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Research article

A prognostic model for triple-negative breast cancer patients with liver metastasis: A population-based study

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ABSTRACT

However, it is still difficult for clinicians to establish prognostic stratifications and therapeutic strategies because of the lack of tools for predicting the survival of triple-negative breast cancer patients with liver metastases (TNBC-LM). Based on clinical data from large populations, a sensitive and discriminative nomogram was developed and validated to predict the prognosis of TNBC patients with LM at initial diagnosis or at the later course.

Introduction/background: Liver metastasis (LM) in TNBC patients is associated with significant morbidity and mortality. The objective of this study was to construct a clinical model to predict the survival of TNBC-LM patients.

Materials and methods: Clinicopathologic data were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database and the Fifth Affiliated Hospital of Sun Yat-Sen University (FAFSYU). Based on patients with newly diagnosed TNBC with LM (nTNBC-LM) from the SEER database, a predictive nomogram was established and validated. Its predictive effect on TNBC patients with LM at later disease course by enrolling TNBC patients from FAFSYU who developed LM later. The prognostic effect of different treatment for nTNBC-LM was further assessed.

Results: A prognostic model was developed and validated to predict the prognosis of TNBC-LM patients. For LM patients diagnosed at the initial or later treatment stage, the C-index (0.712, 0.803 and 0.699 in the training, validation and extended groups, respectively) and calibration plots showed the acceptable prognostic accuracy and clinical applicability of the nomogram. Surgical resection on the primary tumour and chemotherapy were found to be associated with significantly better overall survival (OS).

Conclusion: A sensitive and discriminative model was developed to predict OS in TNBC-LM patients both at and after initial diagnosis.

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1. Introduction

Triple-negative breast cancer (TNBC) was named by lacking expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor-2 (HER2) [1]. Due to its highly aggressive nature, patients with TNBC face a higher risk of relapse and mortality than patients with other subtypes [2,3]. During the disease course, almost 50% of TNBC patients will develop distant metastasis, and after metastasis, the median survival time is only 13.3 months [4].

Liver is one of the most common metastatic sites of BC and the first organ in nearly 30% of metastatic breast cancer (MBC) patients [5,6]. Liver metastasis (LM) is associated with significantly increased mortality, with an overall survival (OS) of only 3–6 months in untreated patients and a median survival time of 12–20 months, although great improvements in diagnosis and treatment have been made in recent decades [7–9]. TNBC-LM patients have an even worse prognosis than patients with other subtypes [5,10–13]. A study including 4285 patients diagnosed with BC with LM (BCLM) revealed that TNBC patients had the worst OS, at only 8 months, while the OS of the entire cohort was 15 months [5].

Nomograms based on a large cohort were developed to predict the OS of patients with BCLM and showed acceptable sensitivity and specificity [10,11,14]. However, another study enrolled BCLM patients from all subtypes to construct a prognostic model, which may result in serious bias when applied to TNBC patients, as TNBC has distinct characteristics and comprises a relatively small proportion of cases. Therefore, to enhance the performance of the prognostic nomogram and guide treatment strategies for TNBC-LM patients, it is imperative to conduct studies and construct nomograms based exclusively on patients with this subtype, especially with a large population.

In present research, a clinical model for predicting OS at 6 months, 1 year, and 2 years was developed and showed great discriminative performance in predicting the prognosis of patients with TNBC with LM at diagnosis (nTNBC-LM) and later (lTNBC-LM). We hope our study will help in the risk stratification of patients with TNBC-LM and assist in making treatment strategy. We present the following article in accordance with the TRIPOD reporting checklist.

2. Materials and methods

2.1. Study population

BC patients diagnosed from 2010 to 2018 were searched in the SEER database, and clinicopathologic data were collected. The eligibility criteria included: (1) pathological confirmation of ER, PR and HER2 negativity and (2) complete follow-up information. The exclusion criteria were as follows (1) age < 18 years or > 100 years, (2) tumours undetected (T0) or in situ (Tis), and (3) unknown race, marital status, laterality, T/N stage, differentiation grade, or metastasis status/site.

A total of 615 nTNBC-LM patients were eligible for further analysis. Among them, 515 patients diagnosed from 2010 to 2016 were used to construct the model as the training cohort. The 100 patients from 2017 to 2018 were assigned to the validation cohort and validate the clinical model.

For the extended cohort, 88 lTNBC-LM patients, from 2002 to 2013, who met the same criteria as above were enrolled from the Fifth Affiliated Hospital of Sun Yat-Sen University (FAFSYU) database.

This study was approved by the Ethics Committee of FAFSYU and was conducted in accordance with the principles of Helsinki Declaration. Since this is a retrospective analysis, we waived the requirement for patient's informed consent.

