Research Square

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Influence of body composition on survival in breast cancer patients with bone metastasis: a clinicopathologic-radiomic web-based nomogram development and validation

Haixiao Wu
Tianjin Medical University Cancer Institute and Hospital
Huiyang Li
Tianjin Medical University General Hospital
Yile Lin
Sechenov University
Jun Cai
Tianjin Institute of Medical and Pharmaceutical Sciences
Maxim A Abakumov
National University of Science and Technology
Elmar R Musaev
Sechenov University
Jun Wang
Peoples' Friendship University of Russia
Wenjuan Ma
Tianjin Medical University Cancer Institute and Hospital
Chao Zhang
drzhangchao@tmu.edu.cn

Tianjin Medical University Cancer Institute and Hospital
Shu Li
Tianjin University of Traditional Chinese Medicine

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Abstract

Background

Bone metastasis (BM) reduces survival in breast cancer (BC) patients. Altered body composition is prognostic but poorly captured by conventional models; radiomics enables precise CT-based quantification. This study aimed to determine the influence of body composition on survival in BC patients with BM and to develop and validate a comprehensive web-based nomogram.

Methods

We retrospectively analyzed 197 breast cancer patients with bone metastasis at Tianjin Medical University Cancer Institute & Hospital, Tianjin, China, between January 2010 and December 2017. Another 38 patients from January 2012 to December 2016 in P.A. Hertsen Moscow Oncology Research Center, Moscow, Russia, as the external validation cohort to test the nomogram. The radiomics score for predicting survival was established by using the least absolute shrinkage and selection operator Cox regression. The Kaplan-Meier method was used for survival analysis. Multivariable Cox regression analysis was used to construct a clinicopathologic-radiomic web-based nomogram based on clinicopathologic and radiomics features of body composition. A clinicopathologic web-based nomogram was also established. Receiver operating characteristic curves and internal validation cohort were used to evaluate aforementioned nomograms. We verified the clinicopathologic-radiomic web-based nomogram model using the external validation cohort.

Results

The Kaplan-Meier analysis showed the 1-year survival in breast cancer patients with bone metastasis in construction cohort was 81.9%, the 3-year was 48.6%, the 5-year was 19.6%. Body composition was proved to be significantly correlated with the prognosis of breast cancer patients with bone metastasis. Eight variables were selected into the clinicopathologic-radiomic model: radscore, bone CT-value, bone metastasis location, pathology subtype, brain metastasis, ALP, Ca and TMI. The clinicopathologic-radiomic web-based nomogram was satisfactory with the C-index of 0.82, which was higher than the clinicopathologic model (C-index was 0.71). The AUCs of clinicopathologic-radiomic web-based nomogram in 1-, 3-, 5-years were internally validated (82.3%, 91.1% and 82.9%, respectively) and externally validated (85.1%, 84.3% and 67.7%, respectively).

Conclusions

Body composition was significantly associated with the prognosis of breast cancer patients with bone metastasis. Individualized rehabilitation training and nutritional support intervention should be encouraged for the patients. The established clinicopathologic-radiomic nomogram was an effective tool for prognostic prediction, and could help clinicians make personalized clinical decisions.

Background

Breast cancer (BC) has become the highest incidence rate of malignancy among women worldwide[1]. Bone metastasis (BM) occurred in 60%~80% of BC patients during the treatment period, the 5-year survival rate is 22.8%[2–4]. The latest studies suggested the potential ability of BM promoting the secondary metastasis to other organs, which

can significantly reduce the survival of patients[5]. The development of BM can result in skeletal related events, including spinal cord compression, pathological fracture, external irradiation, and severe pain, which were widely accepted to further decrease the quality of patient's life and increase the medical burden [6, 7]. Thus, the study of BM attracted broad attention in the field of malignant tumor.

Survival estimation was one of the most important procedures for personalized treatment plan generation. Several studies were performed to identify the prognostic factors in BC patients with BM, including age, marital status, brain and visceral metastasis, HR, HER-2, ALP. [8–10]. However, none of the established nomogram can meet the need of clinic. It was widely accepted that the prognosis of patients at advanced stage was associated with various factors, including tumor-specific factors and nutritional status [11–13]. Currently, seldom study looking into the comprehensive factors on prognosis of BC patients with BM was performed. One of the latest studies reported body composition reduction in cancer patients was caused by the insufficient energy intake, negative nitrogen balance, and high energy consumption[14, 15]. At the same time, a series of adverse events after body composition changes, including frailty, obesity, osteoporosis and sarcopenia can significantly increase the rehospitalization rate and increase the burden of medical insurance[16–18].

Computed tomography (CT) plays an essential role in body composition estimation[19–21]. Previously studies suggested the psoas, paraspinous and pectoralis muscle index from axial CT could be used as the imaging biomarkers to predict the prognosis in liver transplant, cirrhosis, and pancreatic, lung, esophageal, colorectal cancer[22–27]. However, the muscle index itself could not comprehensively reflect the body composition of patients. Thus, new non-invasive strategy describing more characteristics of body composition is needed.

Radiomics, being the image recognition technology, showed its priority ability on both qualitative and quantitative imaging features extract [28]. The extracted features were reported to be used as the alternative biomarker for describing biological tumor characteristics such as tumor morphology and intratumor heterogeneity[29].The latest studies showed that radiomic score (radscore), being a potential imaging biomarker of the lesion range or body composition, can accurately predict the prognosis of patients in several fields, including COVID-19, esophageal cancer and gastric cancer [30–32]. Thus, we hypothesized that the modelling, being composed of accurate patient's body composition estimation and tumor characteristics, can precisely evaluate the survival of BC patient with BM.

Thus, the present study collected and analyzed the clinic-radiologic-pathologic data of BC patients with BM from our center. The correlation between body composition and survival was explored. Radscore was generated by radiomics. The web-based nomogram being composed of clinic-radiologic-pathologic characteristics was created and validated. Such nomogram can be potentially used for precise prognostic prediction in BC patients with BM.

Methods

Study design and participants

This retrospective cohort study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital, Tianjin, China. We retrospectively collected 540 BC patients with BM who received comprehensive treatment between January 2010 and December 2017 at the Department of bone and soft tissue tumor, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China. Inclusion criteria: Patients who were pathologically diagnosed with primary BC, imaging evidence of BM diagnosis, complete chest CT at BM diagnosis, complete clinical record and clear follow-up. Exclusion criteria: patients with uncertain pathological diagnosis, multiple malignancies, bilateral BC, male BC patients, patients with incomplete clinical data, patients without chest CT at BM diagnosis, incomplete follow-up information.

Various characteristics were included: age at BM diagnosis, pathological subtype, Ki-67 index, BM location, synchronous/metachronous BM (BM diagnosis within 6 months after BC diagnosis was defined as synchronous. Otherwise, defined as metachronous BM), site of BM (axial/appendicular skeleton), number of BM (1 ~ 4 sites, ≥ 5 sites), radiotherapy of BM, bone protectants, alkaline phosphatase, and serum calcium, total skeletal muscle index (TSMI), bone CT-value of vertebral bone and radscore of body composition.

