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FULL PAPER

Nomograms predicting recurrence in patients with triple negative breast cancer based on ultrasound and clinicopathological features

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Objectives: The clinicopathological and ultrasound features associated with recurrence in patients with triple negative breast cancer (TNBC) were used to develop a nomogram to predict the prognosis of TNBC.
Methods: Clinicopathological data of 300 patients with TNBC treated between July 2012 and September 2014 were retrospectively reviewed. The endpoint was progression-free survival (PFS). Prognostic factors were screened by multivariate COX regression to develop nomograms. The C-index and calibration curves were used to evaluate the predictive accuracy and discriminatory ability of nomograms.
Results: Of 300 patients with TNBC followed-up for 5 years, 80 (26.7%) had PFS events. Five informative prognostic factors (large size, vertical orientation, posterior acoustic enhancement, lymph node involvement, and high pathological stage) were screened and used to construct a nomogram for PFS. The C-index of the PFS nomogram was 0.88 ($p < 0.01$, 95% confidence interval, 0.85–0.90), indicating good predictive accuracy.
Conclusions: We developed and validated a nomogram for predicting PFS in TNBC. Vertical orientation and posterior acoustic enhancement in ultrasound images of TNBC were associated with worse outcomes.
Advances in knowledge: Patients with TNBC have a very poor prognosis and patients have a high risk of recurrence, and our study developed a nomogram based on ultrasound and clinicopathological features for TNBC patients to improve the accuracy of individualized prediction of recurrence and provide help for clinical treatment.

INTRODUCTION

Triple negative breast cancer (TNBC) accounts for 15–20% of breast carcinomas and is defined by the absence of the three main breast cancer biomarkers, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[1] TNBC is a special subtype of breast cancer owing to its distinct epidemiology, histologic features, and clinical behavior. The relapse pattern of TNBC is strikingly different from that of other subtypes with the risk of recurrence being highest in the first 5 years. Approximately, 40% of patients with stages I–III TNBC relapse after standard treatment.[2] However, TNBCs are a highly heterogeneous group of tumors and the pattern of recurrence varies greatly among different TNBC patients.[3]

Identifying risk factors that predict the relapse of TNBC is important for diagnosing the disease and designing treatment strategies. In the past for a long time, researchers have been focusing on the clinicopathological factors to predict the recurrence in TNBC patients. These researches have similar results that young age, axillary lymph node involvement, lymphatic vessel involvement, and high histological grade were closely related to relapse in TNBC patients.[4] In recent years, some studies found that radiological features were also associated with relapse. For example, Kim et al found that lymph node metabolic and volumetric parameters on 18F-FDG PET/CT were useful in predicting the prognosis of TNBC patients.[5] Bae et al revealed that the absence of preoperative MRI imaging and the presence of dense breast tissue on mammography were associated with an increased risk of relapse in TNBC patients.[6] Furthermore, some studies assessed the prognosis of breast cancer using radiology. For instance, the volumetric-tumor histogram-based analysis of intravoxel incoherent motion and non-Gaussian diffusion MRI can be used to provide prognostic information in

breast cancers.[7] Wang et al assessed the prognostic value of ultrasound features in predicting BC disease outcomes.[8] To better understand the recurrence pattern of TNBC, more biological and clinical markers need to be brought into clinical practice.

In China, breast ultrasound is becoming a preferred method for both physicians and patients, attributed to its advantages such as safety, low cost, and wide popularity. Advances in multiultrasound technologies such as Doppler, elastic, and contrast ultrasound might expand its scope of applications. In the past, ultrasound was mostly used to distinguish benign and malignant breast masses. It is now increasingly used breast ultrasound for prognostic assessment. For instance, shear wave elastography was an adjunct to axillary ultrasound in predicting nodal metastasis in breast cancer.[9] Breast Imaging Reporting and Data System (BI-RADS) category 4A breast lesions tend to recurrence.[10] Vertical orientation ultrasound feature predicted worse disease outcome in TNBC.[11] However, there are few studies focusing on relapse pattern of TNBC using ultrasound.

Nomogram is a model based on multiple regression analysis that can predict the survival outcome of breast cancer. It uses a variety of clinical and informative radiological characteristics or biomarkers, and then uses line segments with high and low scores to reflect the predicted values of multivariate parameters.[12] Some studies have applied nomogram based on ultrasound features deal with some clinical problems. Some researchers used ultrasound radiomics nomogram to distinguish TNBC from fibroadenoma.[13] Ultrasound radiomics nomogram was used to predict disease-free survival of TNBC.[14] But few studies have looked into the association between the ultrasound features and relapse in TNBC patients.

