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Overall survival nomogram for patients with spinal bone metastases (SBM)

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1. Introduction

Tumor metastasis is the leading cause of morbidity and mortality in cancer patients [1,2]. The spine is the third most common site for cancer cells to metastasize after lung and liver, and 30–70% of patients with a tumor have metastatic spinal disease at autopsy [1,3–5]. Primary tumors of the breast, prostate, thyroid, lung, gastrointestinal (GI), and kidney are the most common to metastasize to the spine [1,3–5]. Within the spinal column, metastases are more commonly found in the thoracic spine, followed by the lumbar spine, while the cervical spine is the least likely location to find metastasis. Spinal bone metastases (SBM) account for over 70% of all osseous metastases and are slightly more common in men than in women. Adults between the ages of 40 and 65 are affected more than any other age group [4–6]. The prognosis of SBM is abysmal and heavily depends on the primary tumor [7]. Only 10 to 20 percent of the diagnosed patients have survival of more than two years, which implies that caregivers should tailor treatment based on an individual patient profile for an optimal outcome.

Graphical tools such as nomograms that can be used to estimate an event's probability by assigning scores to each important risk factor known to impact the events of interest combined with a prediction model can be used in such a situation. Since nomograms can estimate patient-specific probability of an outcome, they are an excellent decision support system for clinicians and caregivers. Numerous nomograms have been developed for different cancer-specific outcomes [8–13] and thanks to the technological advancements in the oncological field in the last decade, some of these nomograms have been digitalized [14]. However, until now, no prognostic nomogram has been established for SBM. Therefore, this study aims to develop a nomogram with a user-friendly digital interface that can estimate the 1, 3, and 6-months over-all probabilities of survival for patients with SBM and guide individualized patient management decisions.

2. Materials and methods

Between January 2014 and April 2016, we retrospectively collected a series of 250 cancer patients treated for SBM from the electronic medical record (EMR) system at Maastro Clinic, Maastricht, The Netherlands, after ac-quiring approval from the internal review board. All the patients received radiotherapy for their metastatic tumor. We extracted the following patient demographics and clinical information age, sex, WHO performance status, pathological fracture, spinal cord compression, number of spinal metastases, extra spinal metastases, visceral metastases, brain metastases, lymphatic metastases, pain score, and primary tumor for this analysis. We only included patients with a primary tumor of the breast, prostate, colon, rectum, or lung in this study. Overall survival (OS) at 1, 3, and 6 months was de-fined as the primary outcome of interest. The OS was calculated as the time difference between the date of diagnosis and the date of death or last follow-up.

2.1. Statistics

Descriptive statistics and data visualization were applied to understand and detect the data sets underlying patterns such as missing information and possible outlying values. A 5-fold cross-validation Cox proportional hazard regression model with the least absolute shrinkage and selection operator (LASSO) penalty [35] was used to select features that can predict survival for patients with SBM. The optimal λ values which compromises model complexity and performance, were determine using the cv.glmnet function. Variables with a non-zero coefficient under the λ_{min} value were used to fit a multi-variate Cox proportional hazard regression model. The fitted multivariate Cox proportional hazard regression model was translated to a nomogram for visualization using the nomogram function from the rms package [15] The accuracy of the nomogram on a repeated (R = 10) 5-fold cross validation was measured based on the concordance index (C-index) value with a C-index of 1 indicating a perfect nomogram and a C-index of 0.5 implying the nomogram is as reliable as tossing a coin. An internal bootstrap (B = 500) correction plot of observed against nomogram-predicted survival probability was

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used to calibrate the nomogram at the different time points of interest.

The linear predictors (LP) which are the linear combination of the coefficients of the variables in the nomogram were discretized to create the survival risk groups. Survival difference was visualized and tested using Kaplan-Meier plots and log-rank test, respectively. To evaluate the models ability to classify future patients into the different risk groups, we compared the predicted mean survival curves for each of the risk groups with the true Kaplan-Meier survival curves of each risk group by overlaying the two plots. All statistical analyses were performed using R software [16] and the glmnet package [17] was used for variable selection and model fitting process.