Chest CT analysis and postprocessing

The involved patients underwent chest CT with the following parameters: tube voltage = 120 kVp, slice thickness = 1.25 mm, tube current varied automatically according to the patients' habitus. Patients were examined in the supine position. The scanning range was from the thoracic entrance to the costophrenic angle. Single breath-hold (i.e., end of inhalation) continuous spiral scanning was utilized in the chest CTs. Advantage Workstation AW 4.2 equipped with Functool II software (GE Healthcare) was employed for the image postprocessing. All patients' data were exported in DCM for subsequent radiomics feature extraction.

Radiomic analysis

Regions of interest (ROI) were manually delineated on chest CT images acquired at the diagnosis of bone metastasis using the open-source software ITK-SNAP (version 3.6.0; www.itksnap.org). These included the contralateral pectoralis muscles (PMs) and the area of 1cm^2 vertebral body at the level of T2, together with the erector spinae muscles (ESMs) and the area of 1cm^2 vertebral body at the level of T12. A radiologist with 6 years of experience performed the initial segmentation. Reproducibility was evaluated in 30 randomly selected patients: a second radiologist independently segmented the same images, and the first radiologist repeated segmentation after 1 month. Interobserver and intraobserver intraclass correlation coefficients (ICC) were calculated from the corresponding radiomic features.

Radiomic features were extracted using the open-source python package "Pyradiomics V3.0.1" (https://pyradiomics.readthedocs.io/en/latest/installation.html). A total of 3,376 features were obtained from the PM and ESM ROI, comprising fist order statistics, shape-based (3D), shape-based (2D), gray level co-occurrence matrix, gray level run length matrix, gray level size zone matrix, neighboring gray tone difference matrix and gray level dependence matrix.

Feature selection followed a previously reported framework [33]. Briefly, features with both interobserver and intraobserver ICC > 0.80 underwent univariate screening using the Mann–Whitney U test, with $p < 0.05$ required for retention. Redundancy was subsequently reduced by examining pairwise feature correlations; for pairs with $R > 0.80$, the feature with the larger p value was excluded. The remaining features entered least absolute shrinkage and selection operator (LASSO) Cox regression, and those with nonzero coefficients were used to calculate T2- and T12-derived radiomic scores (RadScores) for each patient as coefficient-weighted sums of their feature values. Statistical analyses were performed in R (version 3.6.3). Figure 1 summarizes the radiomic analysis workflow.

Prognostic Model Construction

The involved patients were divided into the construction cohort and the internal validation cohort according to the statistical random selection method (proportion: 7:3). The univariate and multivariate risk factors affecting patients were screened by statistical analysis. The obtained multivariate risk factors were enrolled to establish two different

prognostic model nomograms (clinicopathologic: demographic and clinicopathologic features; radiomic: demographic, clinicopathologic and radiomic features). The performance of these prediction model was validated by the internal validation cohort. At the same time, another 75 BC patients with BM diagnosed between January 2012 and December 2016 acquired from the P.A. Hertsen Moscow Oncology Research Center, Moscow, Russia was included as the external validation cohort to test the generalizability of the clinicopathologic-radiomic nomogram. Based on the same set inclusion and exclusion criteria, a total of 38 patients were enrolled in the external validation cohort.

In addition, pectoralis (PMI), erector (EMI) and total skeletal muscle indexes (TMI) were calculated. The muscle area in square centimeters (cm^2), normalized indexed values for PM and EM adjusted for height in meters squared (cm^2/m^2) were calculated, which resulted in the PM and EM index. TMI was defined as: TMI = PMI+EMI (PMI: Pectoralis muscle index, EMI: Erector spinal muscle index). The calculation formula of PMI was: PMI= pectoralis muscle area/$height^2$ (height unit: meter). The calculation formula of EMI was: EMI= erector spinal muscle area/$height^2$.

Statistical analysis

In the both training and validation cohorts, the clinicopathologic characteristics were assessed by applying chi-squared test or Mann–Whitney U-test for categorical or continuous variables, respectively. The variables with $p < 0.05$ in the univariate analysis were sent to multivariate Cox analysis. The performance of each model (the clinicopathologic model and the clinicopathologic- radiomic model) was estimated by the concordance index (C-index), which can measure the concordance between the predicted poor outcome and the actual poor outcome (0.5 means poor concordance and 0.7 indicates good concordance). The nomograms of OS for 1, 3 and 5 years were established based on the independent predictive factors. The calibration curves reflecting the goodness-of-fit of the nomograms were plotted. Receiver-operating characteristic (ROC) analysis was applied to assess the performance of the prognostic signatures (the clinicopathologic model and the clinicopathologic-radiomic model) in predicting 1-year, 3-year, and 5-year poor outcome. All statistical analyses were performed using 3.6.3 R software (http://www.Rproject.org). A two-tailed $p < 0.05$ was considered statistically significant.

Results

Description of the characteristics of the included patients

A total of 540 BC patients with BM were retrospectively collected. Based on the inclusion and exclusion criteria, a total of 138 BC patients with BM were included in the construction cohort, 59 patients were included in the internal validation cohort. Additionally, 38 BC patients with BM from the P.A. Hertsen Moscow Oncology Research Center, Moscow, Russia from January 2012 to December 2016 were enrolled as the external validation cohort (Fig. 2).

The analysis of the baseline information on the demographic, clinicopathologic characteristics and imaging features of the whole enrolled 197 patients showed that the median age was 54.0 years old. Median follow-up time was 34.8 years. The pathological types of BC included 55 cases of Luminal A, 81 cases of Luminal B (HER-2-), 18 cases of HER-2+ (HR+), 21 case of HER-2+ (HR-), and 22 case of triple negative subtype. Among all patients, 88 had synchronous BM and 109 had metachronous BM. The cases of BM sites locating in the axial skeleton alone were 43 cases, while 54 cases were found in the appendicular skeleton alone. A total of 100 cases suggested BM sites located in both axial skeleton and appendicular skeleton. A total of 106 cases were found to be with less than four BM sites (≤ 4), and 91 cases were found to be with ≥ 5 sites. Among the 197 BC patients, 66 patients were found to be with bone-only metastases, and 131 patients were found to be with extraosseous metastasis. The most common accompany

metastasis site was lung (44.2%), liver (37.6%), and brain (18.8%). There were 16.8% patients with metastatic lesions treated with radiotherapy and 83.2% patients with BMAs (bone-modifying agents) therapy (Table 1).

Feature selection and radscore construction

A total of 3,376 radiomic features were retained after selection (**Supplementary Materials S1 ~ S4**). The radscore was built based on the above selected textural features. LASSO regression analysis found that, radscore was significantly associated with OS. The lower muscle mass was associated with a higher radscore and a shorter OS of BC patients with BM (Fig. 3).

