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Research Paper

A Nomogram for Distinction and Potential Prediction of Liver Metastasis in Breast Cancer Patients

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Abstract

Liver metastasis from breast cancer has poor prognosis. We aimed at developing a reliable tool for making a distinction and prediction for liver metastasis in breast cancer patients, thus helping clinical diagnosis and treatment. In this study, totally 6238 patients from SEER database with known distant metastasis status and clinicopathologic variables were enrolled and divided randomly into training and validating groups. Logistic regression was used to screen variables and a nomogram was constructed. After multivariate logistic regression, sex, histology type, N stage, grade, age, ER, PR, HER2 status as significant variables for constructing the nomogram. The nomogram for distinguishing and predicting liver metastasis in breast cancer passed the calibration and validation steps and the areas under the receiver operating characteristic curve of the training set and the validation set were 0.6602 and 0.6511 respectively. Our nomogram is a reliable and robust tool for the distinction and prediction of liver metastasis in breast cancer patients, thus helping better choose medical examinations and optimize therapeutic regimen under the cooperation among medical oncologists and surgeons.

Key words: liver metastasis, breast cancer, nomogram, SEER

Introduction

Breast cancer was the leading cancer type for females in US and worldwide which ranked the second in contributing to cancer death in women [1, 2]. Approximately more than 30% of breast cancer patients would present with distant non-nodal metastases [3]. Breast cancer liver metastases (BCLM) are frequent in the clinical course of breast cancer and the liver represents the third most frequent site for breast cancer metastases [4], however, BCLM are considered most lethal compared with other sites of metastases (e.g., the lung, bone, or brain), with 5-year survival rates of only 3.8–12 % (median survival, 4–21 months) [5] and treatment options are usually restricted to palliative systemic therapy [6]. Also, liver metastases are more likely to develop in patients with subtypes like ER/PR-negative in which hormonal therapy is rarely successful [4]. Moreover, Liver metastases may present asymptomatically during a metastatic screen and the survival time is only 4-8 months for breast cancer patients if liver metastasis status was ignored [7, 8]. In fact, all breast cancer patients were in the risk of liver metastasis so it is also important for clinicians to figure out whether the patient have a tendency to have liver metastasis, to take precautions and work out a treatment strategy in the cooperation among medical oncologists and surgeons from both the departments of breast and liver cancer.

On the other hand, as is well known, breast cancer is a heterogeneous disease which is characterized by diverse histopathologic and molecular features that are associated with distinct

clinical outcomes [4]. There have been reports that pathological and biological parameters could be used for predicting individual overall survival or recurrence in breast cancer patients [9, 10]. We hypothesized that liver metastasis could also be distinguished with clinicopathological variables. In this study, we have two objectives. The primary objective was to pick out significant variables and find high risk factors related to liver metastasis. The secondary objective was to construct a predictive model with these variables which could help distinguish liver metastasis and look into its correlation with survival. A well-developed clinical nomogram is a popular decision-tool, which can be used to predict the outcome of an individual, bringing benefits to both clinicians and patients [11]. Thus, we screened and picked out breast cancer patients with distant organ metastasis from Surveillance, Epidemiology, and End Results (SEER) database and created a nomogram with significant variables which proved reliable for quantifying the risk for liver metastasis. Also, the likelihood of whether a patient had a higher risk of liver metastasis could also be used as an independent predicting factor for survival outcomes. Aiding with this tool, clinicians might be able to assess the risk of liver metastasis in breast cancer patients, thus choosing appropriate medical examinations to diagnose and optimized therapeutic regimen to treat.

Methods

Data source and inclusion criteria

We used SEER data released in April 15th, 2016 which covers approximately 30% of U.S. population and includes cases from 18 population-based registries (1973-2013) with routinely collected patient demographics, primary tumor site, tumor morphology, stage at diagnosis and follow-up for vital status. The data from SEER does not need informed patient consent and no case identifying information is provided by the SEER cancer registries. The inclusion criteria for selecting cases were as follows: primary malignant breast cancer patients who had distant metastasis (M1 stage) at diagnosis during 2010 to 2013. Some patients had more than one organ affected, but altogether we selected 6238 patients in model construction after ruling out those whose liver involvement condition was not available.