3. Results

A total of 250 patients with SBM were identified at Maastro Clinic. Of these patients, 195 had a primary tumor of the breast, prostate, colon, rectum, or lung (see table 1). One patient with missing WHO performance status was excluded from this analysis. The variable 'pain score' was excluded from the study due to its high percentage (45%) of missing information. The median age of patients in this study was 69 (39–92) years. There was no statistical survival difference between surviving and non-surviving patients for all considered variables but visceral metastasis and the primary tumor. The median follow-up time for this study was 46.78 (37.03–56.34) months with a 1, 3, and 6-months overall survival probability of 88%, 67%, and 53%, respectively. Table 1 shows the general patient characteristics for this study.

Fig. 1A shows a plot of the model performance (C-index) against the log values of the different λ used in the cross-validation process for variable selection. The values at the top of the plot indicate the number of non-zero variables in the model for a particular λ value and the performance of the said model can be read on the y-axis. Based on the selected λ_{min} value from the repeated 5-fold cross-validation of the LASSO Cox proportional hazard regression model, the 11 considered variables were reduced to 6 potential predictors (age, spinal cord compression, brain metastasis, visceral metastasis, WHO performance status, and primary tumor) with a non-zero coefficient. Fig. 1B shows the coefficients of the 11 variables represented by different colors against the log(λ) values. The vertical dotted gray line was drawn at the selected λ_{min} value which resulted in the 6 variables with nonzero coefficients.

The fitted multivariate Cox proportional hazard regression model with the selected variables was translated to the prognostic nomogram shown in Fig. 2. The variable sex was included in the model thou not selected based on the chosen λ value because it is known to be an important factor based on literature. Also, The Kaplan-Meier plot for sex (Supplementary Fig. 8) showed a significant survival difference. The mean C-index and the 95% confidence interval (CI) of the nomogram was 0.720 (0.683–0.757).

We have also provided a user-friendly online version of this nomogram to facilitate its widespread use by physicians and researchers (https://bich.shinyapps.io/SpinalMets/). The Web application allows predicted survival probabilities and curves for each input information to be stacked making comparison easier.

Table 1
General characteristics for surviving and non-surviving patients.

Variable	Levels	Survivors		Non-Survivors		p-value
Age at RT in years	Mean (sd)	67.8 (8.8)		68.9 (10.4)		0.651
Sex	Female	10	(66.67%)	80	(44.40%)	0.097
	Male	05	(33.33%)	100	(55.60%)	
WHO performance score	Active	01	(6.67%)	05	(2.78%)	0.854
	Restricted	07	(46.67%)	69	(38.33%)	
	Self-care	05	(33.33%)	74	(41.11%)	
	Bed-bound	02	(13.33%)	31	(17.22%)	
	Missing	00	(0.00%)	01	(0.56%)	
Pathological fracture	Yes	11	(73.33%)	141	(78.33%)	0.654
	No	04	(26.67%)	39	(21.67%)	
Spinal compression	No	14	(93.33%)	142	(78.89%)	0.179
	Yes	01	(6.67%)	38	(21.11%)	
Number spinal metastases	One	03	(20.00%)	33	(18.33%)	0.981
	Two	03	(20.00%)	39	(21.67%)	
	Three +	09	(60.00%)	108	(60.00%)	
Extra spinal bone metastases	No	04	(26.67%)	41	(22.78%)	0.731
	Yes	11	(73.33%)	139	(77.22%)	
Visceral metastases	Absent	13	(86.67%)	109	(60.56%)	0.045
	Present	02	(13.33%)	71	(39.44%)	
Brain metastases	Absent	00	(0.00%)	10	(5.56%)	0.348
	Present	15	(100%)	170	(94.44%)	
Lymphatic metastases	Absent	09	(60.00%)	102	(56.67%)	0.802
	Present	06	(40.00%)	78	(43.33%)	
Pain score	No pain	00	(0.00%)	05	(2.78%)	0.431
	Mild	01	(6.67%)	06	(3.33%)	
	Moderate	05	(33.33%)	35	(19.44%)	
	Severe	07	(46.67%)	76	(42.22%)	
	Missing	02	(13.33%)	58	(32.22%)	
Primary tumor	Breast	10	(66.67%)	35	(19.44%)	<0.05
	Prostate	05	(33.33%)	50	(27.78%)	
	Lung	00	(0.00%)	70	(38.89%)	
	Colon	00	(0.00%)	14	(07.78%)	
	Rectum	00	(0.00%)	11	(06.11%)	

WHO = World Health Organization, sd = standard deviation.