Kaplan-Meier analysis of BC patients with BM

By the end of the last follow-up, in the construction cohort, 111 patients died, the median OS was 35.4 months, the first-year OS rate was 81.9% (95% CI 75.7%-88.6%), 3-year was 48.6% (95% CI 40.9%-57.6%), the 5-year was 19.6% (95% CI 13.9%-27.4%). In the internal validation cohort, 46 patients died, the median OS was 33.3 months. The first-year OS rate was 79.7% (95% CI 70.0%-90.6%), 3-year was 49.2% (95% CI 37.9%-63.7%), the 5-year was 22.0% (95% CI 13.6%-35.6%). In the external validation cohort, 26 patients died, the median OS was 47.7 months. The first-year OS rate was 71.1% (95% CI 58.0%-87.0%), 3-year was 57.9% (95% CI 44.1%-75.9%), the 5-year was 31.6% (95% CI 19.8%-50.4%). (Fig. 4).

Independent prognostic factors of OS

Based on the analyzed univariate Cox proportional hazards regression model, various prognostic factors of BC patients with BM were found, including both axial and appendicular skeleton metastasis, pathology subtype and brain metastasis, ALP, TMI, bone CT-value and radscore. Subsequently, the variables with $p < 0.05$ in the univariate analysis were entered into the multivariate analysis to obtain the independent risk factors for OS. The independent prognostic factors for the clinicopathologic model and the clinicopathologic-radiomic model were identified by the multivariate Cox regression analysis, as displayed in Fig. 5.

Construction and validation of the clinicopathologic nomogram

The following identified variables were selected to construct the clinicopathologic nomogram: pathology, BM location, brain metastasis, ALP and Ca. The ROC curves of the clinicopathologic nomogram showed AUCs at 1-year (79.1%), 3-year (78.2%) and 5-year (75.8%) in the construction cohort, respectively. In addition, the calibration curves for the nomogram prediction model were all close to the 45-degree line, and the predicted values were in good agreement with the observed values at different points in time (Fig. 6).

Construction and validation of the clinicopathologic-radiomic nomogram

The clinicopathologic-radiomic nomogram for prognostic prediction in BC patients with BM was constructed based on the identified factors: pathology, BM location, brain metastasis, ALP and Ca, bone CT-value, TMI and radscore. The ROC curves of the clinicopathologic-radiomic nomogram showed AUCs at 1-year, 3-year and 5-year were 89.3%, 91.0% and 87.1% in the construction cohort, respectively. The calibration curves for the clinicopathologic-radiomic nomogram were all close to the 45-degree line, and the predicted values were in good agreement with the observed values (Fig. 7).

Comparative prediction performance between clinicopathologic and clinicopathologic-radiomic web-based nomogram

As shown in Fig. 8, within the internal validation cohort, the AUCs of the predictive nomogram based on the clinicopathologic-radiomic nomogram at 1-, 3- and 5-years were 82.3%, 91.1% and 82.9%, respectively. The nomogram showed good accuracy in prognostic prediction, with a C-index of 0.82. The AUCs of the predictive nomogram based on clinicopathologic nomogram at 1-, 3- and 5-years were 74.9%, 82.1% and 70.3%, respectively. The nomogram showed the C-index was 0.71. The clinicopathologic-radiomic nomogram demonstrated a relatively better performance than the clinicopathologic nomogram.

External validation of the clinicopathologic-radiomic nomogram

As shown in Fig. 9, AUCs of the clinicopathologic-radiomic nomogram at 1-, 3-, 5-year were 85.1%, 84.3% and 67.7%, respectively. The ROC curve showed that the prediction of the nomogram was a good generalizability of the prediction model.

Discussion

In our study, we evaluated radiomics features of body composition and clinicopathologic factors for prognostic prediction in BC patients with BM. Previous prognostic prediction systems didn't involve the patient's body composition[34, 35]. The established clinicopathologic-radiomic nomogram can precisely and individually predict the prognosis of BC patients with BM. Such nomogram can be used as the auxiliary tool for prognostic prediction in BC patients with BM.

Various prognostic factors for BC patients with BM were reported. Some studies reported that triple-negative breast cancer (TNBC), brain metastasis and ALP were the independent prognostic factors for BC patients with BM[8, 36]. Based on the analysis of the SEER (Surveillance, Epidemiology, and End Results, SEER) database, pathology, liver, lung and other visceral metastasis, brain metastasis were the independent prognostic factors for BC patients with BM[9]. In the present study, both axial and appendicular skeleton metastasis, TNBC and brain metastasis were found to be the prognostic factors of BC patients with BM. Compared with previous studies, we considered both axial and appendicular skeleton metastasis was one of the most important independent prognostics factors. Appendicular and axial skeleton metastases usually result in the pathological fractures, spinal cord compression, and paraplegia, leading to various subsequent complications (pendant pneumonia, bedsores, and deep venous thrombosis of the lower extremity) that can significantly reduce the prognosis of patient and the patients' quality of life. The previous study reported that, the median OS in patients with metastases occurring in both the axial and appendicular skeleton was 4.58 years, in appendicular metastasis only was 6.78 years, and in axial metastasis only was 5.62 years[37].

Body composition found to be significantly associated with the prognosis of BC patients with BM. The lower mass of muscle and bone was correlated with the worse prognosis of BC patients with BM. The previous study suggested the anabolism and catabolism imbalance in the advanced cancer can cause the significant body composition changes. Previously, surgery, chemotherapy, radiotherapy and endocrine therapy were reported to result in the change of body composition in BC patients with BM[38].A series of studies reported the cancer patients at advanced stage showed a rapid and severe loss of muscle and bone mass, and showed a high risk of sarcopenia and osteoporosis. Such musculoskeletal changes can significantly increase the occurrence risk of skeletal related event [16, 17, 39]. Musculoskeletal system, as a main component of the body composition, was reported to be one of the important prognostic factors for patients with malignant tumors. The decrease of body composition caused by musculoskeletal

system reduction, was reported to be correlated with the poor performance status, toxic effect of chemotherapy, and dissatisfactory tumor control[40]. The occurrence of osteoporosis can cause the destruction of bone microstructure, thus resulted in the increased risk of bone fracture in BC patients with BM[41].

Several studies reported the muscle index being one of the prognostic indicators in lymphoma and cervical cancer. The muscle index can be also used for evaluating hospital stay, surgical complications, early death and readmission rates of patients[19, 42, 43]. However, in our study we didn't find the significant association between TMI and the prognosis of BC patients with BM. We attributed this to the limited sample size. With the radiomic analysis, we found the significant association between the muscle texture features and the prognosis of BC patient with BM. Thus, we hypothesized, compared with TMI for prognostic evaluation, the identified radscore by radiomics can be more sensitive. The latest studies reported the radscore being the potential imaging biomarker for predicting the prognosis in patients with cervical cancer and in patients with COVID-19[29, 31].

In the present study, compared with the clinicopathologic nomogram, the clinicopathologic-radiomic nomogram showed better ability on prognostic prediction in BC patients with BM. The integration of body composition can significantly improve the predictive ability of nomogram. Thus, the radscore on body composition can be a sensitivity and accurate indicator for prognostic prediction in cancer patients.

Our study has certain limitations. First, it was a retrospective study with a limited sample size, statistical bias cannot be avoided. Future study with larger sample will be needed. Second, the CT images in the external cohort were generated with different CT equipment, the study with more images from multicenter should be performed.