Nomogram construction and validation

We extracted the following variables into this research: T, N stage (derived AJCC stage group 7th edition, 2010), sex, race, histologic type, grade, ER status, PR status, HER2 status, Age at diagnosis, tumor size and marital status. We did a raw logistic regression in all patients and picked out significant variables. We analyzed and releveled some of the variables taking into account the data size, variable performance and frequency of occurrence in clinical manifestation. Histological type was categorized as duct carcinoma and lobular carcinoma or others. We combined grade IV and grade III together to optimize the model. Patients whose ER, PR or HER2 status is unknown or ER or PR in borderline were discarded. Moreover, we reassigned patients into size groups as less than 20 millimeters, between 20 and 50 millimeters, more than 50 millimeters. The outcome variable was liver metastasis and the study aimed at distinguishing liver involvement from other remote metastasis patients and predicting liver metastasis possibility when remote metastasis occurred.

Afterwards, we randomly divided all these patients into 1:1 training and validating groups. the training and validation groups were both made up of metastasis patients and a small portion of them had liver involvement. Multivariable logistic regression was performed in training group to distinguish liver metastasis and all the variables selected above were significant ($P<0.05$). The fitness of the model was assessed by the Hosmer and Lemeshow test. If $P>0.05$ (assuming $\alpha = 0.05$), we conclude that the logistic regression model is a good fit [12]. Then we constructed a nomogram with each predictor assigned to a point whose value ranging from 0 to 100 and the most significant predictor sex was identified as the reference. The other factors were then assigned based on their proportion to the reference axis.

Evaluating nomogram performance.

We validated the model both internally in training group and externally in validating group. First, a calibration method with bootstrapping was utilized internally to illustrate the association between the actual probability and the predicted probability. We have a calibration plot in which apparent, bias-corrected and ideal curves was demonstrated presented with bootstrapping samples. The external method was carried out in validating group by calculating AUC, the area under the receiver operating characteristic (ROC) curve [13]. The training group also had the receiver operation characteristic curve plotted. DeLong method was then performed and there was no significant difference between ROC curves in training and validating group [14]. Calibration and ROC curves was demonstrated in results part.

Other statistical methodologies

Demographic patient baseline characteristics were compared among the marital status groups with

χ^2 test and Wilcoxon-Mann-Whitney test. Kaplan-Meier curves were plotted and Log rank (Mantel-Cox) test was applied to compare the OS in between the groups. We utilized multivariable Cox regression models to analyze the relationship between the prognostic factors and survival outcomes. Overall survival (OS) was defined from the date of diagnosis to the date of death, with death of any cause treated as event. As to survival months, any follow-up beyond the study cutoff will be ignored, i.e., if the date of last contact is later than the study cutoff date, the study cutoff date would be treated as date of last contact. And December 31, 2013 was the cut-off date in this study. All of these statistical methods were performed by IBM SPSS Statistics, version 20 (SPSS Inc, Chicago, IL, USA) or R software version 3.2.1 (http://www.r-project.org) [15-18]. All P values were two-sided and statistical significance was set at P<0.05. All confidence intervals (CIs) were stated at the 95% confidence level.

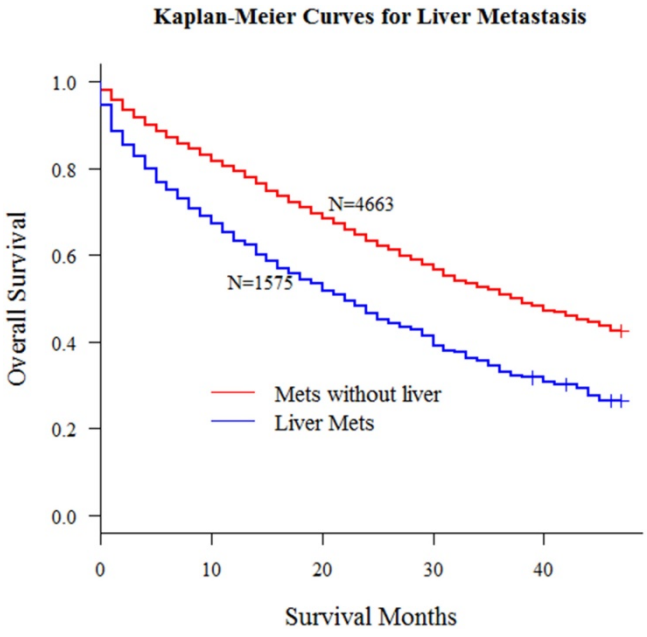

Fig 1. Kaplan-Meier curves for metastatic patients with or without liver metastasis (P < 0.001)

Results

Demographic baseline characteristics

According to the inclusion criteria mentioned in methods, we obtained 6238 patients with distant metastasis from SEER database. In this study, all patients' liver metastasis status at diagnosis was known. Kaplan-Meier curve in Fig 1 demonstrated the significant survival difference between patients with or without liver metastasis.