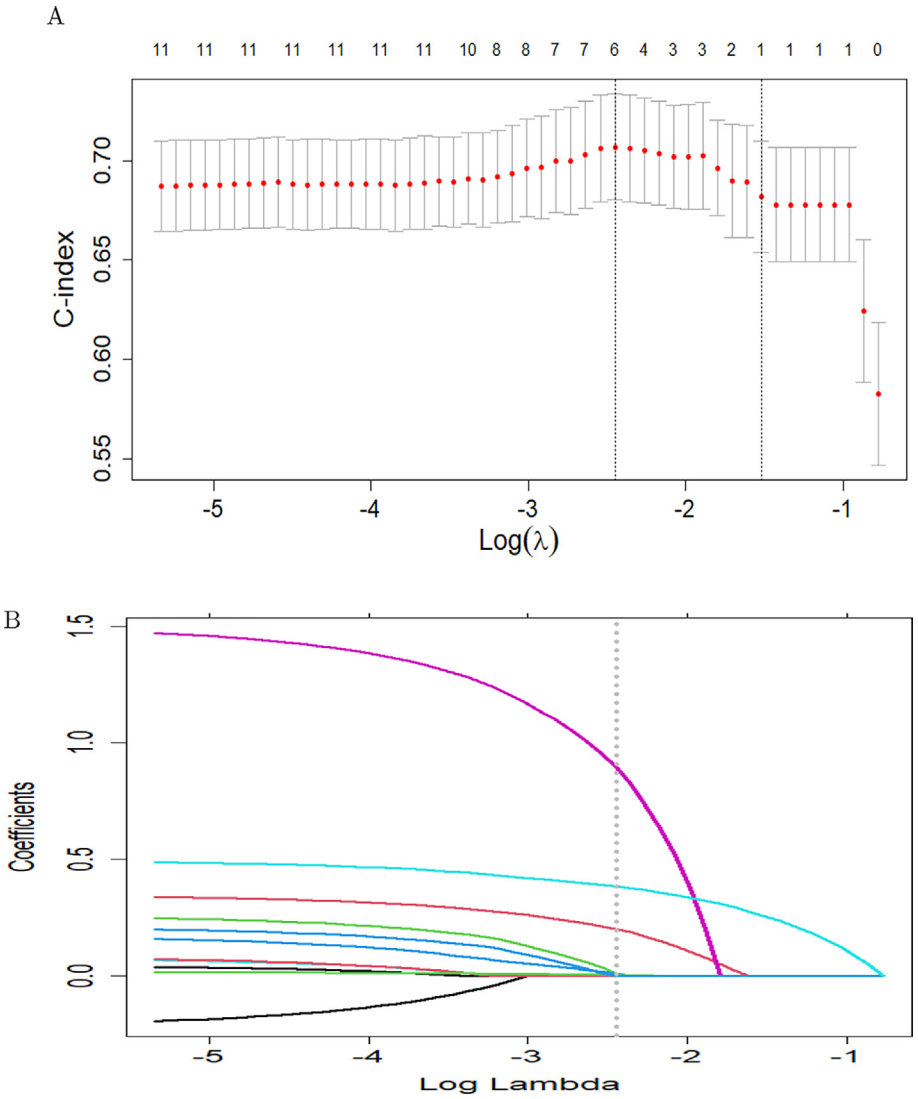

Fig. 1. Variable selection using the LASSO cox proportional hazard regression model. [A] Selection plot of the tuning parameter (λ) for the LASSO model on the repeated 5-fold cross-validation. The C-index values were plotted against the log(λ) values. Dotted vertical lines are drawn at the optimal λ values λ_{min} and λ_{1-SE} respectively. [B] Profile plot of the LASSO coefficient against the log(λ) sequence for the 11 considered variables. The dotted gray line represents the selected λ_{min} value (0.0895) which gives a log (λ_{min}) of −2.413.

