Original Article

Comparison and modification of survival predicting system for breast cancer patients with bone metastases

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Background: Breast cancer is the most common malignancy in the female. Survival for patients with breast cancer has improved substantially over the past two decades, accompanied by increased patients with skeletal-related events. Since surgery is most commonly needed for complete or pending pathological fractures, an accurate preoperative survival estimation for patients with symptomatic bone metastases is crucial in surgical decision making. Several prognostic models for survival estimation in metastatic cancer patients have been developed in western centers without external validation in Asian patient populations and breast cancer-specific cohorts.

Methods: Seven survival prediction models were externally validated by a cohort of metastatic breast cancer patients from an Asian center. The prediction ability and accuracy were valued using receiver operating characteristic analysis and Brier score at different time points. Univariate and multivariate Cox regression was used to identify independent prognostic factors. A multivariable prediction model was further established and validated.

Results: In our metastatic breast cancer patients cohort, the PathFx model demonstrated superior accuracy at predicting 3- and 6-month survival while the SSG model showed the highest accuracy at 12-month. None of these models exhibit accurate predictions beyond 12-month. Cox regression further identified five independent prognostic factors. A prognostic scoring system with breast cancer-specific prognostic factors was established. Internal validation showed consistent discrimination and accuracy.

Conclusions: Current prognostic models showed inconsistent and limited accuracy in Asian metastatic breast cancer patients, especially for more prolonged estimated survival. A disease-based predicting model with cancer-specific prognostic factors would increase the prediction accuracy and help with surgical decision making.

Keywords: Breast cancer; bone metastases; survival prediction; prognostic factor

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Introduction

Breast cancer is the most common cancer type that contributes to about one-third of all female cancer cases which is predicted to have around 0.276 million cases in 2020 in the U.S. and 0.279 million cases in China in 2014 (1,2). With the improvement of treatment regimens in breast cancer, especially hormone therapies and targeted therapies, the survival of patients with breast cancer bone metastases (BCBM) has significantly increased as compared to lung and gastrointestinal cancers (1,2). As a result, an increasing number of BCBM patients are suffering from skeletal-related events (3).

Destruction of bone by metastatic disease reduces its loadbearing capabilities and results initially in microfractures. Microfractures can cause pain and eventually may lead to a complete fracture of the bone. Most bone lesions develop symptoms such as consistent pain and impaired function (3,4). Surgery is most commonly needed for mechanical complications, such as a complete or pending fracture or intractable pain (4,5). The goals of surgery are to relieve the pain, restore structural stability and function, improve life quality, and eventually benefit the patient without increasing the risk of complications. Surgical treatment for metastatic disease is palliative and not curative. In oncologic orthopedics, surgical treatment choice varies from less-invasive stabilization to tumor resection and prosthetic reconstruction procedures. The method of choice depends on patient survival and the site of metastasis. Expected survival is the most crucial factor in determining the treatment modality. An accurate survival estimation will help decide the proper surgical plan and treatment regimen, thereby preventing overtreatment and undertreatment.

Several studies had tried to assess the survival time for patients with bone metastases previously, including Katagiri *et al.* (referred to as the Revised Katagiri model) (6), Janssen *et al.* (referred to as the Janssen nomogram model) (7), Willeumier *et al.* (referred to as the OPTI model) (8), Ratasvuori *et al.* (referred to as the Scandinavian Sarcoma Group SSG model) (9), Forsberg *et al.* (referred to as the PathFx model) (10), Sørensen *et al.* (referred to as the SPRING model) (11), and van der Linden *et al.* (referred to as the SORG model) (12). However, there is no consensus regarding which prognostic model is the most accurate. These models provide inconsistent survival predictions for a given patient at various time points. Lack of external validation could be one of the reasons, especially non-western patient cohorts. Besides, since cancer biology plays a dominant role in patient survival, increasing evidence suggests that tumor type-specific prognostic parameters could contribute to prognostic models' accuracy (13,14).

Therefore, the present study aims to compare the most prevalent scoring systems available to determine BCBM patients' survival at various time points. Besides, we use univariate and multivariate Cox regression to identify independent prognostic factors. A BCBM-specific scoring system was further generated with cancer-specific prognostic variables to increase prediction accuracy and guide surgical intervention.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/aoj-20-120).