Table 1. Clinicopathological variables for patients with four metastatic types

	Liver Metastasis		Chi-square	P value
Variables	**Yes**	**No**		
Age (Mean)	57.99	60.78	45.609*	<0.001
Sex				
Female	1566	4595	7.596	0.006
Male	9	68		
Grade				
I	73	395	82.01	<0.001
II	549	2031		
III	943	2203		
IV	10	34		
Laterality				
Left	818	2391	0.206	0.65
Right	757	2272		
Histology				
Duct	1403	3827	42.676	<0.001
Lobular	172	836		
T				
T1	223	664	2.377	0.667
T2	584	1787		
T3	311	884		
T4	457	1324		
N				
N0	363	1066	22.239	<0.001
N1	774	2074		
N2	221	649		
N3	217	874		
Size				
20-	263	791	3.892	0.143
20-50	728	2268		
50+	584	1604		
ER Status				
Negative	553	982	125.304	<0.001
Positive	1022	3681		
PR Status				
Negative	798	1589	137.168	<0.001
Positive	777	3074		
HER2 Status				
Borderline	42	130	204.004	<0.001
Negative	924	3570		
Positive	609	963		
Race				
Black	300	746	8.005	0.018
Others	124	366		
White	1151	3551		
Marital Status				
Married	719	2081	0.559	0.756
Unmarried	776	2348		

*ANNOVA F-Value

Table 1 showed the clinicopathologic characteristics of all patients. There were two columns in this table which corresponded to patients who had liver metastasis or not. We did Pearson Chi-square test in this table and the result told that for different metastatic sites, there was significant difference in patients for variables including sex (P = 0.006), grade (P<0.001), histology (P<0.001), N stage (P<0.001), estrogen receptor (ER) status (P<0.001), progesterone receptor (PR) status (P<0.001), human epidermal growth factor receptor 2 (HER2) status (P<0.001), race (P=0.018). As for age, we compared the mean values between the groups and utilized ANOVA (analysis of variance) which presented significant P value (<0.001)

as well. The significant presentation implied that it is possible to predict the possibility of liver metastasis when a patient's clinicopathologic characteristics were clearly given. We could summarize some interesting findings from this table. For example, patients who had breast cancer metastasized to liver were comparatively younger than others and this was consistent with the regression and nomogram model in the discussion below.

Table 2. Raw logistic regression results for all variables

Variables	Coefficient	Std. Error	P value
Sex			
Male	-0.7699	0.287	0.0334
Female	Reference		
Histology			
Lobular	-0.2669	0.362	0.005
Duct	Reference		
T			
T1	0.2263	0.2071	0.2744
T2	0.0888	0.1109	0.4233
T3	-0.0387	0.0981	0.6929
T4	Reference		
N			
N0	0.522	0.1045	<0.0001
N1	0.4861	0.0904	<0.0001
N2	0.3601	0.1124	0.0014
N3	Reference		
Grade			
I	-0.135	0.1397	0.3341
II	Reference		
III	0.1968	0.0678	0.0037
IV	-0.1457	0.3732	0.6963
ER Status			
Positive	-0.2744	0.0877	0.0018
Negative	Reference		
PR Status			
Positive	-0.3081	0.0814	0.0002
Negative	Reference		
HER2 Recode			
Borderline	-0.4871	0.1888	0.0099
Negative	-0.6962	0.0668	<0.0001
Positive	Reference		
Age			
Plus 1	-0.0105	0.0022	<0.0001
Size			
50+	0.3031	0.2017	0.133
20-50	0.0892	0.2137	0.6763
20-	Reference		
Race			
Others	-0.1379	0.1297	0.2879
White	-0.0919	0.0811	0.2574
Black	Reference		
Marital Status			
Married	0.0487	0.0643	0.4491
Unknown	-0.0003	0.1408	0.9984
Unmarried	Reference		