To evaluate the developed nomogram, we presented its performance in predicting 1, 3, and 6-months overall in terms of discrimination by plotting the actual survival probabilities against the nomogram predicted probabilities. This plot shows the similarity between the predicted probabilities and the observed probabilities, with all points falling precisely on the perfect model's diagonal line. The calibration curve in Fig. 3 reveals good agreement between the predictions of the nomogram and observation.

The nomograms' ability to discriminate between patients based on their survival probability was evaluated by first making a histogram of the linear predictors, as shown in Fig. 4 with higher values indicating poor prognosis. The linear predictors were then discretized into three risk groups with cutoff values at the 25*th* and 75*th* percentile, as shown on the plot. We considered patients between the cutoff values to have a moderate risk of death. Patients below and above the 25*th* and 75*th* percentile values were considered to have a lower and higher risk of death, respectively.

The percentages of patients in the three risk groups are 25.3%, 49.4%, and 25.3%, respectively. The Kaplan-Meier curves for overall survival stratified by the risk groups, as shown in Fig. 5, agree with the c-index value and calibration plots, indicating that the nomogram has some discriminating power as the three curves are significantly separated with a p-value < 0.005. Patients in the high-risk group had a median survival time of 1.77 (0.92–3.98) months and the moderate group had 6.90 (2.66–15.21) while the low-risk group had 25.72 (13.40–45.47) months as shown in Fig. 5.

To further evaluate the nomogram's performance, we compared the predicted mean survival curves for each of the risk strata with the Kaplan-Meier survival curves, as shown in Fig. 6.

Fig. 6 indicates that the nomogram is well-calibrated given the close similarity between the predicted (dotted lines) and actual (solid lines) survival curve for all except the low-risk group, where the model slightly under predicts at the beginning and over-predict over time.