Methods

Study design and subject inclusion

This research was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval was obtained from the ethics committee of Peking University People's Hospital. Informed consent was not required for this retrospective, non-interventional study, which was considered minimal risk. Patients who underwent surgery for breast cancer metastatic bone tumors at a single institution between 2010 and 2018 were investigated. The inclusion criteria were (I) patient age greater than 18 at the time of surgery; (II) complete and detailed electronic medical records with clinical presentation, imaging, histological and operative information available; (III) breast cancer patient who underwent surgical treatment of a metastatic bone lesion; (IV) pathologic confirmation of primary tumor histology; (V) known survival or most recent follow-up. Patients for whom the date of death was missing due to loss of follow-up were censored at the last time they were known to be alive.

Prognostic models

All patients were assessed using the seven scoring systems most represented in the literature. These scoring systems were calculated based on retrospective data before the time of surgery (6-12). Only objective inputs were utilized. The PathFx model has optional subjective variables that were omitted from the model for this analysis (10). Patient data were complete for all prognostic models at the time of

operative management. A survival probability was calculated for each patient with respect to the given scoring system.

Statistical analysis

Primary demographic data were summarized as categorical variables and mean with range, standard error (SE), or percentage. To assess which variables were marginally significantly associated with survival, we performed univariate Cox regression analysis on all variables collected. Categorical variables were established as body mass index (BMI) less than 20 kg/m^2, age greater than 70 years old, presence of visceral metastases, presence of multiple skeletal metastases, presence of pathological fractures, history of systemic chemotherapy, radiation therapy, hormonal therapy, and bisphosphate therapy. The Karnofsky Performance Score (KPS) greater than 70 versus less than 50 and the intermediated. The Eastern Cooperative Oncology Group (ECOG) performance status equal and less than 2 versus higher than 2. Preoperative lactate dehydrogenase (LDH) greater than 250 U/L, albumin less than 35 g/L, total bilirubin greater than 23 μmol/L, platelets less than <80×10^9/L, hemoglobin less than 8.5 g/dL and serum calcium greater than 2.6 mmol/L. Molecular type classification of breast cancer, luminal A versus luminal B, HER-2 overexpression, triple-negative and undetermined, breast cancer receptor status of hormone-dependent versus hormone-resistant. A multivariate Cox proportional hazards model was constructed using all the marginally significant variables (P<0.10). Subsequently, covariates that were not independently associated with survival (P<0.05) or violated the proportional hazards assumption were removed in a stepwise manner. All patients were categorized into molecular subtype groups defined by Perou *et al.* and Sørlie *et al.* (15,16). The final variables with an independent and statistically significant association with patient survival were retained and reported. The predictive abilities of prognostic scoring algorithms were tested using receiver operating characteristic (ROC) analysis at 1-, 3-, 6-, 12-, 18- and 24-month post-surgery time points using the calculated area under the curve (AUC) and 95% confidence intervals (CIs) for each model. An AUC of 1.0 indicates perfect accuracy, whereas an AUC of 0.5 indicates no relationship or predictive accuracy. An AUC cut-off was set at 0.70 for a scoring system to be considered to have sufficient predictive accuracy (17-19). AUC values were compared with Delong's test (20). The level of significance was set at P<0.05. The Brier score measures a probabilistic model's accuracy summing the difference between expected survival and actual survival period. The scores vary between 0 and 1, with a lower score indicating better predictions for the model. All statistical analyses were performed using R software, version 3.5.3. The ROC curve and the AUC were evaluated using the "survivalROC" package, while Kaplan-Meier analyses and Cox proportional hazards regression were conducted using the "Survival" package.