Table 1. Definition of the ultrasound features criteria

Variables		Definition
Size	≥2 cm	Maximum diameter of the tumor by ultrasound
	<2 cm	
Orientation	Vertical	Long axis, not oriented along the skin line
	Parallel	Long axis of lesion parallels the skin line
Shape	Irregular	Not round or oval
	Regular	round or oval
Boundary	Indistinct	No clear demarcation between mass and its surrounding tissue
	Circumscribed	A margin that is well defined or sharp, with an abrupt transition
Halo	Absent	No thin capsule or echoic halo
	Present	Blurred, irregular hyperechoic rim around the lesion
Posterior acoustic	Non-Enhancement	No enhancement
	Enhancement	Increased posterior echo
Calcification	Absent	No punctuated extensively hyper-echoic foci
	Present	Punctuated extensively hyper-echoic foci
Margin	Angular	Margin is characterized by sharp lines projecting from the mass
	Circumscribed	Smooth, even margin without any irregularity
Echo pattern	Hyperechoic	Hyper- or isoechogenicity compared to fat, *e.g.*, fibroglandular tissue
	Hypoechoic	Hypoechoic compared to fat tissue
Vascularity	0	Vascularity not present
	I	1–2 spot vessels, caliber shorter than 1 mm
	II	1–2 vessels, longer than the radius of the tumor
	III	More than four vessels
Stainratio	low	The mass is 3.5 times less than the surrounding tissue
	high	The mass is 3.5 times more than the surrounding tissue
BI-RADS	I	No lesion found
	II	Benign finding
	III	Probably benign finding
	IV	Suspicious abnormality
	V	Highly suggestive of malignancy

Table 2. Baseline Characteristics of the 300 included patients with TNBC

Variables		Relapse group (n = 80)		Non-relapse group(n = 220)	
		n	Percent (%)	n	Percent (%)
Age	younger age<35	10	12.5	24	11.0
	older age≥35	70	87.5	196	89.0
Size	>2 cm	12	15.0	148	67.3
	<2 cm	68	85.0	72	32.7
Orientation	Vertical	6	7.50	52	23.6
	Parallel	74	92.5	168	76.4
Shape	Irregular	46	57.5	128	58.2
	Regular	34	42.5	92	41.8
Boundary	Indistinct	64	80.0	164	74.5
	Circumscribed	16	20.0	56	25.5
Halo	Absent	7	8.8	124	56.4
	Present	73	91.2	96	43.6
Posterior acoustic	Non-Enhancement	20	25.0	168	76.4
	Enhancement	60	75.0	52	23.6
Calcification	Absent	56	70.0	172	78.2
	Present	24	30.0	48	21.8
Margin	Angular	73	91.3	216	98.2
	Circumscribed	7	8.7	4	1.8
Echo pattern	Hyperechoic	12	15.0	4	1.8
	Hypoechoic	68	85.0	216	98.2
BI-RADS	I-III grade	68	85.0	188	85.5
	IV-V grade	12	15.0	32	14.5
Stainratio	low	22	27.5	130	59.1
	high	58	72.5	90	40.9
Vascularity	0-I grade	18	22.5	112	51.0
	II-III grade	62	77.5	108	49.0
Lymph nodes involvement	Absent	16	20.0	152	69.1
	Present	64	80.0	68	30.9
P53	<1%	14	17.5	48	21.8
	>1%	66	82.5	172	78.2
Ki67	<14%	51	63.8	132	60.0
	>14%	29	36.2	88	40.0
Pathlogy Stage	I-II	18	22.5	128	58.2
	III	62	77.5	92	41.8
Surgery type	Breast-conserving	20	25.0	132	60.0
	Mastectomy	60	75.0	88	40.0
Previous history	Absent	30	37.5	108	49.1
	Present	50	62.5	112	50.9
Family history	Absent	30	37.5	126	57.3
	Present	50	62.5	94	42.7

(Continued)

Table 2. (Continued)

Variables		Relapse group (n = 80)		Non-relapse group(n = 220)	
		n	Percent (%)	n	Percent (%)
Menstruation	Menstrual	22	27.5	132	60.0
	Post-menopausal	58	72.5	88	40.0

Based on above issues, it would be novel to investigate multiultrasound and clinicopathological factors associated with relapse in TNBC using a nomogram. It is expected to provide a workflow for relapse in TNBC patients ultrasound nomogram.

METHODS

Patients

This study was approved by the institutional ethics committee of our institution (approval number, KY-2016–127). This was a two-center, retrospective study. Between July 2012 and September 2014, 2,512 patients with breast cancer including 321 cases of TNBC were treated at two hospitals. Ten patients were excluded due to failure of standard treatment, six patients were excluded because of indistinct ultrasound imaging, and five patients were excluded due to the presence of multiple lesions. Ultimately, 300 TNBC patients were enrolled in the study. Integral clinical, ultrasound, pathological, and immunohistochemical data were available for all patients. Age, tumor size, type of breast surgery, menstrual data, and previous and family history were recorded.