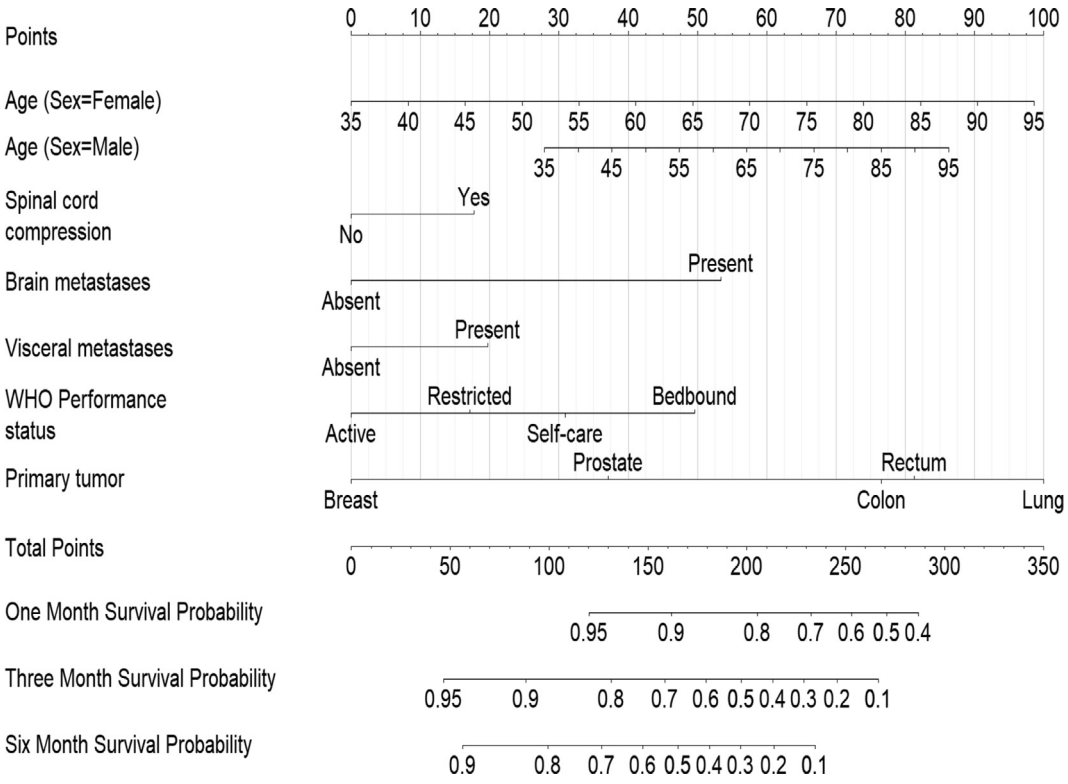

Fig. 2. Developed nomogram to predict 1, 3, and 6-months overall survival for metastatic spinal bone patients using seven clinical characteristics. To use the nomogram, locate the patient's variable on the corresponding axis, draw a vertical line to the points axis, sum the points, and draw a vertical line from the total points axis to the 1, 3, or 6 - months overall survival probability axis.

4. Discussion

The disease burden and mortality rate of SBM have opened up intriguing research possibilities in the field, focusing on improving patients' quality of life via a personalized treatment procedure for an optimal outcome. Despite the significant progress in understanding tumor metastasis and the underlying mechanisms, the precise process remains complicated with multiple sequential and interrelated biochemical events, which still needs elucidation.

The treatment choice for spinal metastases depends on correctly localizing the affected vertebra(e), the patient's priorities for treatment, and other individual patient characteristics. However, no therapy has proven to increase the life expectancy of these patients [5]. Hence, treatment aims to improve quality of life, spinal cord compression, relieve pain, or prevent a vertebral collapse [18].Therefore, assessing a patient's prognosis before treatment is very pivotal for an optimal treatment selection. That is, caregivers should tailor treatment based on each patient's desires and their overall prognosis.

Renowned prognostic scoring systems (Bauer, Tokuhashi, Tomita, van der Linden, Sioutos, Katagiri, and NESMS) have been developed to assist clinicians and care providers in determining the survival prognosis of metastatic spine tumor patients for an optimal therapeutic choice [19–27]. In contrast to this study, none of these scoring systems include demographic features such as age and sex. Logically, these variables should be included in any scoring system given that these variables have been proven from literature to be associated with SBM survival, as the disease is more common in men than women as well as in elderly patients as compared to the younger population [4–6,28]. More to this, men are more at risk of developing a spinal disease than women since men are more susceptible to developing a primary tumor than women [29,30].

Yang, Xu, Liu, et al. [31], Liu, Yang, Li, et al. [32] and Pereira, Janssen, Dijk, et al. [33] have previously developed nomograms to support the personalized predictions of survival probability for patients with spinal metastasis disease from non-small cell lung cancer (NSCLC), colorectal cancer, and operable patients respectively. These nomograms did consider age, sex, performance status, primary tumor, visceral, and brain metastasis as significant prognostic factors associated with spine metastasis survival, which are in concordance with this study. However, none of these studies have considered including both age and sex in the same nomogram. This assumes all patients have an equal risk of dying from the disease irrespective of their age, sex, or both variables despite the sea of literature supporting these difference [4–6,28,30,34,35] especially when more than one primary tumor is considered (Supplementary Fig. 7). This variable omission implies the predicted survival probabilities from such nomograms are less personalized.

We developed a nomogram with seven variables, including an interaction between age and sex, to improve previously developed scoring systems. The developed nomogram captures the age effect within the sex variable as there is over 15 points survival difference between males and females of the same age. From the nomogram, women have relatively better survival than men before 75 years. However, after 75 years, the reverse is seen with men having a somewhat better survival than women. The proposed nomograms have a relatively good c-indexes of 0.72 (95% CI, 0.683 – 0.757) and perform well in calibration. A digital version of the nomogram is also provided for easy insertion into the treatment workflow for better decision-making in managing spinal metastases and offering practical guidance to caregivers.