Generation of BCBM specific prognosis scoring model

The TRIPOD statement was applied to generate the new prognosis scoring model (21). Briefly, statistically significant variables associated with patient survival were retained from the multivariate Cox proportional hazards model. Each risk factor was characterized, and the reference value (W_{ij}) was defined as 0 or 1 for categorical factors, and 0 is defined as the base reference value (W_{iREF}). In the molecular subtype, Luminal A was defined as the base reference value. The difference (D) between each risk factor and its base reference value was defined as $D=(W_{ij}-W_{iREF})*\beta i$. The constants B was defined as 0.953. Each risk factor's point value was calculated as $Points_{ij}=D/B=(W_{ij}-W_{iREF})*\beta i/B$, and results were rounded to the nearest 1 (Table S1). After the model was established, the estimate of risk (^p) at each corresponding point and time point was calculated as:

$$\hat{p}=1-S_0\left(t\right)^{\exp\left(\sum_{i=1}^{p}\beta_i X_i-\sum_{i=1}^{p}\beta_i \bar{X}_i\right)}.$$

Results

Patient demographics and presentation

Upon retrospective review of electronic medical records for patients surgically treated for BCBM, 214 patients were initially identified. Among them, 27 did not have complete medical records, and 49 were lost follow-up were excluded. The remaining 138 patients met all inclusion and exclusion criteria for the current study and were included. *Table 1* summarizes the characteristic of the 138 patients studied. The mean age and BMI for all patients were 54.1± 11.5 years old and 23.8±2.9 kg/m^2, respectively. The ECOG score and KPS measured patients' performance status. The previous treatments, including systemic chemotherapy, hormonal therapy, and radiotherapy, were documented. Pathological analysis in terms of molecular type or receptor status of breast cancer was acquired from the bone lesions or previous breast surgery sample. Luminal B (50.6%) from the molecular type and hormone-dependent (76.6%) for

Table 1 Patient demographics and baseline characteristics

Demographics	Mean
Age (years)	54.1±11.5
BMI (kg/m^2)	23.8±2.9
Pre-op serum markers	
Hemoglobin (g/L)	121.1±16.2
Platelets (×10^9/L)	233.6±86.3
White cell count (×10^9/L)	7.9±3.4
Albumin	42.5±11.0
C-reactive protein	14.1±32.7
Calcium (mmol/L)	2.3±0.7
Lactate dehydrogenase	249.6±183.3
Total bilirubin (mg/dL)	13.3±10.9
CEA (ng/mL)	28.2±55.5
CA-153 (U/ml)	80.2±90.2
KPS performance	
KPS >70	36.7%
70≥ KPS >50	39.9%
KPS ≤50	23.2%
ECOG score	
Score 0–2	61.4%
Score 3–4	38.6%
Staging/treatment	
Multiple skeletal metastases	60.8%
Visceral metastases	36.1%
Previous chemotherapy	83.5%
Previous hormonal therapy	57.6%
Previous radiotherapy	38.6%
Previous bisphosphate	44.9%
Surgical and clinical characteristics	
Pathological fracture	56.9%
Location	
Trunk	5.7%
Extremity	20.3%
Spine	60.1%
Pelvis	13.9%
Surgery	
Resection/curettage and stabilization	86.1%
Resection alone	5.7%
Stabilization alone	8.2%
Tumor molecular type	
Luminal A	22.8%
Luminal B	50.6%
HER-2 overexpression	5.7%
Triple-negative	10.1%
Unknown	10.8%
Tumor receptor status	
Hormone dependent	76.6%
Hormone independent	15.8%
Unknown	6.6%

BMI, body mass index; KPS, Karnofsky Performance Score; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; CA-153, cancer antigen 15-3.

receptor status was the most common type. The majority of patients had metastasis located in the spine (60.1%), followed by in the extremities (20.3%) and pelvis (13.9%). All patients were managed, consulted on, and followed up by a multidisciplinary team of radiologists and oncologists. As such, the decision to pursue surgery was made based on the patient's best interest and clinical judgment by the treating team. All patients had oncologic staging before surgery, and those with significant comorbidities or systemic burden were not offered surgery. The median duration of survival or last follow-up was 34.8 months (95% CI: 26.0–40.7 months) with a range of 0.2–109.1 months. The K-M curve of all patients included in this study was plotted (*Figure 1*).