Multivariate logistic regression results

We performed a raw logistic regression model with all variables from Table 1. Coefficients, standard errors, P values for each was calculated and documented in Table 2. Then we picked out significant variables including age, sex, histological type, N stage, grade, ER status, PR status and HER2 status. Afterwards, 1:1 randomly assigned training and validating groups was divided and we put these significant variables into another logistic model in the training group. It turned out that all variables selected presented with significant P value. Speaking of coefficients, sex was the most significant predictor, much more significant than any other. N0 and N1 stages had P values below 0.0001, N2 had P value 0.0004. HER2 positive also had P value below 0.0001. Age was another highly significant predictor whose P value was 0.0005. Comparatively, ER status and grade performed a little worse but still had P value below 0.05. This was the fundamental step for model construction for a well fitted regression model leaded to a useful and reliable predicting nomogram.

Table 3. Final Logistic Regression for significant variables

Variables	Coefficient	Std. Error	P value
Sex			
Male	-1.0868	0.5332	0.0415
Female	Reference		
Histology			
Lobular	-0.3994	0.1394	0.0042
Duct	Reference		
N			
N0	0.5725	0.1457	<0.0001
N1	0.5549	0.1301	<0.0001
N2	0.5762	0.1617	0.0004
N3	Reference		
Grade			
I	-0.3981	0.2007	0.0474
II	-0.198	0.0948	0.0367
III/IV	Reference		
ER Status			
Positive	0.2468	0.123	0.0448
Negative	Reference		
PR Status			
Positive	0.366	0.1138	0.0013
Negative	Reference		
HER2 Recode			
Unknown	0.0306	0.2414	0.8991
Positive	-0.571	0.0949	<0.0001
Negative	Reference		
Age			
Plus 1	-0.0106	0.0031	0.0005

Nomogram construction and validation

Results of logistic regression model in Table 3 were utilized to construct a nomogram (Fig 2). Sex, the variable which had the largest coefficients absolute value was set as reference whose scale range was from 0 to 100. Each predictor had its factors with points and marks on its line according to the scale above. From this nomogram, total points would be summed and then be converted to the probability for liver metastasis as there were parallel lines below the fig whose scales had linear relationship with each other. The Hosmer and Lemeshow test told the P value was 0.6679 indicating the model was well fitted.

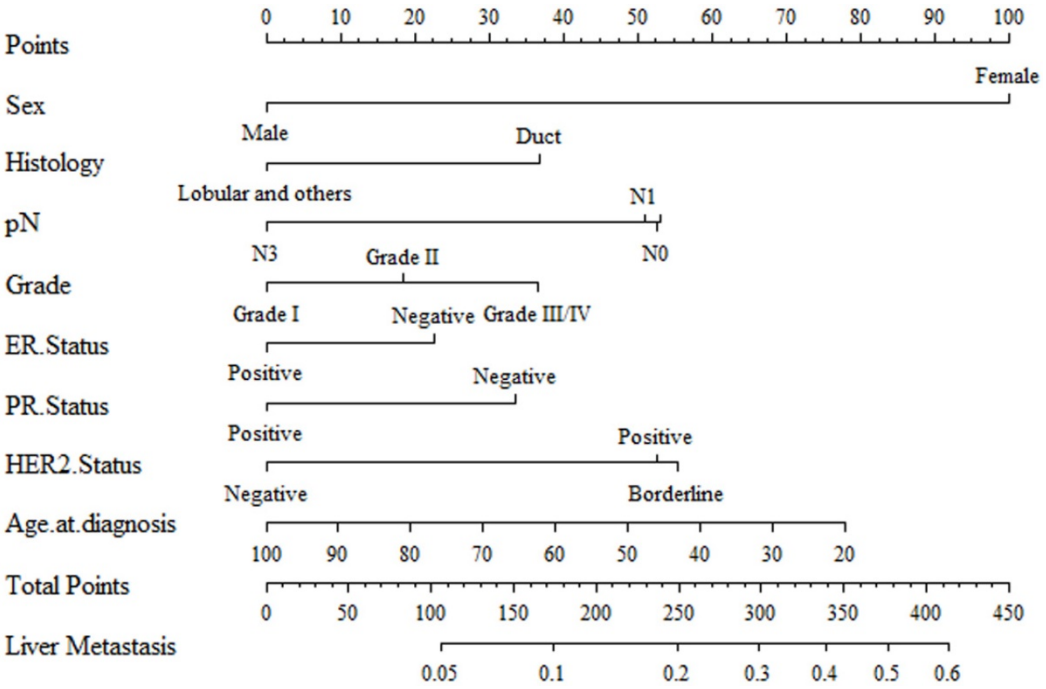

Fig 2. A nomogram for distinction and prediction of liver metastasis for breast cancer patients. Instructions for use of the nomogram: First, assign the points of each characteristic of the patient by drawing a vertical line from that variable to the points scale. Then, sum all the points and draw a vertical line from the total points scale to liver metastasis axis to obtain the probability.