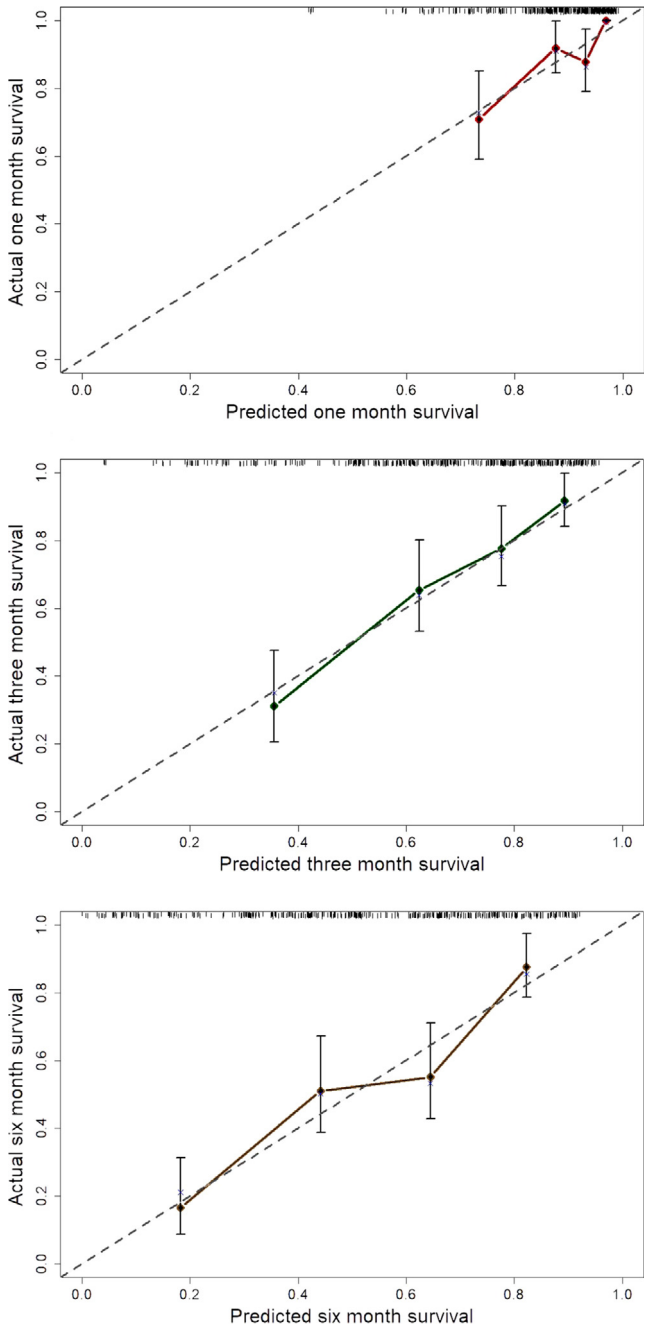

Fig. 3. SBM overall survival nomogram calibration plots for 1, 3, and 6-months, respectively. The nomogram-predicted overall survival is plotted on the x-axis, and the actual overall survival is plotted on the y-axis. The dashed line represents the ideal fit where the nomogram-predicted probability matches the observed probability. The vertical solid lines represent the 95% confidence interval.