Factors associated with survival

Firstly, a univariate Cox regression analysis was performed. Older age [≥70 years, hazard ratio (HR) 2.024, 95% CI: 0.993–4.127, P=0.049], higher LDH level (LDH >250 U/L, HR 1.91, 95% CI: 1.130–3.229, P=0.016), poor KPS

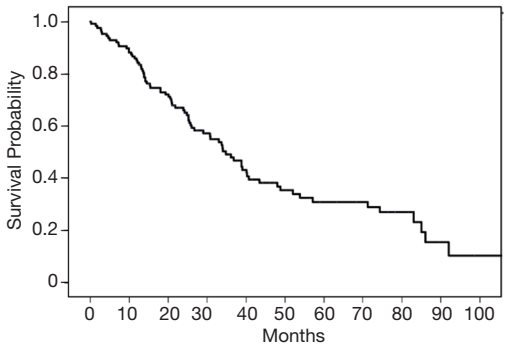

Figure 1 Kaplan-Meier survival curve of overall survival of patients in this cohort.

performance status (KPS <50; HR 2.816, 95% CI: 1.737–4.566, P<0.001), subtype of molecular type (triple-negative subtype, HR 2.09, 95% CI: 1.018–4.289, P=0.045), previous radiotherapy (HR 0.513, 95% CI: 0.320–0.823, P=0.006), presence of pathologic fractures (HR 1.585, 95% CI: 1.001–2.510, P=0.049) and presence of visceral metastases (HR 3.035, 95% CI: 1.893–4.868, P<0.001) were significantly associated with survival (*Table 2*). Upon multivariate analysis, the following covariates had an independent and statistically significant association with decreased survival: older age (≥70 years old, HR 2.385, 95% CI: 1.099–5.179, P=0.028), poor performance status (KPS <50 HR 2.842, 95% CI: 1.679–4.812, P<0.001), higher LDH level (LDH >250 U/L, HR 2.155, 95% CI: 1.251–3.713, P=0.006), presence of visceral metastases metastasis (HR 2.877, 95% CI: 1.756–4.715, P<0.001), and molecular type (HR 1.312, 95% CI: 1.050–1.641, P=0.017) (*Table 3*).

Overall predictive accuracy of survival by seven scoring systems

Among all patients surgically managed for BCBM, the PathFx model demonstrated the highest accuracy at predicting 3-month and 6-month survival (AUC =0.953 and 0.948, respectively) (*Table 4*). Other than the PathFx model, Revised katagiri score (AUC =0.904), Janssen nomogram (AUC =0.811), SPRING 13 (AUC =0.717), and SORG Nomogram (AUC =0.7111) also sufficiently accurate at predicting 3-month survival. Revised Katagiri score (AUC =0.7013) and OPTIModel (AUC =0.7418) also provided sufficient accuracy at predicting 6-month survival. PathFx yielded a Brier score of 0.178 at 3-months and 0.272 at 6-months. SSG scale (AUC =0.864) was the most accurate at predicting 12-month survival with a Brier score of 0.275. Additionally, the Janssen nomogram (AUC =0.803), the OPTI model (AUC =0.814), the PathFx model (AUC =0.861), and SORG Nomogram (AUC =0.838) all achieved sufficient predictive accuracy for 12-month survival (Brier score =0.193, 0.260, 0.276, and 0.215 respectively). However, none of these scoring systems were able to achieve satisfactory accuracy for predicting longer than 12-month. In summary, although it failed to provide accurately beyond one year, the PathFx model was the only scoring system to achieve sufficient accuracy at predicting survival within one year after surgery. The revised Katagiri score can also accurately predict survival within 6-month.

Generation and examination of BCBM specific prognosis scoring model

Covariates that had an independent and statistically significant association with decreased survival from the multivariate analysis were used to establish a new scoring system. Five variates in the system including older age (age >70), poor KPS performance status (KPS <50), higher LDH level (LDH >250 U/L), presence of visceral metastases, and molecular type of luminal B, triple-negative, or Undetermined. Each category contributes 1 point, with a total score range from 0 to 5 (*Table 5*). The estimate of the risk of each point at 3-, 6-, 12-, 18-, 24-month was calculated (*Table 6*). For example, points from 0 to 5 indicate an estimate of risk of 0.09, 0.22, 0.48, 0.81, 0.98, and 0.99 at 24-month. Similarly, a point of 2 indicates an estimate of risk of 0.07, 0.10, 0.22, 0.36 and 0.48 at 3-, 6-, 12-, 18- and 24-month. The K-M curve of patients with different total points showed high distinguish efficiency from each other (log-rank P<0.001) (*Figure 2*).