Then we did the calibration of the nomogram internally with bootstrap sampling for 1000 times and Fig 3 was plotted with Apparent, bias-corrected and ideal curves demonstrated. The bias-corrected curve was close to the ideal curve which fall along the 45-degree line and so was the apparent curve. All these told us that the nomogram fitted very well internally. Then, we plotted the receiver operating characteristic (ROC) both internally and externally in the training and validating set (Fig 4). The calibration method was carried out in validating group by compute the area under the ROC curve (AUC). In the training set, the AUC was 0.6602 (95%CI = 0.6385-0.6819) and in the validation set the AUC was 0.6511 (95%CI = 0.6286-0.6736). There was no significant difference in AUC between the training group and the validating group (P=0.5676). This result meant that our nomogram model well fitted both the randomly assigned training and validating group and there was no difference in utilization of the model between the training and validating groups.

Liver metastasis probability and survival outcome

With this nomogram, we roughly predicted the possibility and distinguish liver metastasis patients merely with simple clinicopathologic variables in patients who already had remote metastasis. Then we extend the model out to all breast cancer patients amounting to 196468 who had no remote metastasis at diagnosis from 2010 to 2013 in consideration of the fact that early metastasis might miss diagnosis and a patient might develop metastasis shortly afterwards. Also, we had an interesting finding that there was a correlation between this liver metastasis risk and survival outcomes and patients with higher liver involvement risk had worse survival outcomes (Fig 5). For all 196468 patients, we defined the risk as a new variable and put this variable into a multiple variable cox regression model together with the other clinicopathologic variables including surgery, radiotherapy, race and marital status. This comprehensive liver metastasis risk was one of the most significant independent variables in predicting survival outcome. We could see in Table 4 that this variable was better than variables radiotherapy, marital status and race. Since marital status, race and radiotherapy had been reported as independent prognosis predictors for breast cancer, this comprehensive liver metastasis risk could play a part as well. Then we categorized the patients into groups whose comprehensive liver metastasis risk was above or below average and then plotted Kaplan-Meier curves to demonstrate its influence on survival outcomes and there was significant difference between the survival curves of the two groups (P<0.001). All these results implied the influence of this comprehensive liver metastasis risk could be used as a prognosis predictor. Those patients who had a potentially higher involvement risk had a worse survival outcome.