All the existing scoring systems for SBM known to us are between 1 and 24 months. The digital version of the present nomogram can make predictions at any given time point as low as half a month. Besides the survival probability, it also provides the confidence interval of the predicted survival probability and a personalized survival curve, which gives the caregiver more insights to

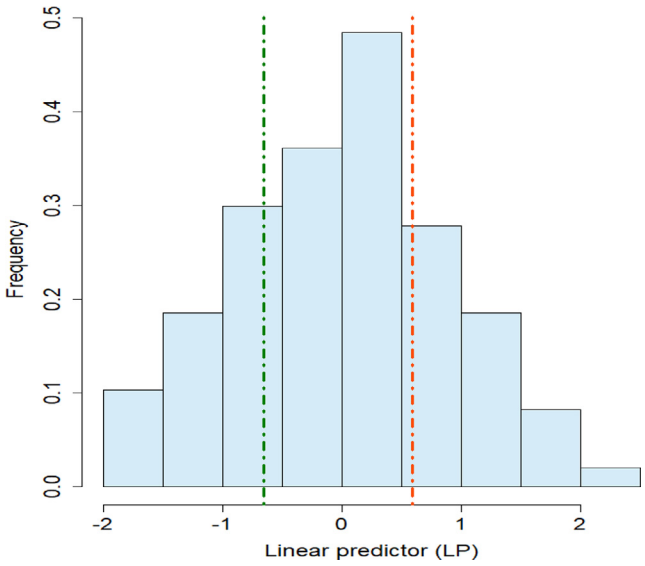

Fig. 4. Histogram of the linear predictor extracted from the nomogram. The vertical lines indicates the 25th (green), and 75th (red) percentile respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

determine the optimal therapeutic strategy for a patient, such as, e.g., stereo-tactic body radiation therapy (SBRT). The personalized survival curve could serve as a good starting point for shared decision making between patients and caregivers. The present nomogram might be a suitable tool for clinical assistance; however, the performance is still not optimal due to some limitations. The nomogram's clinical-reliability could not be evaluated at the moment, given the study's single-center nature. However, we performed a thorough internal validation (bootstrap) and planned to do a proper external validation to ascertain the nomogram's clinical usefulness. A direct comparison between our developed nomogram and the other nomograms was not possible due to population difference. However, Liu, Yang, Li, et al. [32] and Pereira, Janssen, Dijk, et al. [33] did consider hematological parameters such as carcinoembryonic antigen (CEA), hemoglobin levels, and white-blood-cell count (WBC) for their nomogram. Given the pivotal role of blood and lymph in tumor metastasis, we believe these variables could be essential prognostic features but were, however, absent in the current study because of its retrospective nature. Yang, Xu, Liu, et al. [31] on the other hand, used a renowned scoring system called the Frankel score in their nomogram, which was also not included in the present study. However, this feature might not be predictive of spinal metastasis survival since it was only designed to categorize spinal cord injuries [36].

Access to population-based registries and adding other variables to the nomogram, such as (radi)omics, pathology, and hematological parameters, might further improve the nomograms' performance. Also, accessing these databases will make the nomogram more generalizable by including more primary tumors and increase number of patients in each primary tumor.

At present, the nomogram is limited to five primary tumors, which implies that patients with other primary tumors like cervix, kidney, bladder, etc., cannot benefit from this nomogram.