Discussion

This current study validates the seven most relevant prognostic models' survival prediction accuracy using a non-Western single-center BCBM patient cohort. To our best knowledge, this is one of the most extensive studies comparing the accuracy of different scoring systems and the first study that focuses primarily on BCBM patients.

In our comparison, the PathFx model demonstrated the highest accuracy at predicting 3- and 6-month survival for BCBM patients. It was also the most consistently reliable prognostic system within 12-month. The PathFx model was based on a machine-learning Bayesian belief network,

Table 2 Univariate Cox regression analysis

Demographic characteristics	β regression coefficient	Hazard ratio (HR) 95% CI	P value
BMI <20 kg/m^2	0.545±0.306	1.725 (0.947–3.144)	0.075
Age >70	0.705±0.364	2.024 (0.993–4.127)	0.049
Serum markers			
LDH >250 U/L	0.647±0.268	1.91 (1.130–3.229)	0.016
Albumin <37 g/L	0.429±0.271	1.536 (0.903–2.613)	0.113
Total bilirubin >23 μmol/L	–0.947±0.475	0.388 (0.153–0.984)	0.056
Platelets <80×10^9/L	–0.731±0.718	0.481 (0.118–1.968)	0.309
hemoglobin <85 g/L	–0.368±0.597	0.692 (0.215–2.231)	0.538
Calcium >2.6 mmol/L	0.634±0.427	1.886 (0.817–4.355)	0.137
KPS performance			
KPS >70	–0.433±0.253	0.649 (0.395–1.065)	0.087
70≥ KPS >50	–0.358±0.238	0.699 (0.439–1.114)	0.132
KPS ≤50	1.035±0.247	2.816 (1.737–4.566)	0.000
Molecular type			
Luminal A	–0.453±0.278	0.636 (0.369–1.096)	0.103
Luminal B	0.058±0.228	1.06 (0.678–1.658)	0.798
HER-2 overexpression	–0.09±0.464	0.914 (0.368–2.271)	0.847
Triple-negative	0.737±0.367	2.09 (1.018–4.289)	0.045
Undetermined	0.54±0.516	1.716 (0.624–4.722)	0.296
Receptor status			
Hormone-dependent	–0.346±0.295	0.707 (0.397–1.261)	0.241
Hormone-independent	0.393±0.302	1.481 (0.819–2.677)	0.194
Treatment			
Previous chemotherapy	0.068±0.34	1.071 (0.549–2.086)	0.841
Previous radiotherapy	–0.667±0.241	0.513 (0.320–0.823)	0.006
Previous targeted therapy	–0.057±0.355	0.944 (0.471–1.895)	0.872
Previous hormonal therapy	–0.182±0.244	0.834 (0.516–1.346)	0.457
Previous bisphosphate therapy	–0.073±0.237	0.929 (0.584–1.478)	0.757
Multiple skeletal metastases	–0.221±0.243	0.802 (0.498–1.291)	0.363
Pathological fracture	0.461±0.234	1.585 (1.001–2.510)	0.049
Visceral metastases	1.11±0.241	3.035 (1.893–4.868)	0.000

The values are given as the b coefficient and the standard error. The values are given as the hazard ratio (HR) with the 95% confidence interval (CI) in parentheses. The P values were significant and had a two tailed P value <0.05. BMI, body mass index; KPS, Karnofsky Performance Score; LDH, lactate dehydrogenase.