2.2. Selection of variables

Information on the following clinicopathologic variables was collected: age, marital status, race, T stage, N stage, differentiation grade, pathologic histology, laterality, extrahepatic metastasis (brain, lung and bone), surgery (on the breast tumour of primary site), chemotherapy, radiotherapy (on the primary tumour), and survival time. Specifically, the period between the time of detection of LM and the time of death was defined as survival time, for the extended cohort, and the age at diagnosis of LM was used for further analysis. The use of chemotherapy after LM, not the diagnosis of TNBC, was selected as a variable for further study.

2.3. Statistical analysis

In the present research, factors associated with the OS of TNBC patients with LM were determine by performing Cox regression analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) were also calculated. For visually present the model, a prognostic nomogram predicting the survival probability at 6 months, 1 year, and 2 years was developed, and its sensitivity and specificity was assessed by the C-index and calibration curves. The Kaplan–Meier method and log-rank tests were used to estimate survival time. R software was used for all the statistical analyses. Differences were considered significant at a two-sided $p < 0.05$.

3. Results

3.1. Population characteristics

In present study, 615 patients with nTNBC-LM from the SEER database and 88 patients with lTNBC-LM from the FAFSYU database

were included to constructed and validated the prognostic nomogram. The baseline characteristics of the population are presented in Tables 1 and 2.

3.2. Prognostic analysis of TNBC patients with LM at initial diagnosis

Potential prognostic factors in nTNBC-LM patients were analysed by Cox regression analysis. More advanced age (HR:1.014, 95% CI:1.008–1.021, $p < 0.001$) and extrahepatic metastases (including brain, bone and lung metastases) (HR:1.698, 95% CI:1.286–2.243, $p < 0.001$; HR:1.323, 95% CI:1.102–1.589, $p < 0.001$; HR:1.526, 95% CI:1.275–1.827, $p < 0.001$, respectively) were found to be significantly associated with an earlier death. Prolonged survival was also detected in patients who were married (HR = 0.725, 95% CI = 0.605–0.869, $p < 0.001$). Regarding anticancer treatment, surgery (HR = 0.575, 95% CI = 0.477–0.693, $p < 0.001$) or chemotherapy (HR = 0.309, 95% CI = 0.249–0.382, $p < 0.001$) confer a significantly extended survival duration for nTNBC-LM patients; however, no significant association was found between patients who received radiation on primary tumour and those who did not (HR = 0.832,

Table 1
Demographics and clinicopathologic characteristics of invasive triple-negative breast cancer patients in SEER database.

Variables	All patients, (n = 46,902)	2010–2016 With Liver metastasis (Training) (n = 515)	2017–2018 With Liver metastasis (validation) (n = 100)	Without Liver metastasis (n = 46,287)
Age, median (IQR)	59 (49, 69)	59 (49.5, 69)	62 (51,70)	59 (49,69)
Race, n (%)				
White	33674 (71.8)	367 (71.2)	69 (69.0)	33238 (71.8)
Black	9613 (20.5)	123 (23.9)	29 (29.0)	9461 (20.4)
Asian&Pacific Islander	3349 (7.1)	22 (4.3)	2 (2.0)	3325 (7.2)
American Indian&Alaska Nativ	266 (0.6)	3 (0.6)	0 (0)	263 (0.6)
T stage, n (%)				
I	21179 (45.2)	60 (11.7)	9 (9)	21110 (45.6)
II	19118 (40.8)	156 (30.3)	32 (32.0)	18930 (40.9)
III	3766 (8.0)	97 (18.8)	21 (21.0)	3648 (7.9)
IV	2839 (6.0)	202 (39.2)	38 (38.0)	2599 (5.6)
Nodal status, n (%)				
N0/N1	42134 (89.8)	352 (68.3)	61 (61.0)	41721 (90.1)
N2/N3	4768 (10.2)	163 (31.7)	39 (39.0)	4566 (9.9)
Marital, n (%)				
Single	20734 (44.2)	284 (55.2)	59 (59.0)	20391 (44.1)
Married	26168 (55.8)	231 (44.8)	41 (41.0)	25896 (55.9)
Grade, n (%)				
I	884 (1.9)	4 (0.8)	1 (1.0)	879 (1.9)
II	8344 (17.8)	92 (17.8)	12 (12.0)	8240 (17.8)
III	37419 (79.8)	414 (80.4)	87 (87.0)	36918 (79.8)
IV	255 (0.5)	5 (1.0)	0 (0.0)	250 (0.5)
Laterality, n (%)				
Left	24095 (51.37)	268 (52.0)	49 (49.0)	23778 (51.37)
Right	22797 (48.61)	244 (47.4)	50 (50.0)	22503 (48.62)
Bilateral	10 (0.02)	3 (0.6)	1 (1.0)	6 (0.01)
Histologic Type, n (%)				
IDC	43005 (91.7)	475 (92.2)	91 (91.0)	42439 (91.7)
ILC	633 (1.3)	12 (2.3)	0 (0.0)	621 (1.3)
Other	3264 (7.0)	28 (5.5)	9 (9.0)	3227 (7.0)
With Brain Metastasis, n (%)				
No	46689 (99.5)	457 (88.7)	92 (92.0)	46140 (99.7)
Yes	213 (0.5)	58 (11.3)	8 (8.0)	147 (0.3)
With Lung Metastasis, n (%)				
No	46051 (98.2)	319 (61.9)	64 (64.0)	45668 (98.7)
Yes	851 (1.8)	196 (38.1)	36 (36.0)	619 (1.3)
With Bone Metastasis, n (%)				
No	45949 (98.0)	268 (52.0)	43 (43)	45638 (98.6)
Yes	953 (2.0)	247 (48.0)	57 (57)	649 (1.4)
Surgery, n (%)				
No	3211 (6.9)	324 (62.9)	69 (69.0)	2818 (6.1)
Yes	43691 (93.1)	191 (37.1)	31 (31.0)	43469 (93.9)
Radition, n (%)				
No/unkown	24237 (51.7)	385 (74.8)	74 (74.0)	23778 (51.4)
Yes	22665 (48.3)	130 (25.2)	26 (26)	22509 (48.6)
Chemotherapy, n (%)				
No/unkown	12198 (26.0)	121 (23.5)	22 (22.0)	12055 (26.0)
Yes	34704 (74.0)	394 (76.5)	78 (78.0)	34232 (74.0)