The inclusion criteria were as follows: (1) completion of the entire standard treatment plan according to guidelines; (2) clear and complete multimodal ultrasound images; (3) complete and clear clinical endpoint data.

Ultrasound examination

In this study, multiple ultrasound techniques were used as Doppler and elastic ultrasound. Ultrasound images were acquired with a HITACHI Vision 900 system (Hitachi Medical System, Tokyo, Japan) equipped with a linear probe of 6–13 MHz. Real-time scanning was performed by two radiologist with 5 years of experience in breast ultrasound. First, the whole mass was scanned using grayscale ultrasound to identify the section with the maximum diameter, and the maximum diameter was

Table 3. Univariable Cox regression of pre-operation ultrasound and clinicopathological features as prognostic factors for PFS

Variables	Coef	HR	95% CI	P-value
age	−0.069	0.933	0.481–1.810	0.838
Size	2.327	10.250	5.533–18.988	<0.001
Orientation	1.273	3.572	1.554–8.211	0.003
Shape	0.089	1.093	0.701–1.702	0.695
Boundary	−0.467	0.627	0.362–1.085	0.095
Halo	0.091	1.095	0.705–1.701	0.686
Posterior acoustic	1.691	5.423	3.267–9.003	<0.001
Calcification	0.419	1.521	0.943–2.455	0.086
Margin	1.036	2.817	1.296–6.125	0.009
Echo pattern	−1.132	0.322	0.174–0.597	<0.001
BI-RADS	−0.034	0.966	0.523–1.785	0.913
Stainratio	1.394	4.033	2.458–6.615	<0.001
Adler	0.840	2.317	1.370–3.917	0.002
Lymph nodes involvement	1.885	6.589	3.804–11.412	<0.001
P53	0.311	1.365	0.767–2.431	0.291
Ki67	−0.121	0.886	0.561–1.397	0.602
Pathology Stage	1.673	5.329	3.139–9.047	<0.001
Surgery type of breast	0.676	1.967	1.247–3.101	0.003
Previous history	1.486	4.421	2.656–7.360	<0.001
Family history	1.001	2.722	1.724–4.298	<0.001
Menstruation	1.497	4.470	2.723–7.337	<0.001

Table 4. Multivariate Cox regression of pre-operation ultrasound and clinicopathological features as prognostic factors for PFS

Variables	Coef	HR	95% CI	*P*-value
Size	1.472	4.360	2.065–9.204	<0.001
Orientation	1.152	3.166	1.216–8.244	0.018
Posterior acoustic	1.377	3.965	2.221–7.079	<0.001
Margin	0.841	2.319	0.806–6.670	0.119
Echo pattern	0.409	1.505	0.593–3.822	0.390
Stainratio	0.667	1.949	0.548–6.936	0.303
Adler	−0.398	0.672	0.369–1.223	0.193
Lymph nodes involvement	1.690	5.421	2.913–10.087	<0.001
Pathology Stage	1.393	4.025	1.304–12.422	0.0158
Surgery type of axillary	0.098	1.102	0.559–2.176	0.779
Surgery type of breast	−0.559	0.572	0.121–2.707	0.481
Family history	0.317	1.373	0.654–2.883	0.402
Menstruation	−0.930	0.394	0.124–1.258	0.116

then measured and recorded. The static images and cine clips of multiultrasound were saved in the database for double-blind analysis. Three breast radiologists with 7, 9, and 13 years of clinical experience, respectively, reviewed the ultrasound images retrospectively and independently. Consensus interpretations were reached in cases of disagreement.

The grayscale ultrasound criteria were assessed using the standardized lexicon for ultrasound Breast Imaging Reporting and Data System.[15] The blood flow was evaluated by Adler grade.[16] The elastic ultrasound criteria were based on WFUMB guidelines.[17] The specific classification and definition of the ultrasound features criteria are shown in Table 1.

Histological examination

All tumors and sentinel lymph nodes (SLN) were excised or assessed pathologically by needle biopsy for pathology. Tissues were formalin-fixed, paraffin-embedded, and subsequently used for immunohistochemical staining with the appropriate antibodies. According to the guidelines of the 2019 WHO classification,[18] breast tumors were classified into the corresponding histological types and grades. SLN were evaluated for involvement according to the seventh edition of the AJCC.[19] The cutoff points for ER-positive, PR-positive, and P53 were 1%. HER-2 status was graded as 0, 1+, 2+, and 3+. Only 3 + was considered positive, whereas 0 and 1 + were considered negative. Fluorescence *in situ* hybridization was performed on all Grade 2 samples. Samples with <2-fold-change in expression were regarded as negative, and samples with >2 fold increase were regarded as positive for gene amplification.[20,21] Ki67 was visually scored for the percentage of tumor cell nuclei that were positive for immunostaining over background. Staining >14% was considered high expression, whereas <14% was considered low expression.[22]

TNBC was defined by the absence of the three main breast cancer biomarkers, ER-negative, PR-negative, and HER-2 grade = 0 or 1+.