Table 3 Multivariate Cox regression analysis

Explanatory variables	β regression coefficient	Hazard ratio (HR) 95% CI	P value
Age >70	0.869±0.395	2.385 (1.099–5.179)	0.028
KPS <50	1.045±0.269	2.842 (1.679–4.812)	<0.001
LDH >25 0U/L	0.768±0.278	2.155 (1.251–3.713)	0.006
Visceral metastases	1.057±0.252	2.877 (1.756–4.715)	<0.001
Molecular type	0.272±0.114	1.312 (1.050–1.641)	0.017

Variables found to be non-significant in multivariate analysis are not shown. The values are given as the b coefficient and the standard error. The values are given as the hazard ratio (HR) with the 95% confidence interval (CI) in parentheses. The P values were significant and had a two tailed P value <0.05. KPS, Karnofsky Performance Score; LDH, lactate dehydrogenase.

which applies to both axial and appendicular lesions. This model includes both objective and subjective variables. Although only objective elements were applied in our study, the model remained accurate.

Meanwhile, the PathFx model has also been externally validated in different patient populations in European and Asian centers in Japan (22,23). Specifically, a study focused only on femoral metastatic bone disease found a robust prediction accuracy within 6-month (24). As survival of fewer than three months was considered a relative contraindication to surgical management of specific metastatic lesions, the PathFx model can serve as a screening method for this purpose in BCBM patients. Interestingly, the revised Katagiri score also showed accurate prediction with a lower Brier score at 3-month than the PathFx model, indicating that the Revised Katagiri score can also exclude high-risk BCBM patients that may not benefit from surgery.

For the 12-month survival prediction, the SSG Model showed a slightly better predictive accuracy than the PathFx model in our cohort. In the literature, more mixed results were made based on different patient populations. A comparison of nine scoring systems focused on metastatic spine disease found original Tokuhashi score was the most accurate (25). Another similar study focused on femur lesions found OPTI model was better than the PathFx model (24). Although heterogeneity of patient cohorts and study focus may contribute to this inconsistency among studies, it is not surprising to see a decrease in prediction accuracy with the increase of predicted duration.

Our analysis found that none of the seven models included can provide efficient survival prediction beyond 12-month. These seven models were all generated from patients of multiple disease types, including cancers of various prognoses. When specifically applied to breast cancer patients, a cancer type that is considered with relatively favorable prognosis, these models failed to provide an accurate prediction. This finding is discouraging because relative long-term survival prediction is also crucial for surgical planning. Longer life expectancies warrant more-durable reconstruction surgical procedures. Prosthetic reconstruction is preferred in patients with prolonged survival than simple fixation. Thus, highlighting the need to search for new prognostic factors and more specialized approaches to better predict the longer survival in BCBM patients.

The presence of a pathological fracture was found associated with survival only in univariate analysis but not in multivariate analysis in our patient cohort. The SPRING nomogram and PathFx model include preoperative pathological fracture in their assessment, yet the other models do not utilize it for survival estimation (10,11). Studies have reported pathological fracture as a prognostic factor in metastatic cancer patients, however discordant results were also found, and no consensus in BCBM has been achieved yet (4,5,26). Further work and a multi-institutional validation may be required to investigate the prognostic value of pathological fracture. If the pathological fracture was an independent adverse prognostic variable, this would strengthen the argument to lower the threshold of prophylactically surgically managing impending fractures.

Among the serum markers that were included in our study, only LDH showed significance in both univariate and multivariate analyses. LDH is a crucial catalyze in the final step of glycolysis, which is found highly enhanced in cancer status (27). Although elevated plasmatic LDH levels were found in various malignancies, few prognostic studies put it into consideration, and were only included by the revised Katagiri score model (27). In fact, the LDH level has been correlated strongly with survival, especially in BCBM patients across different cohorts (28-30). A meta-analysis

Table 4 Operating characteristic (ROC) analysis for all patients at different time periods after surgical management

