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]        | 2.68 [2.17–3.30]         | <.001 | -    | -    |         | -    | -    |         |

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.

| Points | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 10K |
|--------|---|----|----|----|----|----|----|----|----|----|-----|
| Age (years) | | | | | | | | | | | |
| Menopausal | No | Yes | | | | | | | | | |
| Unilateral oophorectomy | | | | | | | | | | | |
| Pregnancy period | No | Yes | | | | | | | | | |
| HBAg | | | | | | | | | | | |
| Region of residence | NW | SE | | | | | | | | | |
| T (cm) | | | | | | | | | | | |
| LN | | | | | | | | | | | |
| Clavicular LN | No | Yes | | | | | | | | | |
| PR | No | Yes | | | | | | | | | |
| Lymphvessel invasion | | | | | | | | | | | |
| Total Points | | | | | | | | | | | |

### 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. 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.

(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.\textsuperscript{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−).\textsuperscript{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 died 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.\textsuperscript{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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