SEER: Surveillance, Epidemiology, and End Results; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; IQR: interquartile range.

Table 2
Demographics and clinicopathologic characteristics of invasive triple-negative breast cancer patients in FAFSYU database.

Variables	Patients with Liver metastasis latter (Extended group) (n = 88)
Age, median (IQR)	50 (41.8, 56)
Marital, n(%) rowhead	
Single	35 (39.8)
Married	53 (60.2)
With Brain Metastasis, n(%) rowhead	
No	78 (88.6)
Yes	10 (11.4)
With Lung Metastasis, n(%) rowhead	
No	55 (62.5)
Yes	33 (37.5)
With Bone Metastasis, n(%) rowhead	
No	48 (54.5)
Yes	40(45.5)
Surgery, n(%) rowhead	
No	9 (10.2)
Yes	79 (89.8)
Chemotherapy, n(%) rowhead	
No/unkown	26 (29.5)
Yes	62 (70.5)

FAFSYU: Fifth Affiliated Hospital of Sun Yat-Sen University; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; IQR: interquartile range.

95% CI = 0.677–1.023, p=0.081) (Fig. 1A). Multivariate Cox regression analysis was performed to further analyse the associations between significant factors above and the survival of nTNBC-LM patients. Age (older age: HR = 1.007, 95% CI = 1.000–1.014, p = 0.039), marital status (married: HR = 0.791, 95% CI = 0.658–0.950, p = 0.012), extrahepatic metastasis (including brain and bone) (brain: HR = 1.488, 95% CI = 1.111–1.992, p=0.008; bone: HR = 1.224, 95% CI = 1.015–1.476, p = 0.034), surgery (HR = 0.637, 95% CI = 0.524–0.773, $p < 0.001$) and chemotherapy (HR = 0.352, 95% CI = 0.280–0.443, $p < 0.001$) were further confirmed to be independently associated with the prognosis of nTNBC-LM patients (Fig. 1B). The results are shown in Table 3.

Based on the significant factors above, a prognostic model was developed to predict the 6-month, 1-year, and 2-year OS of nTNBC-LM patients (Fig. 2). The weighted contribution of each predictive factor was assessed to calculate the OS probabilities at 6 months, 1 year, and 2 years.

3.3. Calibration and validation of the nomogram for predicting the prognosis of nTNBC-LM patients

To assess the predictive accuracy of the prognostic nomogram, we employed both the C-index and calibration curves in both training and validation cohorts. In the training cohort, the C-index for predicting prognosis using the clinical model reached 0.712 (95% CI: 0.688–0.736). Furthermore, calibration curves demonstrated good alignment between predicted and observed outcomes at 6 months, 1 year, and 2 years (Fig. 3A–C, E). In the validation group, the C-index of the model was 0.803 (95% CI, 0.744–0.862).