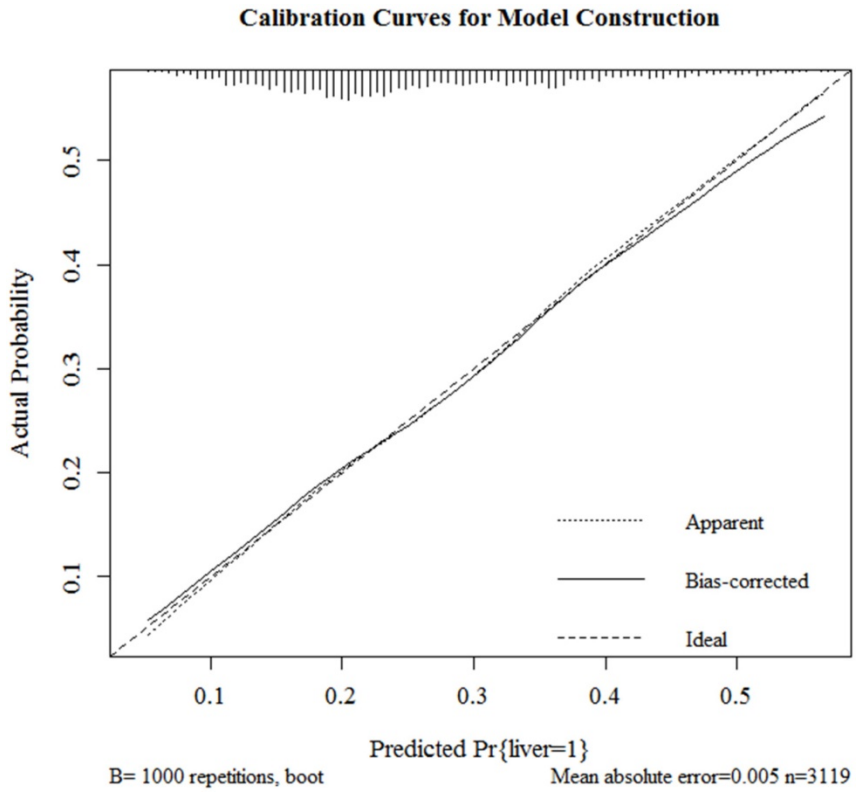

Fig 3. Internal calibration curves for probability of liver metastasis nomogram construction (Bootstrap = 1000 repetitions).

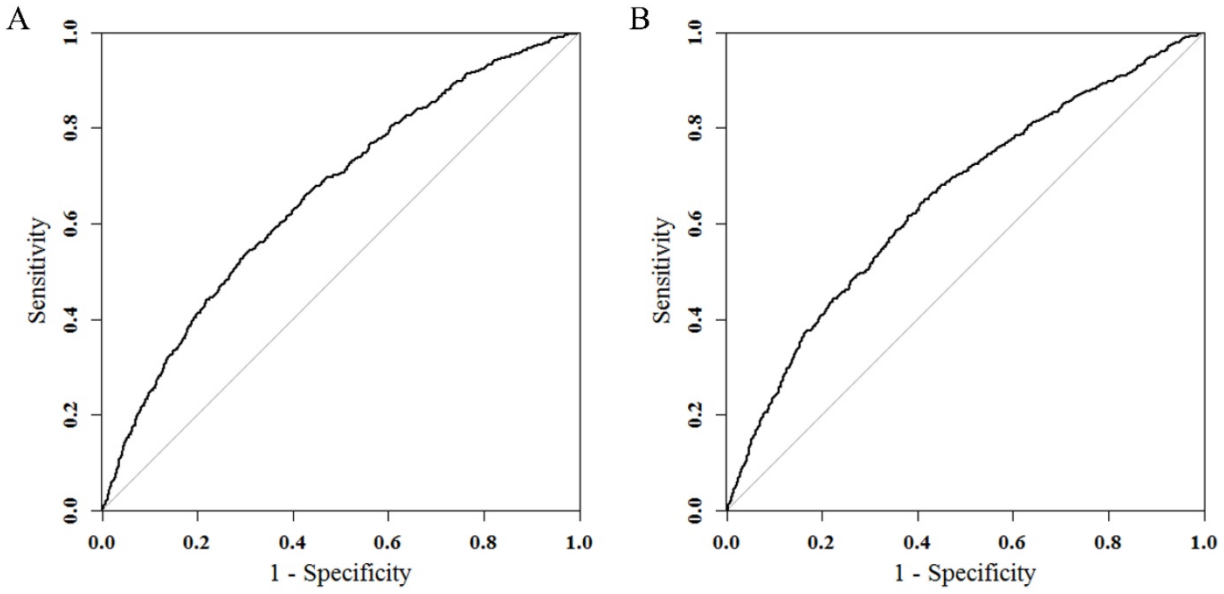

Fig 4. ROC curves in training (A) and validating groups (B) for validating nomogram model. In the training set, the AUC was 0.6602 (95%CI = 0.6385-0.6819) and in the validation set the AUC was 0.6511 (95%CI = 0.6286-0.6736).

Discussion

For liver metastases from breast cancer, the chances of a cure are nil and there is little hope of long-term survivors after non-surgical management alone even though there are remarkable advances in personalized drug therapy according to tumor phenotype [19]. Palliation is the primary goal for those patients but surgical approaches including liver resection allow good quality prolonged survival though in selective groups [20]. TACE (trans-arterial chemoembolization), chemotherapy and endocrine- or HER2-targeted therapy also get involved in the management of diseases [21-24]. Multidisciplinary team, group composed of members with varied but complimentary experience, qualifications, and skills

that contribute to treatment including surgeons and medical oncologists is necessarily needed.