Follow-up and clinical endpoint

Follow-up data were obtained mostly via patient record, few patients via telephone interviews. In this study, local recurrence and distant metastasis were collectively referred to as breast cancer recurrence. All patients were followed-up every 6 months for at least 60 months. To avoid extended follow-up and provide an efficient tool for early personalization of treatment, we chose progression-free survival (PFS) as an endpoint. We calculated PFS from the first day of treatment to the date of disease progression (locoregional recurrence or distant metastasis), death from TNBC, or the date of the last follow-up visit (censored).

DATA ANALYSIS AND STATISTICS

Development of the prognostic model

PFS was estimated based on ultrasound and clinicopathological variables. Univariate COX regression analyses were performed to identify potential risk factors. Significant factors ($p < 0.05$) obtained from univariate COX regression were applied to multivariate COX regression. The Cox proportional hazard models were used to develop multivariate models to predict the 5 year PFS of the patients.

The coefficient of the selected feature in multivariate COX regression was defined as the U-Score. The U-score was calculated for each patient as a linear combination of selected features that were weighted by their respective coefficients. The patients were divided into high-risk and low-risk groups according to the median U-score. Survival curves for potential risk factors were depicted using the Kaplan-Meier method, and high-risk and low-risk patients were compared using the log-rank test. Based on a multivariate model from the Cox proportional hazards model, a nomogram was constructed to generate the PFS probability at 5 years.

Model validation

We used bootstrap sampling to extract 80% of the original sample as the training set, and the remaining 20% as the

internal validation cohort. We sampled (1000 times) to obtain 1000 training subsets and 1000 internal validation cohorts. The C-index was used to evaluate nomogram performance, and the calibration curve was drawn to evaluate the calibration effect. The probability that the model generates a higher risk for those who experience an event than those who cannot be expressed by the C-index. The C-index statistic correcting for potential overfitting can be obtained by bootstrap analysis (1000 resamples). Calibration measures the degree to which the predicted probabilities agree numerically consistent with the actual outcomes. The calibration curve can be evaluated by plotting the observed survival score against the probability assessed by the nomogram.

We can use R software (R Core Team) to perform the statistical analysis. (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org, 2016). Cox proportional hazards regression and Kaplan-Meier survival analysis were performed with the "survival" software package. The nomogram and calibration curve were plotted by "rms" package. The C-index can be analyzed with the "hmisc" package. All statistical analyses were performed using a two-tailed Student's t-tests, and p-values$<$0.05 as the statistically significant.

RESULTS

Study population

The study included 300 TNBC patients, all of whom received standard treatment. The average age of enrolled patients was 51.1 (33–75) years and 146 (48.7%) patients were post-menopausal at diagnosis. The majority of primary cancers (286 of 300 cases, 95.3%) were invasive ductal carcinoma; 154 (51.3%) were high-grade tumors, and 132 (44.0%) showed axillary lymph node involvement. During the 5 years of follow-up, 80 (26.7%) patients had PFS events and 51 (17%) were censored for other causes (myocardial infarction, stroke, and accident). Among the 80 PFS events, there were 18 (22.5%) patients with locoregional recurrence, 38 (47.5%) with distant metastasis, 3 (3.75%) with contralateral breast cancer, and 21 (26.25%) patients died from breast cancer. We classified 51 patients in the non-relapse group and the follow-up data were non-relapse during the time from operation to the events. The baseline characteristics of the patients are summarized in Table 2.

Univariate and multivariate COX regression of prognostic factors of preoperative ultrasound and clinicopathological parameters in TNBC

Univariate Cox regression of PFS found 13 characteristics to be statistically significantly associated with PFS, including large tumor size ($p < 0.001$), vertical orientation ($p = 0.003$), posterior acoustic shadowing ($p < 0.001$), circumscribed margin ($p = 0.009$), hypoechoic pattern ($p < 0.001$), high staining ratio ($p < 0.001$), high Adler grade ($p = 0.002$), lymph node involvement ($p < 0.001$), high pathological stage ($p < 0.001$), breast conserving surgery ($p = 0.003$), previous history ($p < 0.001$), present family history ($p < 0.001$), and menstrual status ($p < 0.001$) (Table 3).

Significant factors ($p < 0.05$) identified in univariate Cox regression analysis were applied to multivariate COX regression, which identified large size [hazard ratio (HR), 4.360; 95% confidence interval (CI), 2.065–9.204, $p < 0.001$], vertical orientation (HR, 3.166; 95% CI, 1.216–8.244, $p = 0.018$), posterior acoustic enhancement (HR, 3.965; 95% CI, 2.221–7.079, $p < 0.001$), lymph node involvement (HR, 5.421; 95% CI, 2.913–10.087, $p < 0.001$), and high pathological stage (HR, 4.025; 95% CI, 1.304–12.422, $p = 0.0158$) as independent prognostic factors for PFS (Table 4).