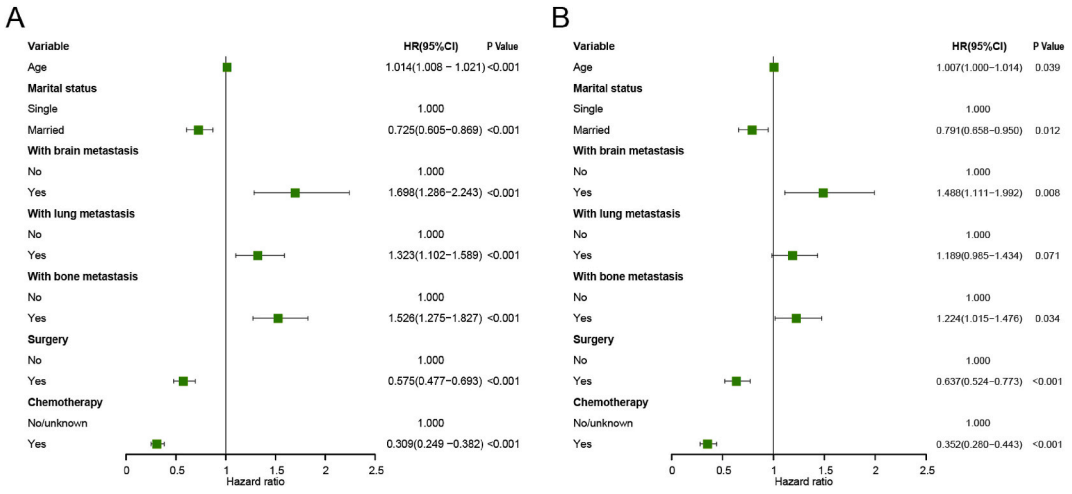

Fig. 1. Forest plot for the potential prognostic factors for overall survival in triple-negative breast cancer patients with liver metastasis at diagnosis by (A) univariate cox analysis and (B) multivariate cox analysis.

Table 3
Univariate and multivariate cox analysis of overall survival of the training cohort.

Variables	Univariate analysis			Multivariate analysis		
	HR	95%Cl	*p-value*	*HR*	95%Cl	*p-value*
Age	1.02	1.012–1.028	<0.001	1.009	1.000–1.017	0.029
Race						
White	1.000					
Black	1.178	0.937–1.481	0.162			
Asian&Pacific Islander	1.319	0.754–2.309	0.332			
American Indian&Alaska Nativ	1.689	0.236–12.065	0.602			
T stage						
I ~ III	1.000					
IV	1.354	1.104–1.660	0.004	1.348	1.090–1.667	0.006
Nodal status						
N0	1.000					
N+	0.771	0.600–0.992	0.043			
Marital status						
Single	1.000			1.000		
Married	0.700	0.57–0.860	<0.001	0.856	0.690–1.061	0.155
Laterality						
Left	1.000					
Right	1.152	0.943–1.408	0.165			
Bilateral	0.954	0.134–6.817	0.963.			
Histologic type						
IDC	1.000					
ILC	1.729	0.714–4.185	0.225			
Other	0.830	0.539–1.278	0.396			
Extrahepatic metastasis sites						
0	1.000			1.000		
1	1.383	1.092–1.752	0.007	1.396	1.096–1.778	0.007
2	2.293	1.720–3.058	<0.001	2.095	1.556–2.821	<0.001
3	3.350	2.076–5.406	<0.001	3.729	2.234–6.223	<0.001
Surgery						
No	1.000			1.000		
Yes	0.615	0.498–0.760	<0.001	0.733	0.586–0.916	0.006
Radiation						
N/unknown	1.000					
Yes	0.873	0.692–1.101	0.251			
Chemotherapy						
NO/unknown	1.000			1.000		
Yes	0.200	0.156–0.257	<0.001	0.248	0.188–0.327	<0.001

IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; IQR: interquartile range; CI: confidence interval; HR: hazard ratios.