Prediction period	Revised Katagiri score		Janssen nomogram		OPTI model		SSG model		PathFx		SPRING 13		SORG nomogram	
	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score
1 month					0.805* (0.616–0.993)	0.012*							0.633 (0.236–1)	
3 months	0.904* (0.830–0.977)	0.08*	0.811* (0.5197–1)	0.007*	0.555 (0.312–0.798)		0.656 (0.542–0.769)		0.953* (0.907–0.999)	0.178*	0.717* (0.512–0.923)	0.044*	0.711* (0.511–0.911)	0.074*
6 months	0.701* (0.576–0.826)	0.18*	0.672 (0.401–0.943)	0.06	0.742 (0.591–0.891)	0.122*	0.522 (0.378–0.666)		0.948* (0.909–0.986)	0.273*	0.6 (0.426–0.775)			
12 months	0.5 (0.399–0.601)		0.803* (0.710–0.894)	0.193*	0.814 (0.711–0.917)	0.26*	0.864* (0.800–0.924)	0.275*	0.861* (0.802–0.936)	0.276*	0.599 (0.471–0.727)		0.838* (0.764–0.912)	0.215*
18 months									0.647 (0.545–0.749)					
24 months					0.475 (0.372–0.577)				0.571 (0.468–0.673)					

Each scoring system was cited in the manuscript and presented with an abbreviate name. Scoring systems that were sufficiently accurate (AUC >0.70) appear with *. Values are given as the AUC [95% confidence interval (CI)] for values achieving sufficient accuracy. Brier scores are only given for models achieving sufficient accuracy (AUC >0.70).

that included more than six thousand patients further confirmed LDH as a prognostic factor in breast cancer patients (31). Additionally, persistent elevated LDH levels and LDH low-to-high variation was strongly correlated with worse chemo-response and progression-free survival (32,33). These results corroborate our finding that LDH is a prognostic factor in BCBM patients and contribute to prognostic models. Further meta-analysis studies are still needed to clarify whether the prognostic role of LDH only exists in breast cancer rather than other cancer types. Another issue about LDH is that it can be easily affected by systemic treatment or other comorbidities. Multiple testing or a trend of LDH should be considered instead of a single-time result when applied to the prognostic analysis.

Table 5 Breast cancer-specific prognostic model

Risk factor	Points
Age >70	
No	0
Yes	1
KPS <50	
No	0
Yes	1
LDH >250 U/L	
No	0
Yes	1
Visceral metastases	
No	0
Yes	1
Molecular type	
Luminal A	0
Luminal B	1
HER2-overexpression	0
Triple-negative	1
Undetermined	1

KPS, Karnofsky Performance Score; LDH, lactate dehydrogenase.

An increasing number of studies have shown that breast cancer molecular subtypes, the classification into either a luminal A, luminal B, HER-2 overexpression, or triple-negative tumors, are biologically distinct, respond differently to adjuvant therapy, and have different outcomes (3,34-37). Additional studies suggest that tumor biology and molecular heterogeneity within breast cancer subtypes, rather than therapy choice, determined the survival trends (13,14). Consistent with that, our study revealed that the survival of BCBM patients in our cohort differs by subtype, suggesting that subtype classification is clinically useful and will help determine estimated survival. In literature, luminal A tumors showed the best, and triple-negative tumors presented the poorest outcome across studies and ethnicities (3,34-36), while those with missing receptor status tend to have worse prognostic features (38). Besides, positive HER-2 expression is related to better survival regardless of hormone receptor status (38,39). Understanding the biological nature and prognosis of molecular subtypes will benefit future prognostic analysis and improve prediction accuracy. It also explains the moderate accuracy in survival prediction models that consider all types of breast cancer as a whole.

The prognostic model proposed in this study after considering the molecular subtypes. Besides, this model is an easy-to-use scoring system with only five variables and

Table 6 Estimate of risk of each point total at different time

Points total	Estimate of risk				
	3 months	6 months	12 months	18 months	24 months
0	0.011	0.017	0.037	0.066	0.093
1	0.029	0.044	0.093	0.163	0.223
2	0.073	0.11	0.225	0.37	0.481
3	0.179	0.26	0.483	0.698	0.817
4	0.4	0.542	0.819	0.955	0.988
5	0.734	0.868	0.988	1	1

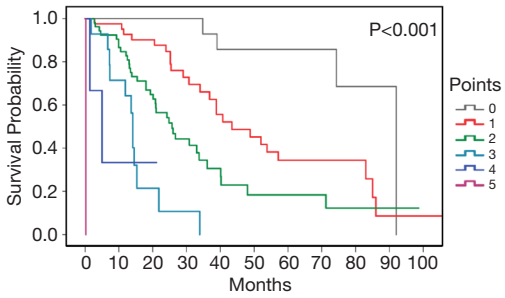

Figure 2 Kaplan-Meier survival curves of patients with each corresponding point using the breast cancer prognostic model.