A significant difference between PFS in high- and low-risk patients was observed according to the overall profile of the five informative characteristics and is shown in the boxplot (Figure 1a) and Kaplan-Meier survival analyses (Figure 1b). There

Figure 1. The degree of distribution of expression for U-score in high-risk patients and low-risk patients according to the five informative features. (a) The middle bar represents the median, and the box represents the interquartile range. (b) In the Kaplan-Meier curve, the difference between high- and low-risk patients is statistically significant.

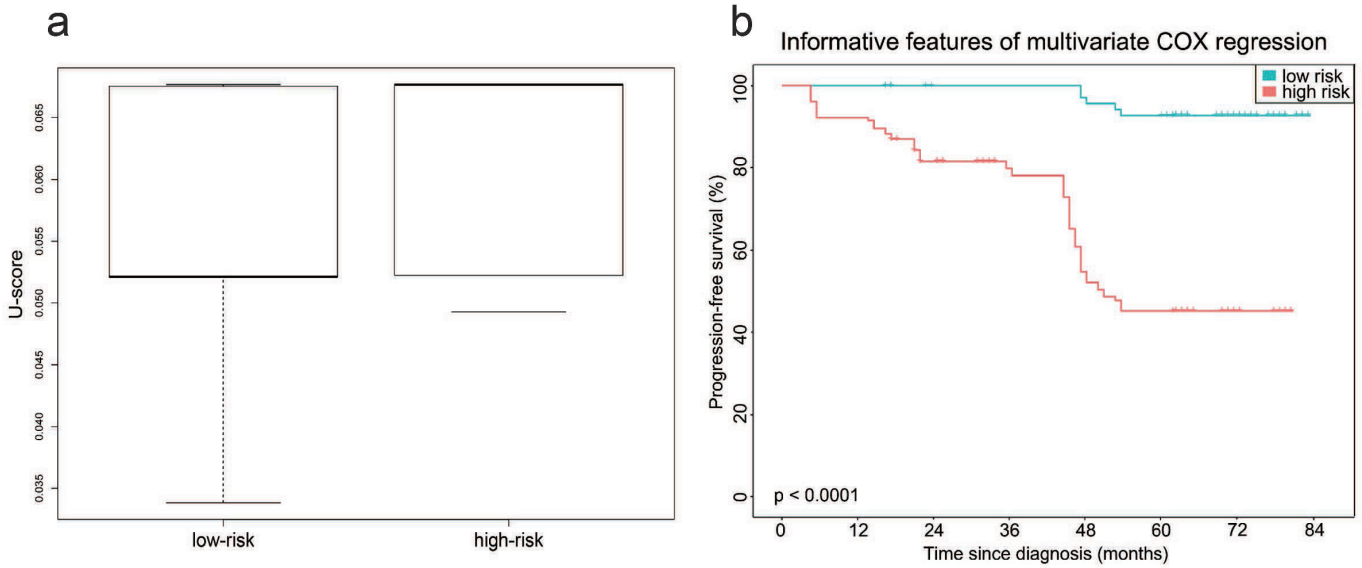
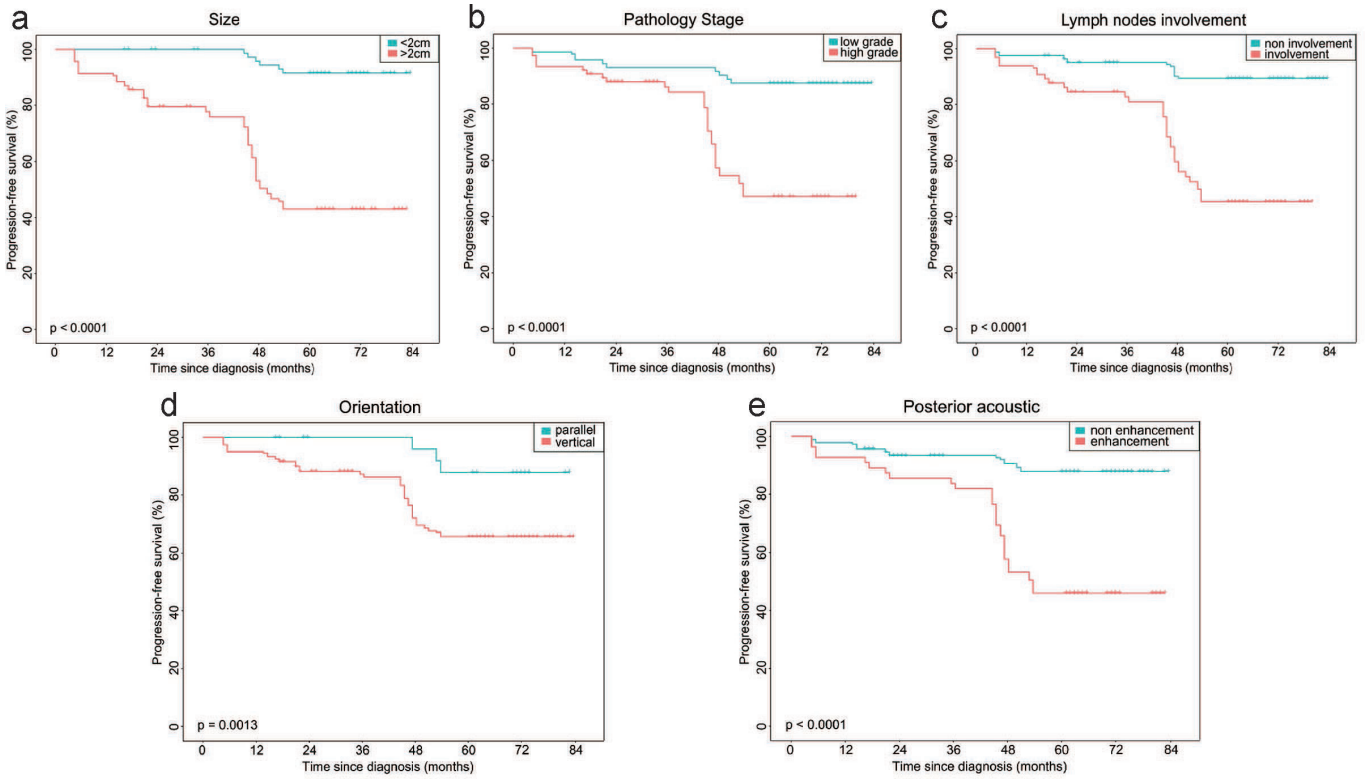