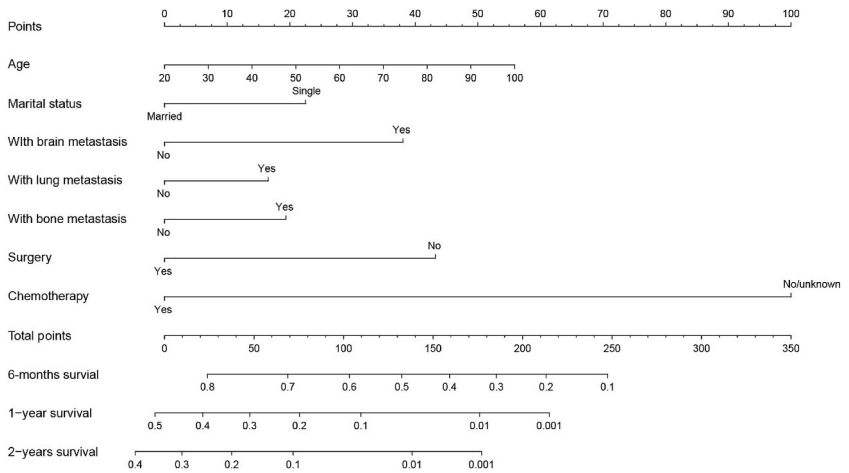

Fig. 2. Nomograms for predicting 6-month, 1-year, and 2-year overall survival of triple-negative breast cancer patients with liver metastasis at diagnosis.

Visually, the calibration curves for survival probabilities at 6 months, 1 year, and 2 years showed a precise overlap between the predicted OS probabilities and the actual outcomes for nTNBC-LM patients (Fig. 3B–D, F). These findings underscore the clinical relevance and reliability of this model in prognosticating the outcomes of nTNBC-LM patients.

3.4. Validation of the nomogram for predicting the prognosis of lTNBC-LM patients

Eighty-eight lTNBC-LM patients were also included in our study as an extension group to explore whether the nomogram was able to predict the OS of TNBC patients diagnosed LMs at later disease course. The model showed acceptable predictive accuracy and clinical applicability, as indicated by a C index of 0.699 (95% CI = 0.642–0.756), and the calibration curves also demonstrated a favorable consistency between the nomogram predictions and the observed outcomes of 6-month, 1-year, and 2-year OS in lTNBC-LM patients (Fig. 4A, B, C).

3.5. Survival analysis based on treatment in TNBC patients with LM at initial diagnosis

To further evaluate the survival advantage of the treatment, survival curves were plotted to show the prognostic efficacy of surgery, chemotherapy and radiotherapy directly in 615 nTNBC-LM patients. The results showed that patients who underwent surgery (median OS: 13 months vs. 7 months) on primary tumour or chemotherapy (median OS: 12 months vs. 2 months) exhibited significantly longer survival time. However, no significant difference in OS was found between TNBC-LM patients who received radiotherapy and those who did not (median OS: 10 months vs. 8 months) (Fig. 5A, B, C).