a range of 0 to 5 points in total. This model overcomes the relative long-term survival prediction gap for BMBC patients. Although further studies are still needed to validate this model, it provides help with surgical planning. Take extremity metastasis as an example, since resection and prosthetic reconstruction is preferred in patients with more prolonged survival (24,26), patients who scored 0–2 points by our model could be potential candidates for prosthetic reconstruction rather than nailing alone if surgical management is deemed necessary. However, we did notice that our prediction model lose its distinguishability after 30 months for patients rated within 0-2 points. The relatively small total sample size in this study and fewer survivors after 80 months may explain this. Additionally, the prediction accuracy also decreases when applied to a more extended survival prediction due to the increase of uncontrollable interfering factors. More comprehensive analysis is needed when applying our proposed model for more extended survival prediction. Fortunately, this imperfection did not affect clinical usage and surgical decision-making.

There are several limitations in this study. Possible selection bias may present in this study inherently associated with retrospective studies, the sample size is also relatively small, in which 66 out of 204 patients were excluded in this study due to a lack of crucial information or loss of follow-up. Patients included in this study were not randomly allocated to treatment. Although each patient's treatment plan was made by multidiscipline consultation, the surgical team's surgical treatment decisions were not based on standardized protocols. Further, applying the previous prognostic models to a potentially homogenous breast cancer patient group may introduce bias to the analysis and render the accuracy. Additionally, the newly developed prognostic model was based on data from a single institution. As such, further prospective multi-institutional studies are appropriate to replicate and confirm the findings presented here.

Conclusions

Accurate preoperative estimated patient survival is paramount to an informed operative plan and treatment decision-making for BCBM patients. The PathFx model demonstrated superior accuracy at predicting short-term survival after surgery than other models for Asian BCBM patients. Although multiple prognostic models are available, none of them provide sufficient prediction beyond one year. A better long-term estimation is needed for breast cancer patients, which are generally considered with relatively more prolonged survival as compared to other cancer types. Since cancer biology plays a dominant role in survival, identify cancer-type specific prognostic variables will improve survival prediction accuracy. Our proposal for an easy-to-use scoring system fills the gap for long-term survival predictions for BCBM patients after adding cancer-specific prognostic factors. Although further validation is needed, the Modification in this present study can improve clinical decision-making in patients with metastatic breast cancer and offer a more individualized tool for informing patients.

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Supplementary

Table S1 Generation of BCBM specific prognosis scoring model

Risk factor	Categories	Reference value (W_{ij})	W_{iREF}	βi	$D=(W_{ij}-W_{iREF})*\beta i$	$Points_{ij}=(Wij-W_{iREF})*\beta i/B$
Age >70				0.953=B		
	No	0	$W_{1REF}=0$		0	0
	Yes	1			0.953	1
KPS <50				1.118		
	No	0	$W_{2REF}=0$		0	0
	Yes	1			1.118	1
LDH >250 U/L				0.82		
	No	0	$W_{3REF}=0$		0	0
	Yes	1			0.82	1
Visceral metastases				1.118		
	No	0	$W_{4REF}=0$		0	0
	Yes	1			1.118	1
Molecular type						
Lumina A				Base		
	No	0	$W_{5REF}=0$		0	0
	Yes	1			0	0
Luminal B				0.611		
	No	0	$W_{5REF}=0$		0	0
	Yes	1			0.611	1
HER-2 overexpression				0.385		
	Np	0	$W_{5REF}=0$		0	0
	Yes	1			0.385	0
Triple-negative				0.849		
	No	0	$W_{5REF}=0$		0	0
	Yes	1			0.849	1
Unknown				1.309		
	No	0	$W_{5REF}=0$		0	0
	Yes	1			1.309	1

W_{iREF}, base reference value; βi, constants B was defined as 0.953; D, difference between each risk factor and its base reference value; $Points_{ij}$, the point value for each risk factor; KPS, Karnofsky Performance Score; LDH, lactate dehydrogenase.

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