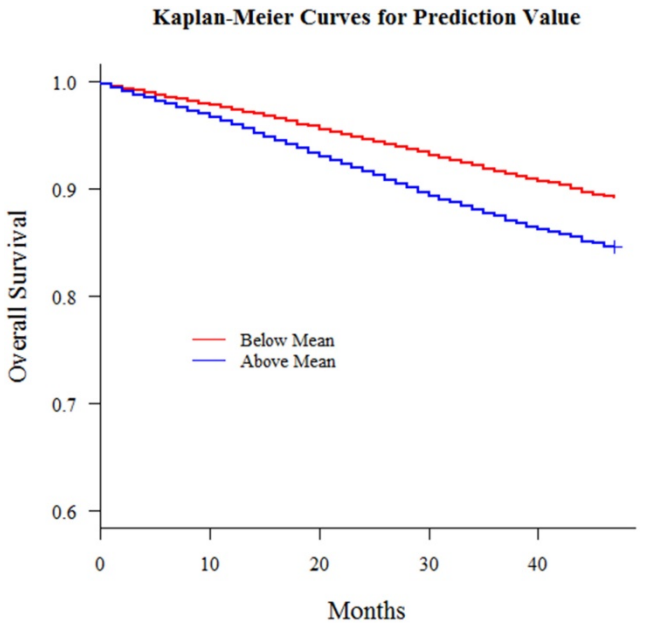

Fig 5. Kaplan-Meier curves for all breast cancer patients with predicted liver metastasis possibility above or below mean (P < 0.001)

Table 4. Cox regression model results for all breast cancer patients with predicted liver metastatic possibility

Variables	Coefficient	Std. Error	P value
Marital Status			
Unmarried	0.5858	0.0193	<0.0001
Married	Reference		
Surgery			
No	Reference		
Unknown	-0.5822	0.0798	<0.0001
Yes	-1.3718	0.0273	<0.0001
Radiotherapy			
No	Reference		
Unknown	-0.2865	0.0513	<0.0001
Yes	-0.6118	0.0208	<0.0001
Race			
Black	Reference		
Others	-0.6424	0.0444	<0.0001
White	-0.2019	0.0249	<0.0001
M			
M0	Reference		
M1	1.468	0.0276	<0.0001
Liver Mets Prediction	0.7513	0.0881	<0.0001

In this study, we put forward the idea for the first time that patients with liver metastasis might have particular clinicopathologic characteristics which could in turn distinguish themselves from those who had no liver metastasis and the variables could be used in a risk model for liver metastasis. For breast cancer liver metastases was on the intersection of different departments and researchers had not collected enough clinical samples in a uniform standard for a long time. Thanks to SEER database who released its collected data in with records of distant metastases types for all patients, we could be able to analyze the relationship between liver metastasis and mere clinicopathologic variables and construct a nomogram based on logistic regression which proved reliable in following calibration and validation.

We firstly screened all available variables and discarded those which were of no significance in multivariate logistic regression. Then we randomized the population into 1:1 training and validating group and nomogram was constructed in training group with remaining variables all of which also showed significance (P<0.05) in this optimized logistic regression model. Then the nomogram passed calibration and validation step. After bootstrapping method for 1000 repetitions, Fig 3 presented the apparent and bias-corrected curve which both well fitted the diagonal ideal line. The receiver operating characteristics (ROC) were plotted (Fig 4) with calibration method carried out by computing areas under the receiver operating characteristic curve (AUC). In the training set, the AUC was 0.6602 (95%CI = 0.6385-0.6819) and in the validation set the AUC was 0.6511 (95%CI = 0.6286-0.6736). There was no significant difference in AUC between the training group and the validating group (p=0.5676). Thus, we concluded that our nomogram model reliable and its predicting ability robust. Since it was the first time that SEER database recorded patients with their metastasis condition, the logistic regression model and nomogram could be improved with larger number of samples added on in the future.

Also, we extended this model to those patients who had no metastasis at diagnosis because early metastasis might miss diagnosis and a patient might develop metastasis shortly afterwards, we could still try to predict the risk of liver involvement if metastasis occurred later on because the clinicopathological factors remain stable in progression of the disease. As one result of the study, patients with a higher liver involvement possibility when metastasis happened has worse survival outcomes and this risk also shows significant predictive effects in multiple Cox regression model. In a word, this model could show the risk of liver involvement, and if it gives a high probability, we might recommend the patient to take close inspection of the liver, such as regular B-ultrasonography or MRI.