Conclusions

This study described the characteristics and prognostic situation of BC patients with BM. With the radiomics analysis, the decreased body composition was found to be significantly correlated with the worse prognosis. Besides the body composition, bone CT-value, brain metastasis, both axial and appendicular skeleton metastasis were all found to be the independent prognostic factors in BC patients with BM. The clinicopathologic-radiomic nomogram was built based on the identified factors. After the internal and external validation, the established nomogram was proved to be a valid tool for prognostic prediction in BC patients with BM. Such nomogram can be an auxiliary tool guiding clinicians make personalized clinical decisions.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (Approval No.bc2021245) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Ethics Committee because of the retrospective nature of the study.

Consent for publication

Not applicable. This study does not include any identifying images or personal or clinical details of participants that could compromise anonymity.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contribution

H.W., H.L., and Y.L. contributed equally to this work. H.W., H.L., and Y.L. conceived and designed the study. H.W., J.C., W.M., and C.Z. collected and curated the clinical data. H.L., Y.L., M.A.A., and E.R.M. performed radiomic feature extraction and image analysis. J.W., S.L., and H.L. performed statistical analysis and model construction. H.W., H.L., and Y.L. drafted the manuscript. All authors reviewed, critically revised, and approved the final manuscript.

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Not applicable.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1

Characteristics	Construction cohort (n=138)			Internal validation (n=59)			External validation (n=38)		
	No	Yes	p	No	Yes	p	No	Yes	p
Age (median [IQR])	27	111		13	46		12	26	
Pathology (%)	58.00 [52.50, 63.00]	53.00 [46.00, 61.00]	0.09	49.00 [45.00, 58.00]	54.00 [47.25, 60.75]	0.464	50.50 [48.75, 54.75]	51.00 [47.00, 54.00]	0.962
luminal A			0.012			0.453			0.458
luminal B (HER2-)	5 (18.5)	36 (32.4)		5 (38.5)	9 (19.6)		4 (33.3)	14 (53.8)	
HER2+ (HR+)	19 (70.4)	38 (34.2)		5 (38.5)	19 (41.3)		6 (50.0)	8 (30.8)	
HER2+ (HR-)	1 (3.7)	11 (9.9)		1 (7.7)	5 (10.9)		2 (16.7)	4 (15.4)	
triple negative	0 (0.0)	14 (12.6)		0 (0.0)	7 (15.2)		9 (75.0)	24 (92.3)	0.342
Ki-67 >14% (%)	2 (7.4)	12 (10.8)		2 (15.4)	6 (13.0)		10 (83.3)	19 (73.1)	0.779
Metachronous BM (%)	18 (66.7)	72 (64.9)	1	10 (76.9)	33 (71.7)	0.986			0.191
BM location (%)	15 (55.6)	66 (59.5)	0.88	7 (53.8)	21 (45.7)	0.835	1 (8.3)	2 (7.7)	
appendicular			0.05			0.095	0 (0.0)	6 (23.1)	
axial	11 (40.7)	29 (26.1)		6 (46.2)	8 (17.4)		11 (91.7)	18 (69.2)	
both	8 (29.6)	20 (18.0)		2 (15.4)	13 (28.3)		11 (91.7)	19 (73.1)	0.38
BM number ≥ 5 (%)	8 (29.6)	62 (55.9)		5 (38.5)	25 (54.3)		2 (16.7)	5 (19.2)	1
Radiotherapy (%)	13 (48.1)	57 (51.4)	0.933	7 (53.8)	14 (30.4)	0.219	4 (33.3)	9 (34.6)	1
Surgery (%)	7 (25.9)	17 (15.3)	0.307	3 (23.1)	6 (13.0)	0.652	11 (91.7)	15 (57.7)	0.086
BMAs (%)	1 (3.7)	4 (3.6)	1	1 (7.7)	3 (6.5)	1	5 (41.7)	16 (61.5)	0.427
Lung metastasis (%)	21 (77.8)	93 (83.8)	0.649	11 (84.6)	39 (84.8)	1	7 (58.3)	6 (23.1)	0.078
Liver metastasis (%)	14 (51.9)	50 (45.0)	0.674	5 (38.5)	18 (39.1)	1	2 (16.7)	14 (53.8)	0.071
Brain metastasis (%)	10 (37.0)	40 (36.0)	1	6 (46.2)	18 (39.1)	0.892	96.50 [88.50, 122.75]	112.50 [87.50, 140.75]	0.489

ALP (median [IQR])	1 (3.7)	22 (19.8)	0.084	1 (7.7)	13 (28.3)	0.242	2.39 [2.31, 2.42]	2.45 [2.37, 2.53]	0.036
Ca (median [IQR])	102.00 [69.50, 131.50]	136.00 [99.00, 215.50]	0.012	83.00 [66.00, 96.00]	110.00 [83.25, 163.50]	0.009	155.00 [134.12, 164.25]	118.75 [90.50, 137.25]	0.006
TMI (median [IQR])	2.30 [2.21, 2.39]	2.39 [2.29, 2.46]	0.038	2.25 [2.14, 2.39]	2.36 [2.25, 2.48]	0.056	7.09 [6.08, 8.52]	7.11 [6.17, 8.81]	0.925

Note: No: alive; Yes: death; BM: bone metastasis; BMAs: bone-modifying agents; ALP: alkaline phosphatase; TMI: total skeletal muscle index.