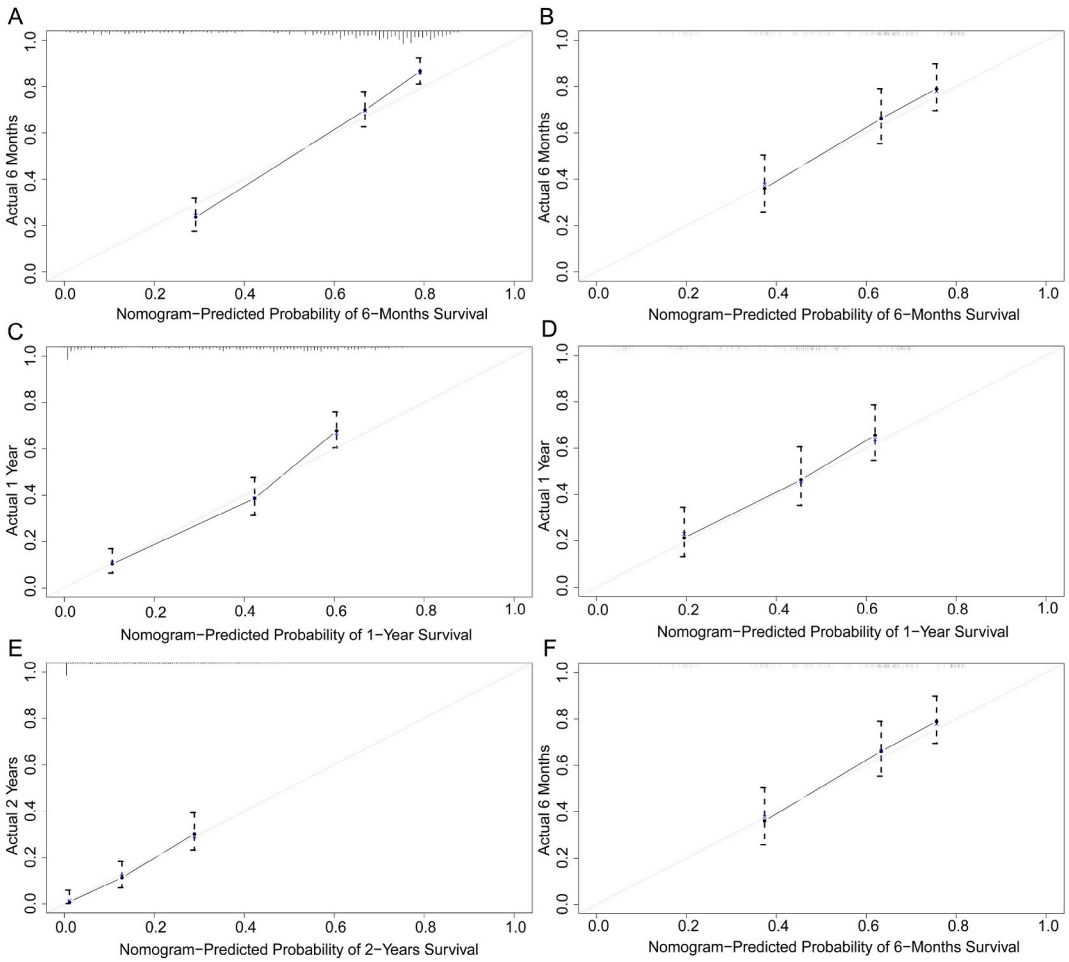

Fig. 3. The calibration curve for predicting patient survival at (A) 6 months, (C) 1 year, and (E) 2 years in the training cohort and at (B) 6 months, (D)1 year, and (F)2 years in the validation cohort. Nomogram-predicted probability of overall survival is plotted on the x-axis; actual overall survival is plotted on the y-axis.

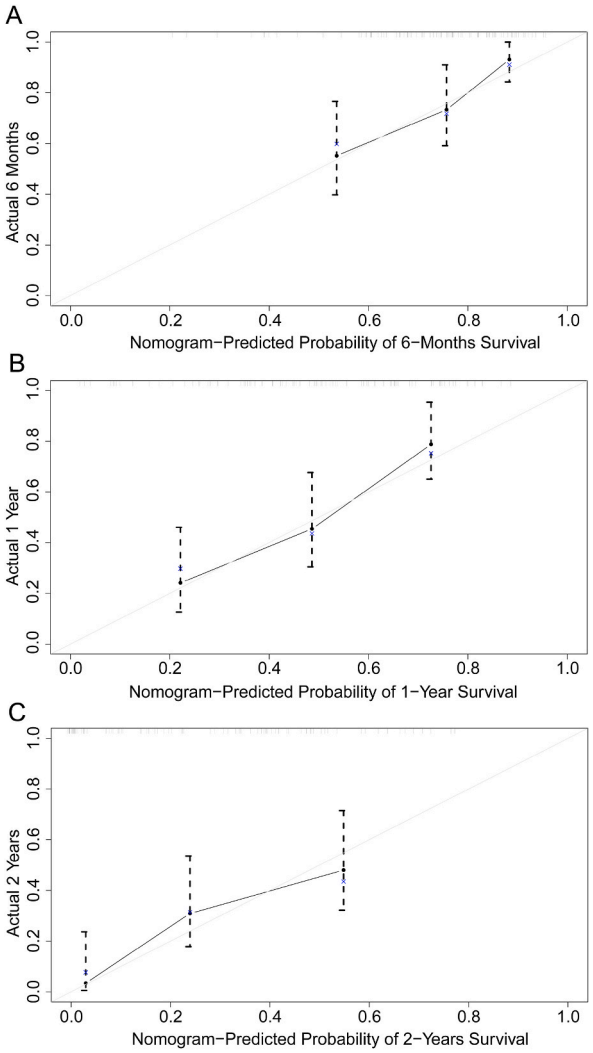

Fig. 4. The calibration curve for predicting patient survival at (A) 6 months, (B) 1 year, and (C) 2 years in the extended cohort (TNBC patients with liver metastasis during latter disease course).

4. Discussion

Due to its high invasiveness and aggressiveness, TNBC is a distinct entity in BC [15,16]. Among BCLM patients, TNBC patients with LM have the worst prognosis, and it is still a challenge for clinicians to stratify patients according to prognosis and predict the outcome of TNBC-LM patients, although great efforts have been made by researchers [5,10–13]. Therefore, a clinical model based on a large population for predicting the survival of TNBC-LM patients is warranted. Hence, in our study, a prognostic nomogram was developed and validated to predict OS at 6 months, 1 year, and 2 years in nTNBC-LM patients. Moreover, our model was validated in an extended cohort and showed acceptable accuracy in predicting the OS of lTNBC-LM patients.