Figure 2. Stratified analyses were performed to estimate progression-free survival in various subgroups, comparing large and small size (a), high and low pathological stages (b), lymph node involvement and non-involvement (c), vertical and parallel orientations (d), posterior acoustic enhancement and non-enhancement (e).



were significant differences between the two groups according to the t-test ($p < 0.0001$) and Log-rank test ($p < 0.0001$).

As shown in Figure 2, prognostic stratification was performed between large and small size tumors ($p < 0.0001$, Log-rank test, Figure 2a), high and low pathological stage ($p = 0.0013$, Log-rank test) (Figure 2b), lymph node involvement and non-involvement ($p < 0.0001$, Log-rank test, Figure 2c), vertical and parallel orientation($p < 0.0001$, Log-rank test, Figure 2d), and posterior acoustic enhancement and non-enhancement ($p < 0.0001$, Log-rank test, Figure 2e).

Prognostic nomogram for PFS

The nomogram was constructed based on five informative factors from the multivariable COX regression to predict the relapse of TNBC. The prognostic nomogram integrating all significant independent factors for PFS is shown in Figure 3a. Internal validation performed using 1000 bootstrap resampling revealed that the C-index of the proposed nomogram was 0.88 ($p < 0.01$, 95% CI, 0.85–0.90). The calibration plot for the probability of survival at 5 years after standard treatment showed an optimal agreement between the prediction by nomogram and actual observation in Figure 3b.

In the nomogram, the estimated probability of relapse could be obtained by summing the scores of each variable and locating such on the total score scale. For instance, a patient with lymph node non-involvement (0 points), >2 cm size (100 points), posterior acoustic enhancement (58 points), high-grade pathological stage (30 points), and vertical orientation (50 points) would score 238 points, which can be converted into >90% probability of relapse (Figure 4).

DISCUSSION

TNBC with poor prognosis is a clinical problem. The identification of factors associated with recurrence would improve our understanding of the biological behavior of TNBC. Clinicopathological factors including large tumor size, lymph node involvement, and high grade are related to a high rate of recurrence in TNBC. Radiological features such as high breast tissue density on MRI,[23] casting-type calcification, and architecture distortion in mammography are associated with recurrence of TNBC.[24] However, relatively few studies have focused on the relation between sonographic features and disease outcome in TNBC. In our study, the correlation between TNBC recurrence and multimodality ultrasound images and clinicopathological factors was demonstrated. In addition, we constructed nomogram-based prognostic models to predict recurrence in TNBC. We showed that ultrasound features of vertical orientation and posterior acoustic enhancement were independent factors of PFS in TNBC.

Clinicopathologic features including large size, lymph node involvement, and high pathological stage, and two ultrasound features were identified as prognostic factors for recurrence. The three clinicopathologic features identified were consistent with those reported previously.[11] It is worth mentioning that

Figure 3. (a) Nomogram integrating the five informative factors from ultrasound and clinicopathological features. (b) calibration curve of the nomogram. The diagonal line represents an ideal evaluation, whereas the light-colored lines represent the performance of the nomogram. A closer fit to the diagonal line indicates a better evaluation.