Figures

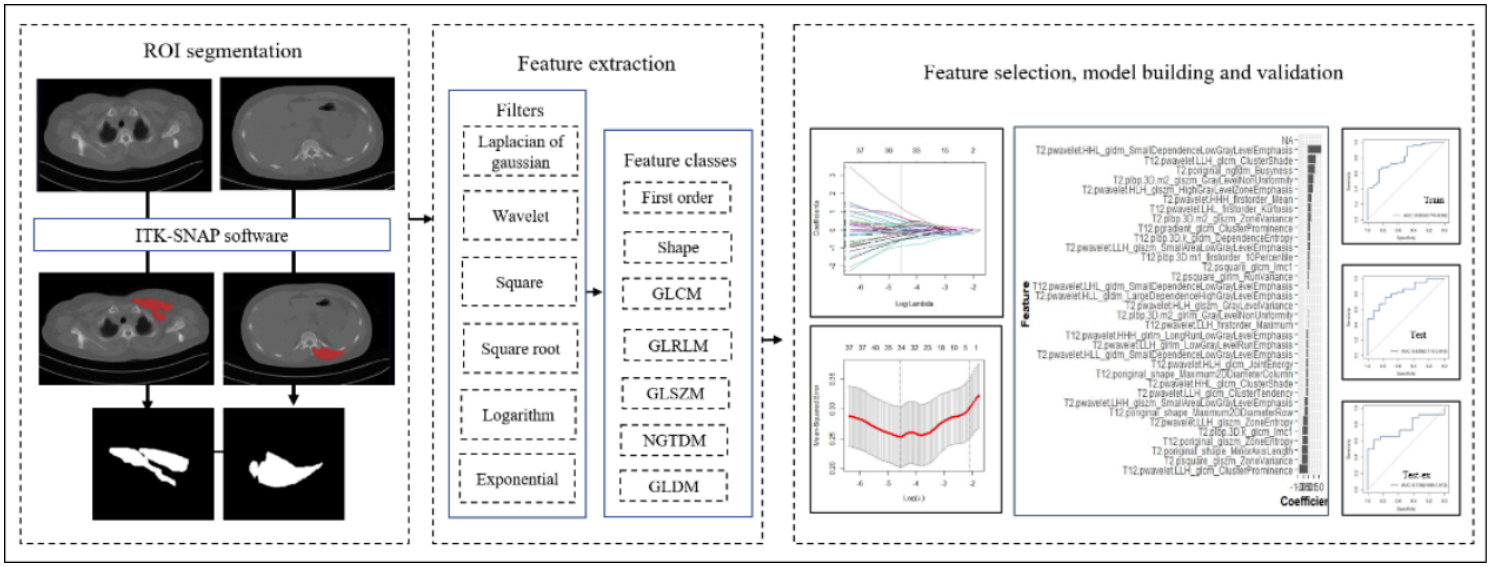


Figure 1

Flow chart of the study.

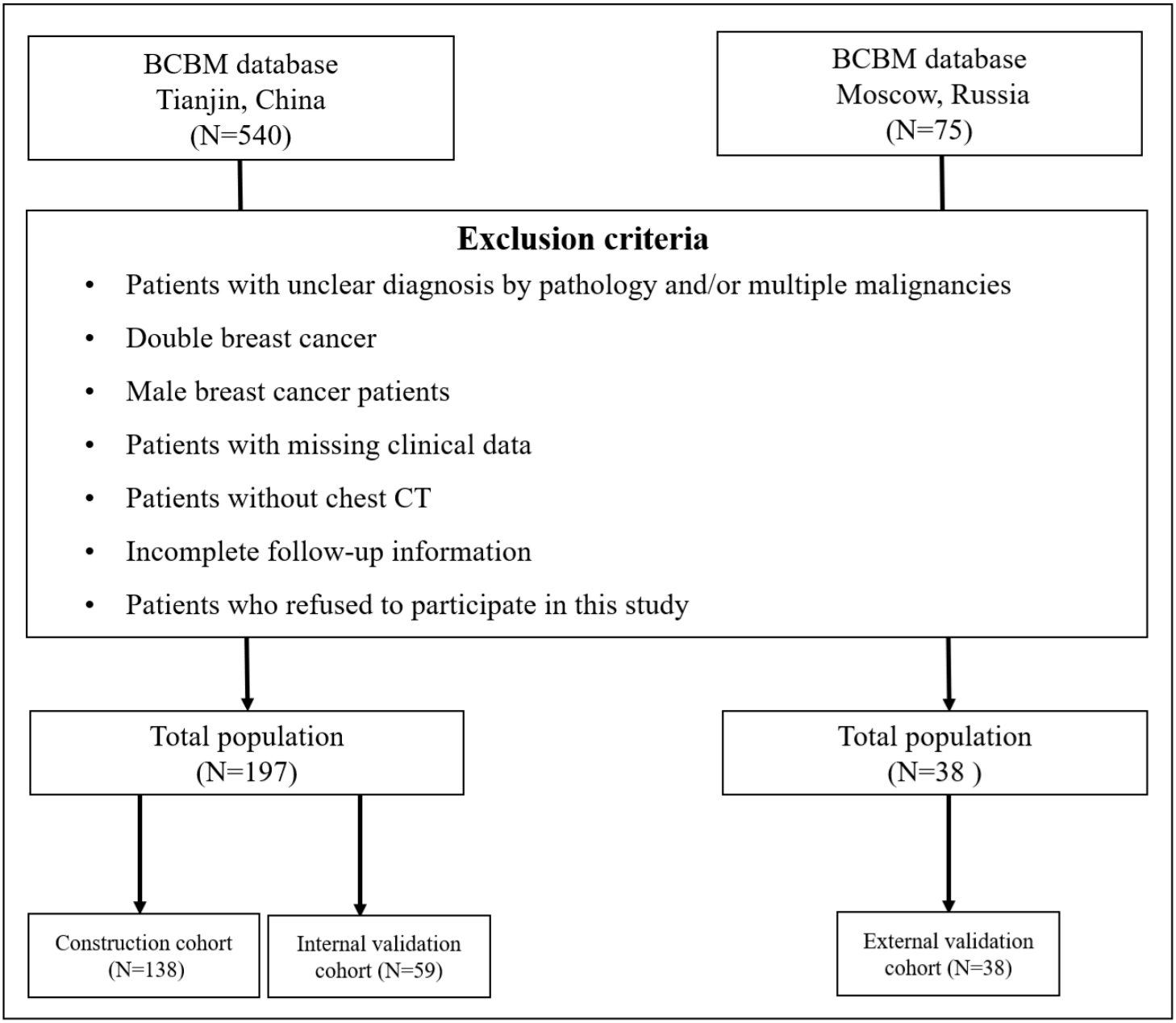


Figure 2

Flowchart for the selection of BC patients with BM.