Age, marital status, extrahepatic metastasis (including brain and bone), surgery and systemic chemotherapy were found to be associated with better prognosis in nTNBC-LM patients according to multivariate Cox regression analysis significantly and be independent prognostic factors. Advanced age has been found to be associated with poorer prognosis in BC patients with LM.[10-13]Among the MBC patients with a dismal prognosis, those who were younger tended to have better Karnofsky performance scores and fewer complications [17], which allowed them to receive more and/or more aggressive systemic treatment (e.g. chemotherapy) after the diagnosis of LM. Marital status was another independent variable correlated with improved prognosis in nTNBC-LM patients. This may be influenced by economic and social psychological variables. More stable financial support from spouses or partners of married patients may be an important reason for patients' better treatment adherence. A study enrolling 5709 patients revealed that more patients in the married group had medical insurance [18]. Psychosocially, single patients face more distress, depression and anxiety due to less companionship and comfort [19], and these negative emotions have been suggested to facilitate tumour progression and influence treatment efficacy [20,21]. Extrahepatic metastasis (including brain, lung and bone metastasis) was also found to be an

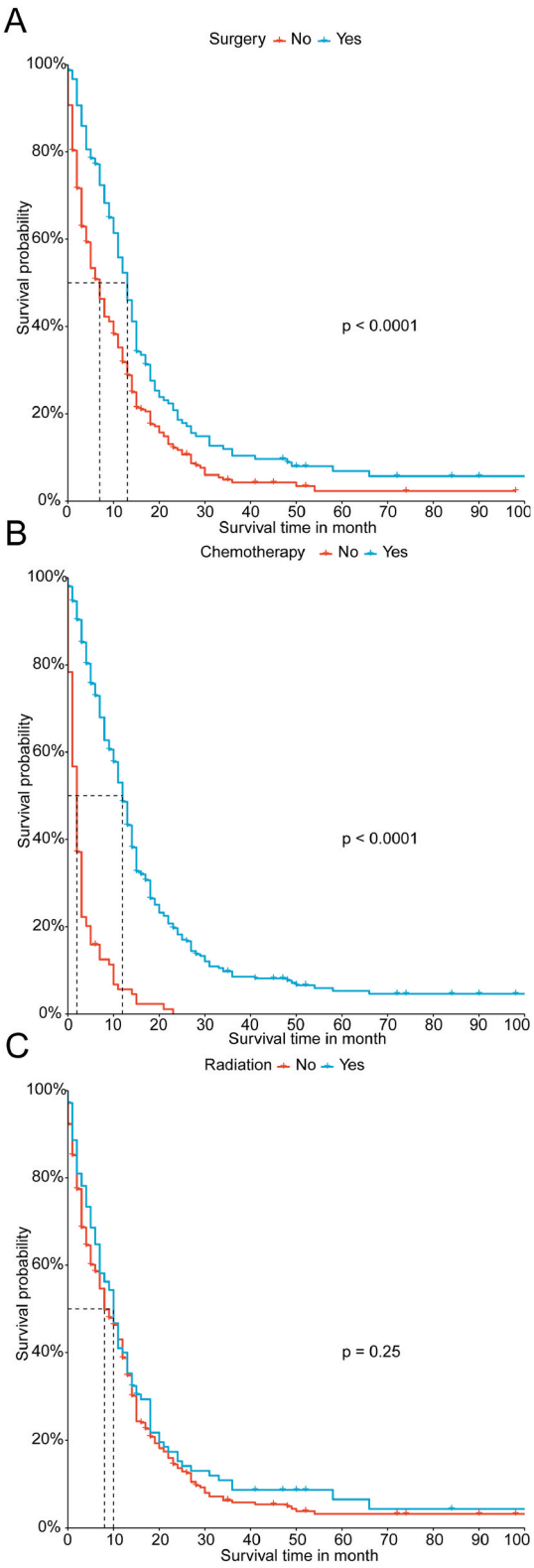

Fig. 5. Kaplan–Meier survival curve for overall survival in triple-negative breast cancer patients with liver metastasis at diagnosis, stratified by (A) surgery, (B) chemotherapy, (C) radiotherapy.

independent prognostic variable. TNBC patients with more organs metastases have a heavier tumour burden and greater tumour heterogeneity and thus are more susceptible to treatment resistance. Unexpectedly, lung metastasis was no longer significant according to multivariate Cox regression analysis, which may be due to the sample size.