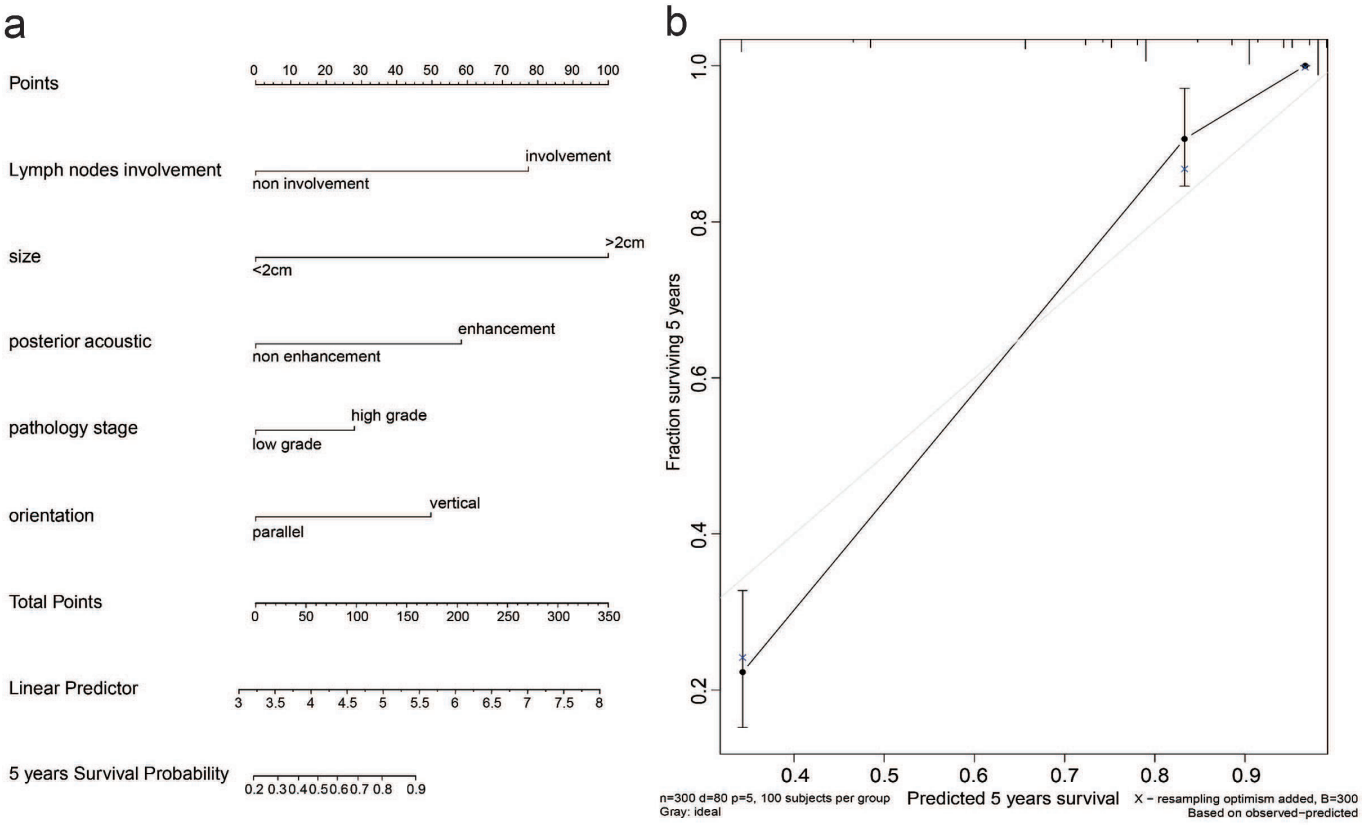
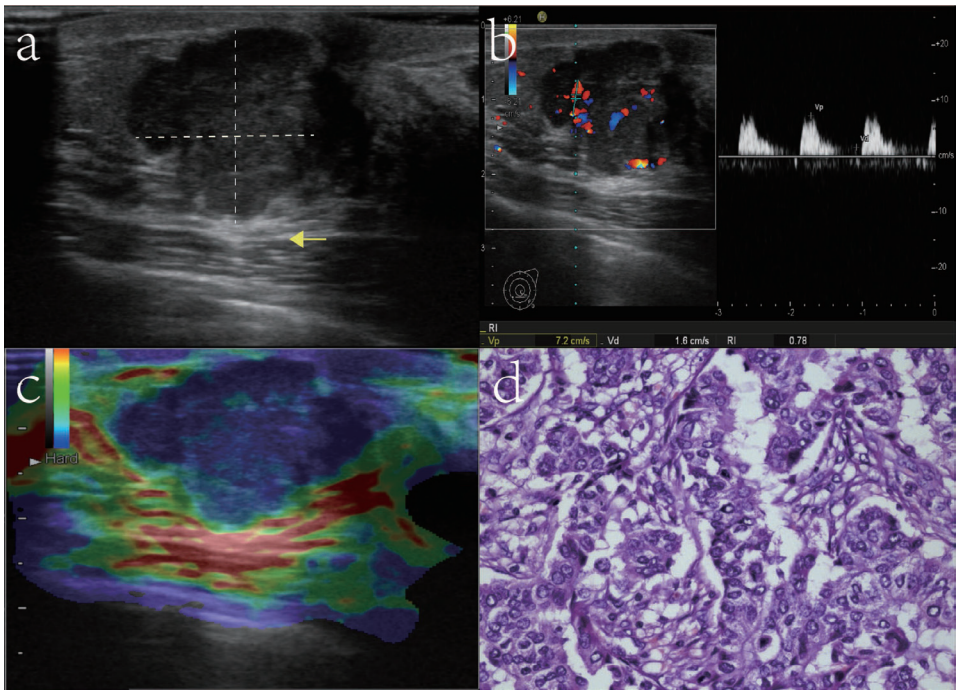