Intriguing facts on the relationship between clinicopathologic factors and liver metastasis could be drawn out from this nomogram. A man was almost unlikely to have liver metastasis compared to a woman but we could not rule out the possibility for still 9 men had their tumor metastasized to liver in

Table 1. Duct carcinoma, accounting for over 80% in all breast cancer patients, consisted of infiltrating duct carcinoma, intraductal carcinoma, noninfiltrating, comedocarcinoma and so forth and was in positive correlation with liver metastasis. N0, N1, N2 patients were more likely to develop liver metastasis than N3 patients, which is controversial to common sense. Previously, it has been reported that there was significant correlation between histological grade and multiple liver metastasis [25]. And in this study, we found that a low differentiated cancer is safer but grade III and IV were at a higher risk. Catharina B et al had published that patient Patients with HER2 overexpressing subtype had an increased risk for the development of visceral-only metastasis [26]. Molnár IA et al concluded that HER2 positive tumors carried a higher risk for distant metastases and HER2 positive had lung and liver as the most frequent second metastatic sites [27]. Kennecke H. et al reported that HER2-positive subtypes had a significantly higher rate of brain, liver, and lung metastases [28]. In our study, we discovered that ER negative, PR negative and HER2 positive were significant predictors and this finding was also in accord with statements by Gerratana L et al that HER2 overexpressing subtypes metastasize most likely to the liver and by Kast K et al that triple negative patients frequently presented with visceral metastases only at first presentation [29-31] In a conclusion, triple negative subtypes were more likely to develop visceral metastasis but HER2 positive with ER and PR double negative patients were more likely to have liver metastasis. Catharina B et al also argued that age at primary diagnosis, the nodal status and tumor size had no influence for visceral metastasis [26]. Moreover, Purushotham A found there is a surprising inverse relationship between age at diagnosis and distant metastasis in breast cancer [32]. Even so, we found age at diagnosis could be used to distinguish liver metastasis and others. It was a significant predicting factor, e.g. from the nomogram a 20-year-old girl turned more likely to have liver metastasis than a 90-year old grandma. As for nodal status, we noticed that N3 patients were less likely to have liver metastasis. Also, Catharina B et al argued tumor size had no influence for visceral metastasis [26]. Though larger tumor size was considered predictive of a slightly higher incidence of central nervous system (CNS) involvement [33], this variable tumor size had nothing to do in distinguishing liver metastasis from others.

This idea of constructing a nomogram and distinguishing and predicting metastasis status for a cancer disease was novel. We also hoped that this idea could be further carried out, extended and improved in further clinical work and research. Inevitably, this study had its limitations and this nomogram still had a lot of space to improve. With data volume increasing and the development other studies such as BRENDA [34], researchers could get larger population and more complete information for clinicopathologic variables. SEER database did not record characteristics such as occupation, education and family history. Also, we only knew the metastasis status at diagnosis and if we did know the metastasis status later on, we might be able to further prove its predictive efficacy. Last but not least, what we did was a retrospective analysis and the hypotheses raised remained to be proven in further investigation with larger data volume and advanced follow-up system.

This nomogram was constructed with all breast cancer patients whose metastasis status known. We could distinguish liver metastasis if metastasis incidence occurred. Also, all breast cancer patients had these clinicopathologic characteristics and they might have missed the diagnosis or develop metastasis shortly afterwards, hence, for those who had not been found with distant metastasis at diagnosis, this model could also be applied in predicting the risk which help decide whether to take a close watch on the liver, even though the following-up data for the patients has not been obtained yet and this hypothesis would be further validated in the long run. Because cancer metastasis is like the sword of Damocles. Moreover, we found that all patients who potentially had higher liver metastasis risk according to our nomogram had worse survival outcomes both in Kaplan-Meier curve and from cox regression model. This risk obtained was a significant factor in affecting survival. All these were consistent with our hypothesis that this model might be able to perform well in all patients, not merely in those with distant metastasis. This nomogram could be used as a supportive graphic tool in breast cancer which helps clinicians to distinguish, assess and evaluate the risk of liver involvement with clinicopathological factors and decided whether to pay more attention to liver in the course of disease.

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Competing Interests

The authors have declared that no competing interest exists.

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