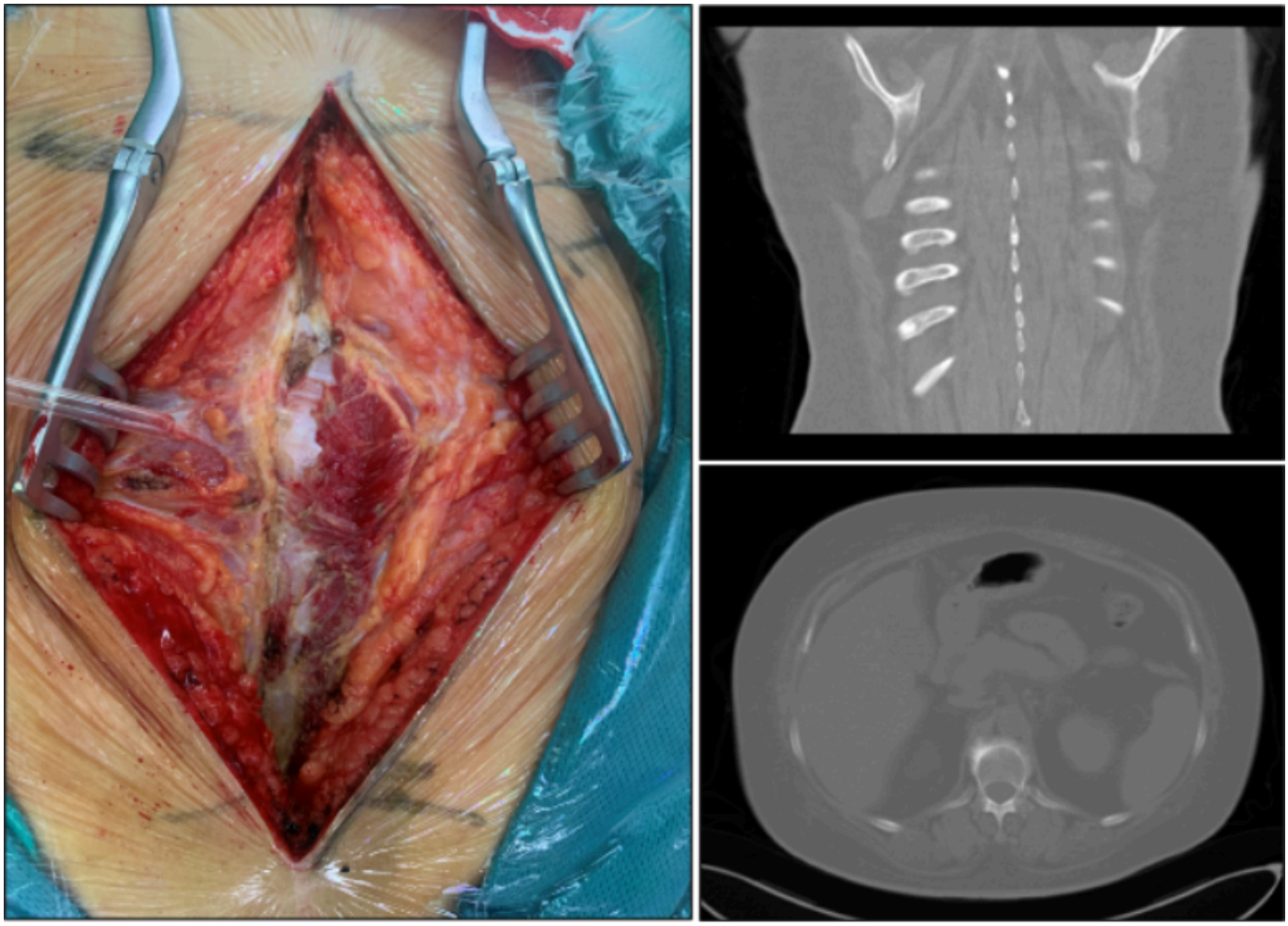


Figure 3

A 43-year-old BC patient with BM showed the survival level of 16.7 months. Intraoperative, axial and coronal CT images showed a significant increase in the adipose tissues of the erector spine muscle.

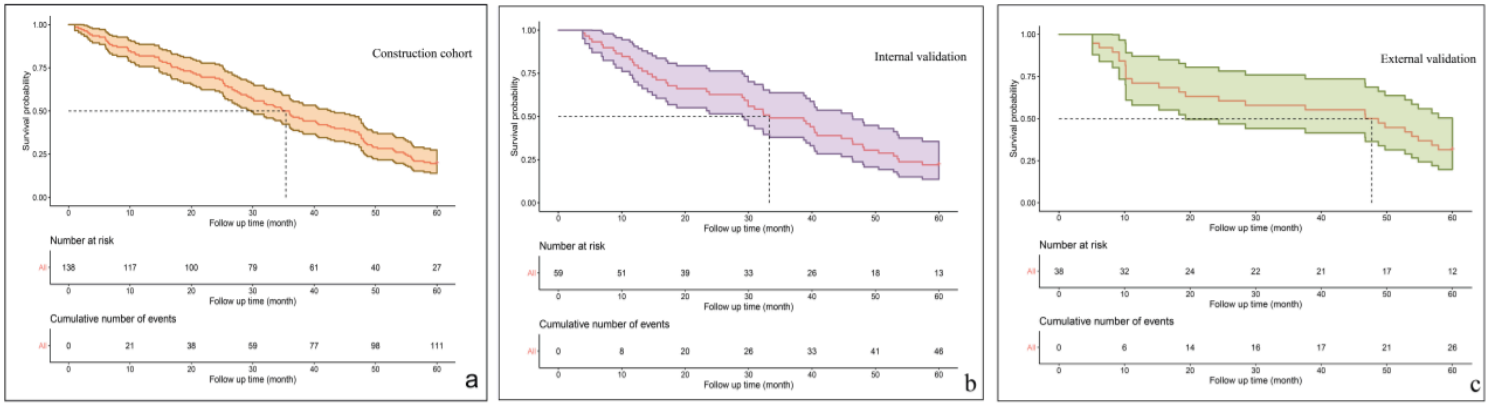


Figure 4

Kaplan-Meier analysis. a: KM curves in construction cohort; b: KM curves in internal validation cohort; c: KM curves in external validation cohort.

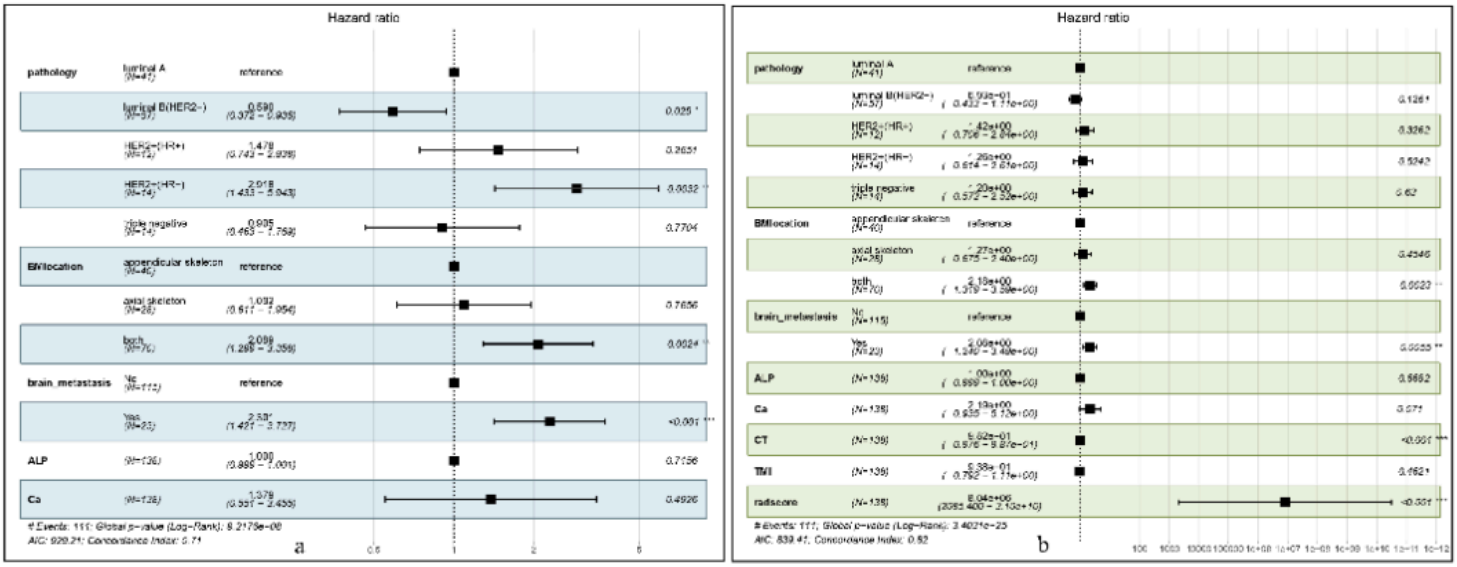


Figure 5

Multivariate Cox proportional hazards regression model. The results showed that in clinicopathologic prediction model: pathology, BM location and brain metastasis were independent prognostic factors (a). In clinicopathologic-radiomic model: BM location, brain metastasis, bone CT-value and radscore were the independent prognostic risk factors for OS (b).