Figure 4. Example of one triple-negative breast cancer. (a) B-mode ultrasound: the yellow arrow refers to the posterior acoustic enhancement, and the two-dotted line indicates the vertical orientation. (b) Color Doppler ultrasound: blood flow is abundant. (c) Elastic ultrasound: the lesion was hard with rendered blue. (d) HE-stained pathological image reveals the high pathological stage.



the ultrasound features of vertical orientation and enhancement posterior acoustic were independent factors.

The utility of ultrasound in the diagnosis of breast lesions has increased in the past decade. Many ultrasound features are associated with the clinical behavior of breast tumors. For instance, the echogenic halo of ultrasound is present in low-grade tumors,[25] and the presence of calcifications and vascularity are associated with the expression of HER2.[26] In this study, vertical orientation and posterior acoustic enhancement were identified as the independent prognostic factors of PFS. Vertical orientation was defined as a horizonal-anteroposterior ratio of <1.0 and reflected a growth process that progressed beyond the normal tissue-plane boundaries in the breast. Vertical orientation is associated with an aggressive biological behavior and is a predictor of worse outcomes.[11] Consistently, we found that vertical orientation was an ultrasound manifestation of worse outcomes in TNBC. A posterior acoustic pattern was a good predictive indicator.[27] Posterior acoustic enhancement was defined as a reduced attenuation of the ultrasound waves compared with the surrounding tissue, which is suggestive of increased cellularity and high-grade tumors.[28] The presence of posterior acoustic shadowing is strongly associated with low-grade tumors, whereas posterior acoustic enhancement suggests high-grade tumors.[29] The present results were consistent with these findings. TNBC with posterior acoustic enhancement was associated with relapse, worse outcomes, and high-grade tumors.

Cancer researchers and clinicians are becoming increasingly interested in statistical models for predicting the recurrence or the outcome of cancer, along with the efficacy of treatments. Among several predictive models, nomograms provide personalized reasonable risk estimates that facilitate management-related decisions.[30] The present nomogram can be used to calculate the probability of recurrence of TNBC after standard treatment based on clinicopathologic and ultrasound features. If the total points calculated using lymph node involvement,>2 cm size, posterior acoustic enhancement, high-grade pathological stage, and vertical of orientation are >150, the probability of recurrence of TNBC exceeds 90%. The present nomogram revealed good discriminatory power with a C-index of 0.88 in the bootstrap. In addition, the calibration plot showed good agreement between the observed and predicted probabilities. These findings indicate that the proposed nomogram is suitable for predicting the probability of recurrence in TNBC.

The present study had several limitations. Firstly, the generalizability of the nomogram should be externally validated with an independent population before its application to clinical practice. Hence, our nomogram model requires further externally validation through prospective studies with a larger sample size and longer follow-up time. Secondly, the study did not include classification of TNBC into subtypes. To improve these models, further studies including TNBC subtypes and integrating other factors are necessary.

CONCLUSION

In conclusion, the nomogram based on preoperatively clinicopathological and ultrasound features could estimate the relapse pattern of TNBC, which could help clinicians' decision-making. It would be novel to found that the ultrasound features vertical orientation and posterior acoustic enhancement were independently associated with prognostic deterioration in patients with TNBC. In addition to traditional clinicopathological factors, these two features could be considered as complementary risk factors for TNBC, which deserves further clinical evaluation.

CONTRIBUTORS

Zhang L, Tian J and Cui H conceived and designed the experiments. Zhang X, Zhao D,Kong H, Peng F and Han P collected and analyzed data. Hu N, Fan W, Zuo X and Wang P validated the method and data. Zhang L, Tian J and Cui H wrote this manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing financial interests

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ETHICS APPROVAL

This study was approved by the institutional ethics committee of our institution (approval number, KY-2016-127)

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