In terms of therapy, we found that nTNBC-LM patients who received palliative surgery or systemic chemotherapy exhibited significantly longer survival (in months), but no difference was found in radiotherapy. Previously, palliative surgery on the primary tumour in MBC patients was performed only to relieve symptoms. When diagnosed with distant metastasis, patients are believed to have lost the opportunity for surgery, and the only option is receiving systemic therapy [22]. However, a prospective clinical trial recently reported a 34% lower risk of death and a 17.2% greater 5-year OS in patients with MBC at initial diagnosis who underwent surgical resection of the primary tumour than in patients who did not [23]. Moreover, based on large cohorts, multiple retrospective studies have showed that BCLM patients may achieve significantly better prognoses after primary tumour resection.[10,12,13]Moreover, chemotherapy was significantly correlated with improved OS in LM patients in our study. According to the latest clinical guidelines, chemotherapy, including BCLM, remains a cornerstone treatment for metastatic breast cancer [24]. In addition, studies have shown that TNBC patients show significantly greater response than patients with the luminal subtype after receiving neoadjuvant chemotherapy, and this treatment is associated with a better survival in patients with TNBC [25,26]. Thus, future researches should explore the appropriate chemical drugs and optimize chemotherapy strategy to improve outcomes and prognosis in TNBC patients with LM.

Here, a model was developed to predict the prognosis of TNBC-LM patients, leveraging significant variables identified by Cox regression analysis. To assess the predictive power of our model, the C-index was computed, and calibration plots were generated. Our prognostic nomogram achieved C-index values of 0.707 and 0.801 in the training and internal validation cohorts, respectively. According to previous studies, a nomogram with a C-index exceeding 0.7 is considered to possess satisfactory sensitivity and specificity [27]. Furthermore, the reliability of our nomogram was evident from the calibration curves, which demonstrated excellent alignment between predicted and observed outcomes in both cohorts. In the extended group, although the C-index of 0.685 was slightly below 0.7, this may be attributed to the relatively small sample size. Nevertheless, the calibration curves still exhibited favorable consistency. Therefore, the model developed in our present study performs well in predicting the survival of patients with TNBC-LM at initial diagnosis or later. This is a rare study involving the construction of a visual clinical model aimed at improving the prognosis of both nTNBC-LM and lTNBC-LM patients, and we hope that this model can aid in risk stratifying and clinical decision making.

Limitations exist in our present study. First, this study was retrospective, inherently carrying some unavoidable bias. Second, the study focused on a relatively small cohort from a single centre in the extended cohort, and larger population from multiple centres are needed. Third, clinicopathological factors, such as the number and size of liver metastases, which have been previously identified as prognostic variables in BCLM patients [28], may potentially impact the survival outcomes of TNBC-LM patients and therefore deserve consideration in our future studies. Unfortunately, these crucial details were not available in the SEER database, thus limiting their inclusion in our current model. However, the prognostic effects of these factors in TNBC-LM patients deserve further research. Fourth, there have been a tendency of precision and individualization in the treatment of patients with cancer, and multiple mechanism was found to be involved in the BCLM and these may be potential target of patients [29–32]. Our present study was a clinical trial without the further exploration of the mechanism, so more efforts are needed in experimental research.

5. Conclusions

In conclusion, age, marital status, extrahepatic metastasis (including brain, lung and bone), surgery and systemic chemotherapy were found to be associated with prognosis in nTNBC-LM patients; of these factors, all but lung metastasis were independent prognostic factors. Based on these results, our study are the first to established and validate a model for predicting prognosis in TNBC-LM patients, including those with LM at initial treatment or later, and this model can help stratify patients for further treatment and develop a more appropriate treatment strategy.

Clinical practice points

For lacking a tool to predict the survival of TNBC patients with LM, it is difficult for clinicians to stratify patients according to prognosis and make therapeutic strategies.

We are the first to construct and validate a sensitive and discriminative model for overall survival at 6 months, 1 year, and 2 years in TNBC patients who were diagnosed with liver metastasis at initial treatment or later.

This model may provide a valuable reference for clinicians to stratify patients for further treatment and develop a more appropriate treatment strategy.

Ethics statement

The ethical review was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-Sen University(K135-1).

Data availability statement

No. Data will be made available on request.

The data in training and internal validation cohort is available at https://seer.Cancer.gov/. The data from FAFSYU database are available on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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CRediT authorship contribution statement

Liguo Zhang: Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Zhen Qiao:** Visualization, Validation, Data curation, Conceptualization. **Yinsheng Yao:** Validation, Formal analysis. **Zhiqiang Li:** Validation, Formal analysis. **Lingzhi Hu:** Visualization, Validation, Formal analysis, Data curation. **Yinyan Mao:** Data curation. **Xiuling Liu:** Validation. **Weirong Chen:** Supervision, Data curation, Conceptualization. **Qing'an Zeng:** Writing – review & editing, Supervision, Funding acquisition. **Hong Zhao:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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