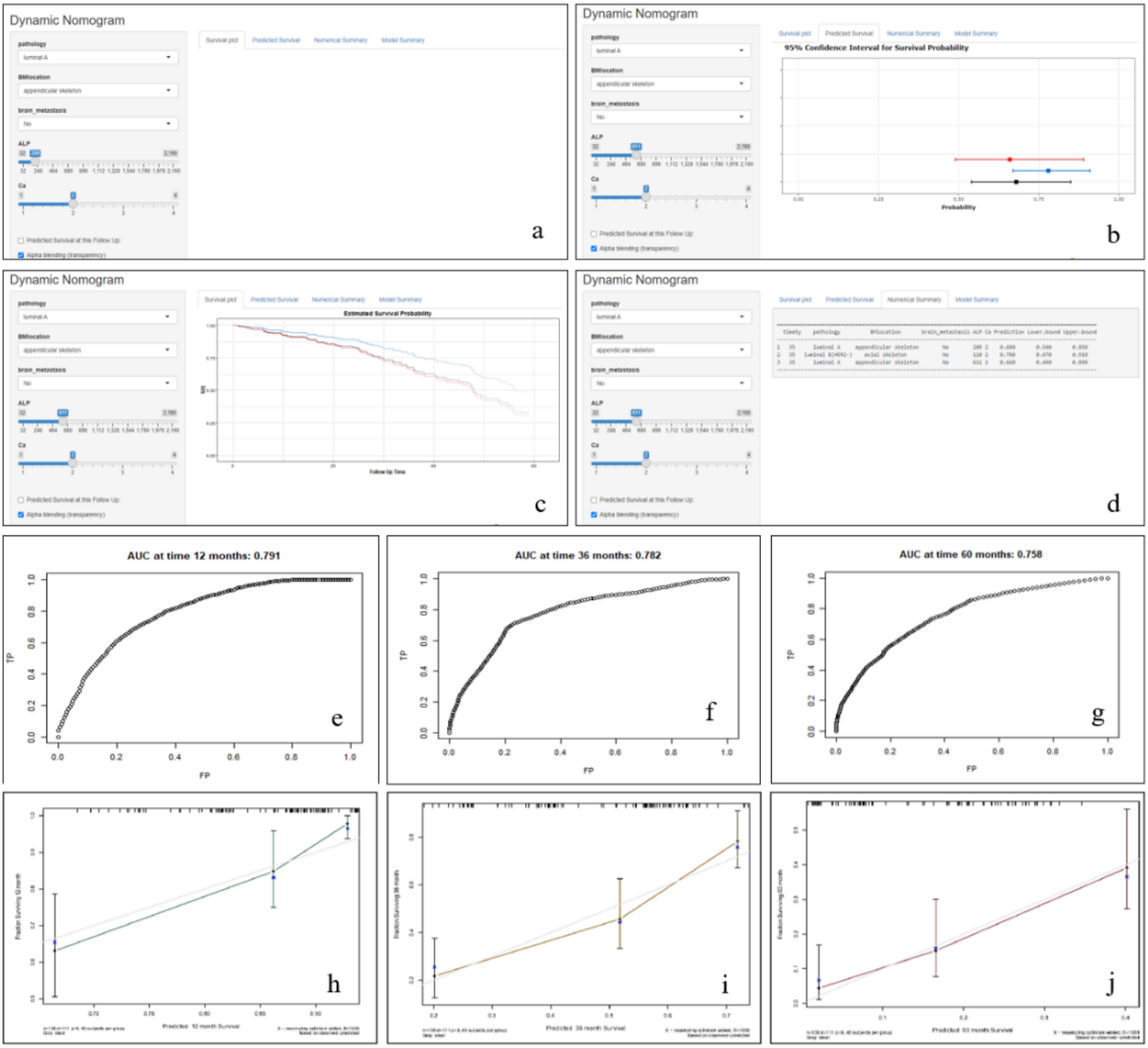


Figure 6

The clinicopathologic nomogram was established (a~d). ROC curves were used to evaluate the predictive ability of the nomogram at different time points (e~g). The calibration curves for the nomogram prediction model were all close to the 45-degree line (h~j).