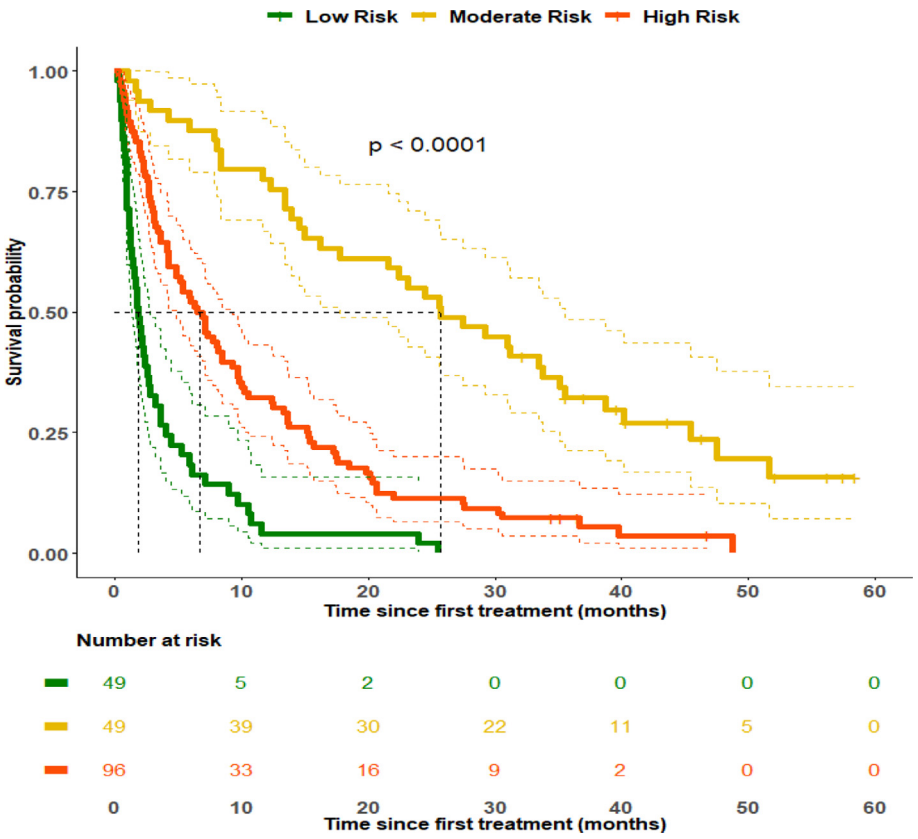

Fig. 5. The Kaplan-Meier survival curve for the low, moderate, and high-risk groups based on the percentile cutoff values.

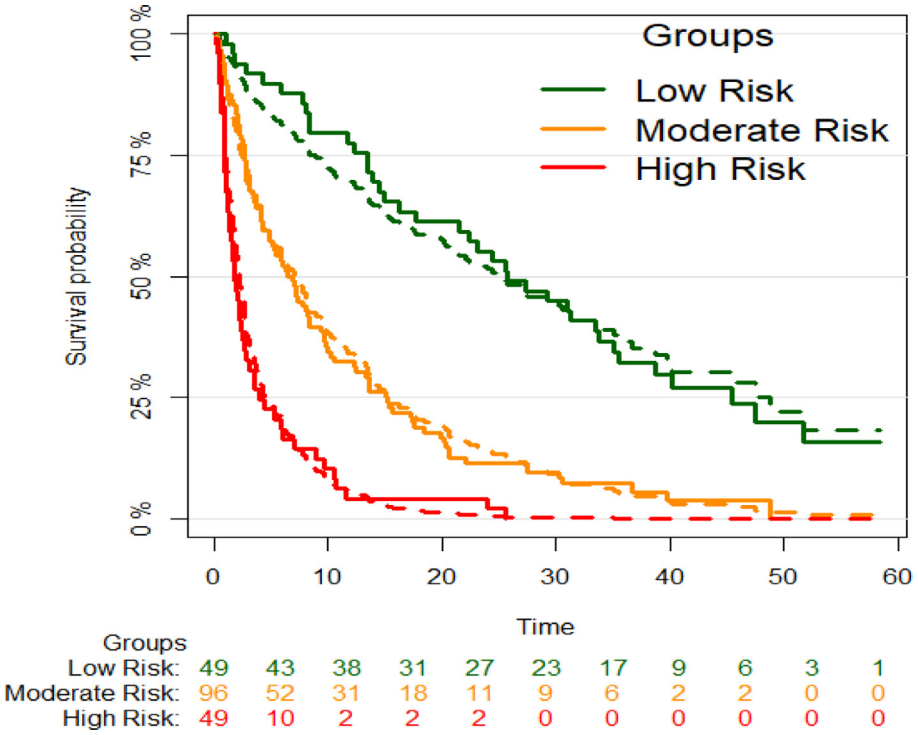

Fig. 6. Comparison of predicted mean survival curves (dotted lines) and stratified Kaplan-Meier (solid lines) for the different risk groups.

5. Conclusions

We have established a user-friendly and easy to use prognostic nomogram for patients with SBM using seven known clinical parameters. It has a digital version that can be integrated into the current treatment workflow to aid treatment decision-making in managing cancer patients with SBM. However, proper external validation is needed to ascertain its clinical reliability.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.02.010.

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