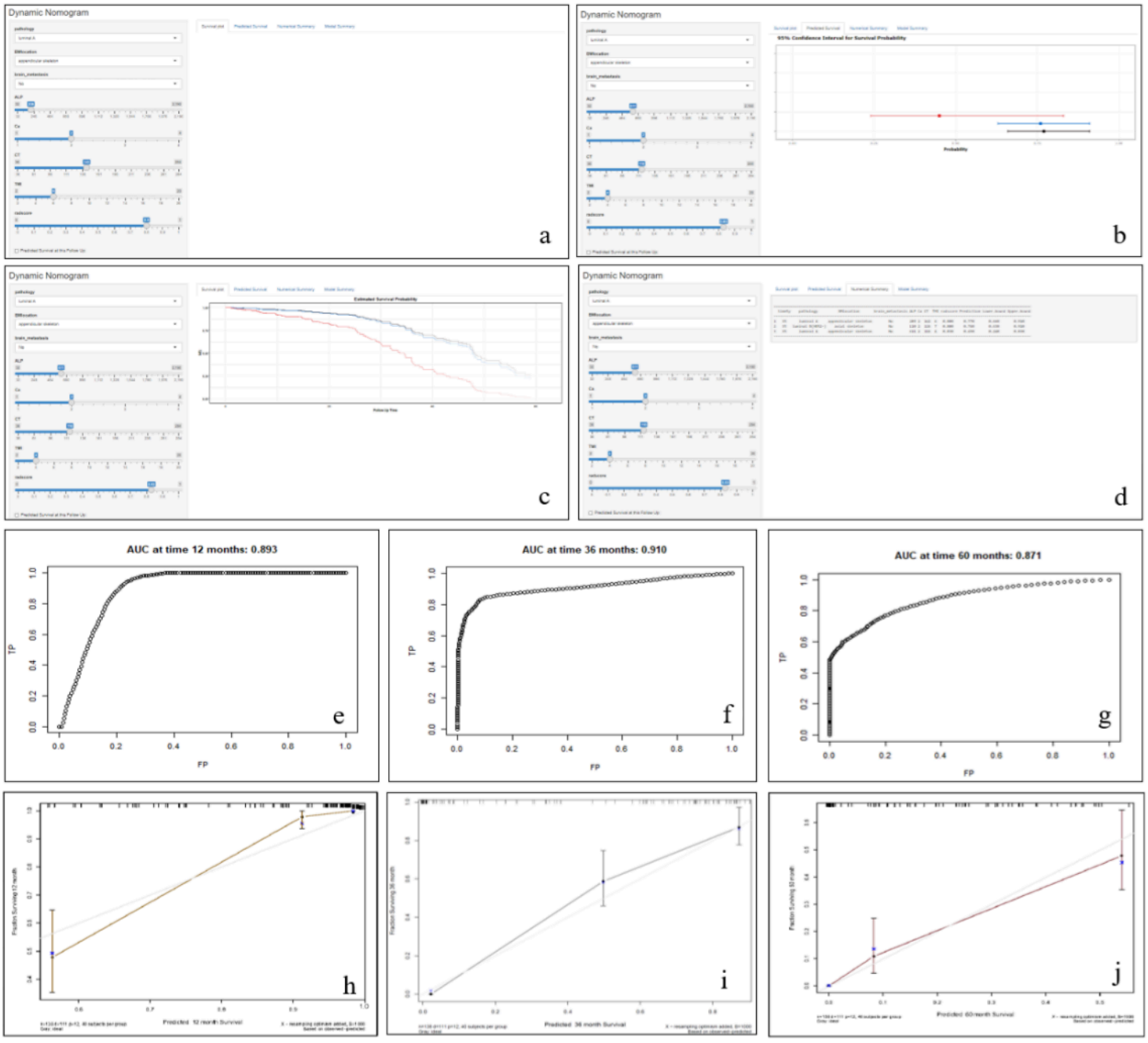


Figure 7

Theclinicopathologic-radiomic nomogram was established (a~d). ROC curves were used to evaluate the predictive ability of the nomogram at 1-,3-,5-year (e~g). The calibration curves for the nomogram prediction model were all close to the 45-degree line (h~j).

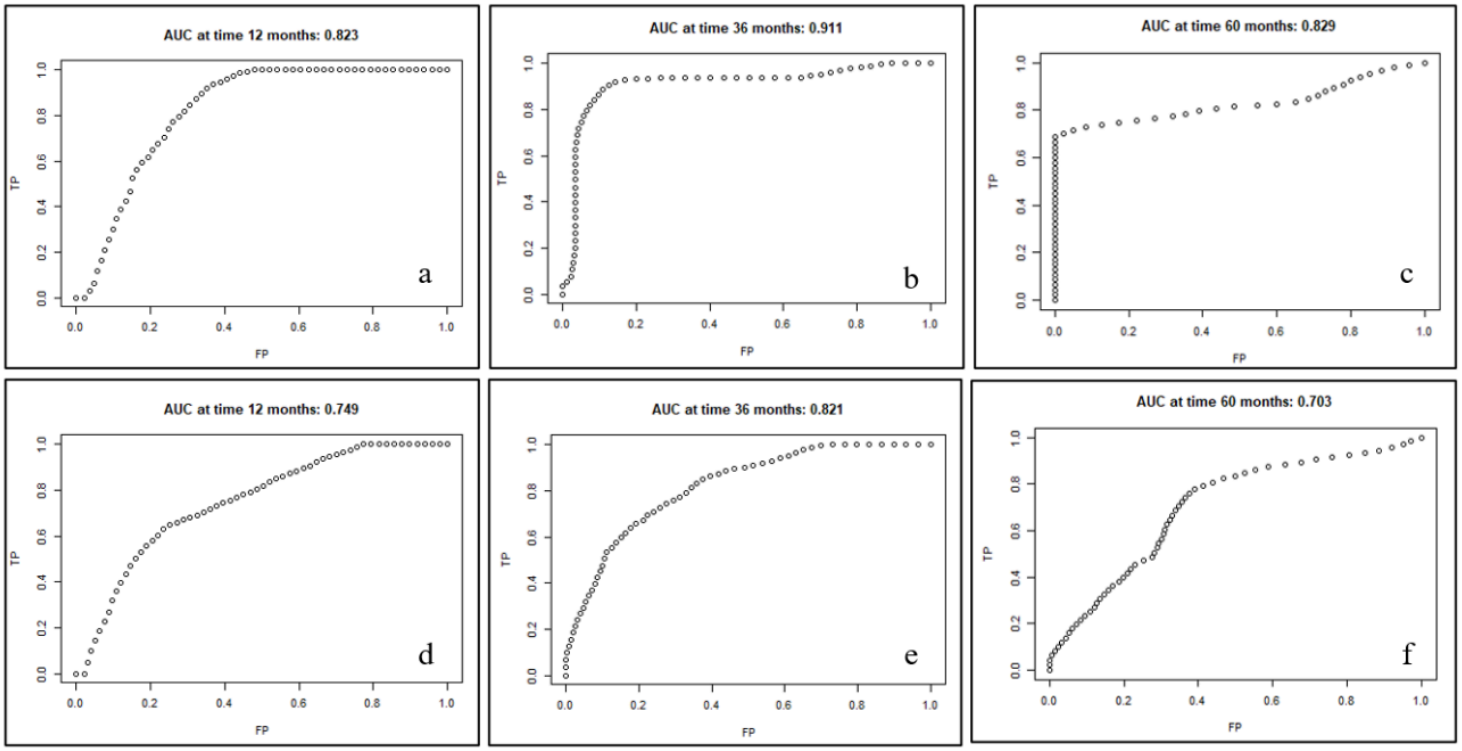


Figure 8

the AUCs of the predictive nomogram based on the clinicopathologic-radiomic nomogram (a~c) and clinicopathologic nomogram (d~f) at different points in time. The results demonstrated a relatively better performance in the clinicopathologic-radiomic web-based nomogram.

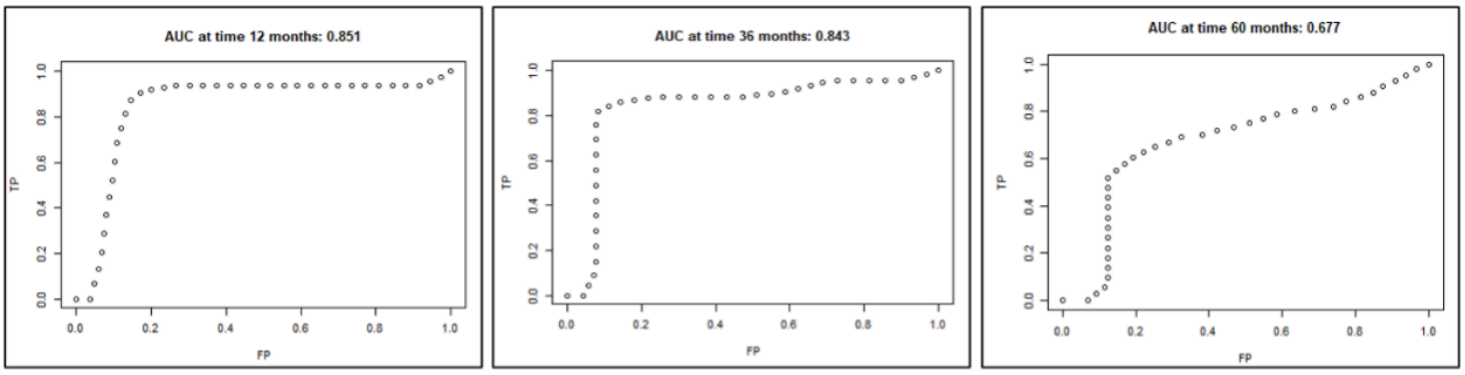


Figure 9

the ROC curve of the clinicopathologic-radiomic nomogram at different time points in the external validation cohort (a~c).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx