Establishment and assessment of a nomogram for predicting prognosis in bone-metastatic prostate cancer

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Abstract

Purpose For the purposes of patients' consultation, condition assessments, and guidance for clinicians' choices, we developed a prognostic predictive model to evaluate the 1-, 3-, and 5-year overall survival (OS) rates of bone-metastatic prostate cancer (PCa) patients.

Methods We gathered data from 5522 patients with bone metastatic PCa registered in the Surveillance, Epidemiology, and End Results (SEER) database to develop a nomogram. A total of 359 bone-metastatic PCas were collected from two hospitals to validate the nomogram and assess its discriminatory ability. In addition, we plotted the actual survival against the predicted risk to assess the calibration accuracy. Moreover, we designed a web calculator to quickly obtain accurate survival probability outcomes.

Results Univariate and multivariate Cox hazards regression analyses suggested that age, marital status, prostate-specific antigen, Gleason score, clinical T stage, N stage, surgery, and chemotherapy were closely associated with OS rates. The calibration charts in the training and validation groups showed high accuracy and reliability. The decision curve analysis (DCA) suggested a favorable clinical net benefit.

Conclusion: Based on demography and clinical pathology, we developed a reliable nomogram to help clinicians more accurately predict the 1-, 3-, and 5-year OS rates of patients with bone metastatic PCa to guide evaluation and treatment.

Introduction

Prostate cancer (PCa) is the second most common cancer and fifth most common cancer-related cause of death in men worldwide [1–3]. In 2012, approximately 1.1 million men were diagnosed with PCa worldwide [4], and there were approximately 1.3 million newly confirmed cases in 2018 [1–3], suggesting a tendency to increase.

The most common metastasis site for PCa is the bone, accounting for nearly 14% of all cases at the time of initial diagnosis [5]. Once bone metastasis occurs, patients often experience pathological fractures, bone pain, and other problems [6]. The 5-year survival rate of patients with bone metastases is remarkably lower than that of patients without bone metastases (3% versus 56%) [7].

To date, only three nomograms have been targeted for bone metastatic PCa. Unfortunately, independent predictors of bone-metastatic PCa are currently disputed [1, 4, 8], and this shortcoming may confuse doctors and patients. Therefore, the development of predictive models is necessary to achieve early precision in medicine.

Materials And Methods

Patient samples

The National Cancer Institute operates the publicly available Surveillance, Epidemiology, and End Results (SEER) database [9], which covers approximately 30% of the United States population. We collected 5522 bone-metastatic PCa cases registered from January 1, 2010, to December 31, 2016, as the training cohort. We searched 359 patients with bone metastatic PCa from two hospitals to constitute the validation cohort. Because of the public availability of the data[10], approval from the institutional ethics review committee was obtained, except for the SEER data.

Eligibility criteria

The inclusion criteria were as follows: (i) prostate carcinoma was diagnosed on the local specimen histopathological examination derived from transrectal biopsy or transurethral resection, and PCa was the first cancer for patients; (ii) bone metastases were based on bone scans or bone biopsy, and there was no metastasis other than bone metastasis and lymph node involvement. (iii) All patients were confirmed to have metastatic castration-resistant prostate cancer and received standard androgen deprivation therapy.

The tumor, node, and metastasis (TNM) clinical stages were applied based on the 2010 American Joint Committee on Cancer staging manual. The pathological grades of PCa were based on the Gleason score (GS) derived from the 2005 International Society of Urological Pathology.

Calculation methods

Edition 8.3.6 SEER∗Stat software was used for data extraction. To develop and validate the model, patients from the SEER database were assigned to the training group(n = 5522), and patients from multiple hospitals were included in the validation group(n = 359). The analyzed independent predictors were integrated to form a nomogram to predict OS [10].

Decision curve analysis (DCA) was used to assess the clinical utility of the nomogram by quantifying the net benefit under entirely different probabilities. Calibration charts were assessed by observing the coincidence of predicted and actual outcomes. Prediction lines crossing a 45 °diagonal indicated a perfect fit, suggesting that the model was well calibrated. The ROCs, calibration charts, and DCA curves were plotted using R edition 3.6.3 (http://www.r-project.org) [10, 11].

Statistical analyses

IBM SPSS (version 26.0; SPSS, Inc., Chicago, IL, USA) was used for all the statistical analyses. The chi-square test and t-test were used to determine the associations between the training and validation groups. Independent prognostic factors for OS were confirmed based on univariate and subsequent multivariate Cox regression analyses. Descriptive statistical analysis was applied for demographic and clinical factors.95% CIs were applied to hazard ratios (HRs). Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics of the study population

Demographic and clinical factors of the primary and external validation cohorts are presented in Table 1.

Table 1
Baseline of patients in training group and validation group

	level	SEER(N = 5522)	Validation group(N = 359)	p
times (mean (SD))	NA	27.70 (22.54)	27.75 (22.62)	0.967
Age (mean (SD))	NA	70.01 (10.22)	72.92 (42.27)	< 0.001
Race ethnicity (%)	black	944 (17.1)	0 (0.0)	< 0.001
	Chinese	417 (7.6)	0 (0.0)	
	Other	68 (1.2)	359 (100.0)	
	white	4093 (74.1)	0 (0.0)	
Marital (%)	Married	3266 (59.1)	254 (70.8)	< 0.001
	unknown	354 (6.4)	0 (0.0)	
	unmarried	1902 (34.4)	105 (29.2)	
T (%)	T1	1568 (28.4)	107 (29.8)	0.289
	T2	1975 (35.8)	133 (37.0)	
	T3	949 (17.2)	68 (18.9)	
	T4	617 (11.2)	33 (9.2)	
	TX	413 (7.5)	18 (5.0)	
N (%)	N0	3174 (57.5)	204 (56.8)	0.003
	N1	1654 (30.0)	129 (35.9)	
	NX	694 (12.6)	26 (7.2)	
Radiation (%)	None/Unknown	4192 (75.9)	265 (73.8)	0.403
	yes	1330 (24.1)	94 (26.2)	
Chemotherapy (%)	None/Unknown	4591 (83.1)	273 (76.0)	0.001
	yes	931 (16.9)	86 (24.0)	
System treatment (%)	None/Unknown	4819 (87.3)	273 (76.0)	< 0.001
	yes	703 (12.7)	86 (24.0)	
Gleason Score (mean (SD))	NA	8.56 (0.90)	8.57 (0.85)	0.81

	level	SEER(N = 5522)	Validation group(N = 359)	p
surgery (%)	Local tumor destruction	43 (0.8)	7 (1.9)	< 0.001
	Local tumor excision	523 (9.5)	41 (11.4)	
	no surgery	4835 (87.6)	288 (80.2)	
	other/unknown	13 (0.2)	0 (0.0)	
	Radical prostatectomy	108 (2.0)	23 (6.4)	

In the training group, the mean age was 70.01 years (SD 10.22), and most of the patients were married (59.1%). Regarding TNM stage, T2 stage (35.8%) and N0 stage (57.5%) were the majority. Most patients did not receive radiation therapy, systemic treatment, or surgery. The mean GS is 8.56 (SD 0.90).

In the validation group, the data characteristics were similar. The mean age was 72.92 (SD 42.27) years. The proportion of married patients was also higher (70.8%). The mean Gleason score was 8.57(SD] 0.85).

Independent predictors for OS

Through univariable analysis and subsequent multivariable Cox analysis, age ($P \leq 0.001$, HR = 1.02, 95%CI 1.02–1.03), marital status (unmarried or separated or divorced or widowed)($P \leq 0.001$, HR = 1.18, 95%CI 1.09–1.28),GS(8,9,10)($P \leq 0.001$, HR = 1.36, 95%CI 1.3–1.42), T2 stage(P = 0.0177, HR = 1.12, 95%CI 1.02–1.23),T4 stage($P \leq 0.001$, HR = 1.34, 95%CI 1.18–1.53),Tx stage(P = 0.0334, HR = 1.18, 95%CI 1.01–1.39),N1 stage (P = 0.0275, HR = 1.1, 95%CI 1.01–1.21), Nx stage (P = 0.0158, HR = 1.15, 95%CI 1.03–1.29) and Radical prostatectomy($P \leq 0.001$, HR = 0.24, 95%CI 0.12–0.47) were confirmed independent predictors for the OS ($P<0.05$) (Table 2).

Table 2
Univariate and multivariate Cox regression

Characteristics	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	Uni P	HR (95% CI)	P
Age	1.02 (1.02–1.03)	< 0.001	1.02 (1.02–1.03)	< 0.001
Chemotherapy				
No/unknown	Ref	Ref	Ref	Ref
yes	0.8 (0.72–0.9)	< 0.001	0.83 (0.74–0.94)	0.0024
Gleason Score	1.41 (1.35–1.47)	< 0.001	1.36 (1.3–1.42)	< 0.001
Marital status				
Married	Ref	Ref	Ref	Ref
unknown	1.09 (0.93–1.27)	0.28	1.03 (0.88–1.2)	0.7535
unmarried	1.22 (1.13–1.32)	< 0.001	1.18 (1.09–1.28)	< 0.001
N				
N0	Ref	Ref	Ref	Ref
N1	1.13 (1.04–1.23)	0.005	1.1 (1.01–1.21)	0.0275
NX	1.29 (1.15–1.44)	< 0.001	1.15 (1.03–1.29)	0.0158
Race ethnicity				
Black	Ref	Ref	Ref	Ref
Chinese	0.74 (0.62–0.88)	0.001	0.65 (0.55–0.78)	< 0.001
Other	0.52 (0.34–0.79)	0.002	0.41 (0.27–0.63)	< 0.001
White	0.93 (0.85–1.03)	0.167	0.84 (0.76–0.93)	< 0.001
Radiation				
No/unknown	Ref	Ref	Ref	Ref
yes	1.03 (0.95–1.13)	0.455	NA	NA
Sequence number				
More	Ref	Ref	Ref	Ref
only one primary	0.94 (0.85–1.03)	0.198	NA	NA
Surgery				
Local tumor destruction	Ref	Ref	Ref	Ref

Characteristics	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	Uni P	HR (95% CI)	P
Local tumor excision	1.28 (0.85–1.92)	0.238	1.09 (0.72–1.64)	0.6874
no surgery	0.93 (0.63–1.38)	0.726	0.93 (0.61–1.42)	0.7383
other/unknown	2.46 (1.21-5)	0.013	1.85 (0.91–3.76)	0.0907
Radical prostatectomy	0.15 (0.08–0.3)	< 0.001	0.24 (0.12–0.47)	< 0.001
System treatment				
No	Ref	Ref	Ref	Ref
yes	1.15 (1.03–1.28)	0.013	1.04 (0.85–1.28)	0.6958
T				
T1	Ref	Ref	Ref	Ref
T2	1.12 (1.02–1.23)	0.019	1.12 (1.02–1.23)	0.0177
T3	0.93 (0.82–1.05)	0.217	0.95 (0.84–1.07)	0.4221
T4	1.51 (1.33–1.71)	< 0.001	1.34 (1.18–1.53)	< 0.001
TX	1.27 (1.1–1.48)	0.002	1.18 (1.01–1.39)	0.0334

Development and validation of the nomogram

The nomogram was developed by integrating all independent predictors of OS. The length of the line was directly proportional to the contribution of each predictor to OS. The nomogram showed that the Gleason score made the most significant contribution to the predicted results. In addition, age and surgery also played an important role. Moreover, marital status, T stage, N stage, and chemotherapy contributed relatively little. The total points were the sum of the points for each factor in the nomogram. Total points corresponded to the 1-year,3-year,5-year survival possibility. Higher total points indicated worse outcomes (Fig. 1). It is worth mentioning that we designed a web calculator for our nomogram that can quickly obtain accurate outcomes when patients enter their own data. software (https://drli0910.shinyapps.io/BMPCNomapp/).

The internal and external validation calibration curves (the imaginary line in the chart) indicated that there was no difference between the prediction and observation [12], that is, a favorable consistency was achieved between the prediction of the nomogram and the actual OS, ensuring its accuracy (Fig. 2). We also conducted interior and exterior DCA experiments (Fig. 3). The clinical net benefit was measured by summing the true positives and eliminating the false positives.

Discussion

To date, nomograms have been established for some cancers compared with traditional prediction tools. They are more accurate in predicting OS [13–15]. ROC, AUC, and DCA showed that our nomogram had good discrimination ability, accurate prediction ability, and instructional significance.

There are five highlights in our study. First, our nomogram is the first to find that marital status is an independent risk predictive factor for OS in bone-metastatic PCa. The outcomes for patients who were USDW were worse than those of married patients, which is similar to the findings of Udumyan et al. [16] and Libby Ellis et al. [17]. Married people have a higher quality of material and spiritual life due to the care and support of their spouses, which is in accordance with the bio-psycho-social medical model [18]. Second, our study was the first to include chemotherapy treatment variables. For example, taxane-based chemotherapy, which can improve the OS of castration-resistant PCa, has started in the last few years [19]. Third, the present study is the only one to use DCA for the OS of bone-metastatic PCa. Our nomogram offers greater net clinical benefits than the TNM system, indicating that the nomogram is better than the TNM system for predicting the OS of bone-metastatic PCa. Fourth, we converted continuous variables into categorical variables. Fifth, we developed a web calculator for our nomogram that can quickly obtain accurate survival results when patients enter their clinical characteristics.

In 2015, Miyoshi et al. published a nomogram for Japanese patients with bone metastatic PCa [8]. Unlike our results, the contribution of PSA to OS in their study suggested that lower PSA indicated worse outcome and GS did not have the greatest effect on OS, which might have been caused by racial diversity. In Hou et al.'s model, GS had the most significant impact on prognosis, similar to our study [1]. They found that liver metastasis significantly contributed to predicted OS. Bosaily et al. found that GS predicted OS in metastatic PCa [20], and GS $\geq$ 8 significantly increased mortality [1, 21].

Moreover, the outcomes of our study confirmed that black, white, and American Indian or Alaska Native (AIAN) patients with bone-metastatic PCa had several-times higher mortality risk than API patients, which was similar to the findings of Hou et al. According to Petrovics et al., the genetic spectra of Caucasian and African-American patients with PCa are different [22]. It is worth mentioning that our nomogram can be used in Western and Asian patients.

The limitations of this study are as follows. First, the number of bone lesions was not analyzed because no information was available in the SEER. Second, our study was a retrospective study, and there may be data bias because patients with missing information were excluded. Third, although we innovatively included chemotherapy and surgical treatment in our nomogram, we did not categorize the treatment and provided a specific plan. Finally, our study lacked data on hemoglobin and alkaline phosphatase levels, which were found to be predictors of bone-metastatic PCa. Despite these limitations, our model was well-calibrated and showed superior discrimination and universal applicability.

In conclusion, our nomogram can guide clinicians to accurately predict the 1-year, 3-year and 5-year OS for patients with bone metastatic PCa, which will be valuable for patients' consultations, clinical evaluations, and choices regarding therapeutic schedules.

Declarations

Ethics approval and consent to participate

The study was conducted retrospectively and was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University (identifier: 2021122). The investigations conform to the principles of the declaration of Helsinki. The Ethics Committee of the Second Affiliated Hospital of Dalian Medical University waived the need for a written, informed consent as it was no longer necessary due to most patients being deceased at the time of data collection.

Consent for publication

Not applicable (No identifying information is reported).

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available to ensure participant confidentiality, as was stated in the Institutional Review Board approval, but are available in de-identified manner from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

WFL collected data and performed analysis, ZYW searched the literature and collected data, LCL designed the study, and wrote and revised the manuscript.

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Not applicable.

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Figures

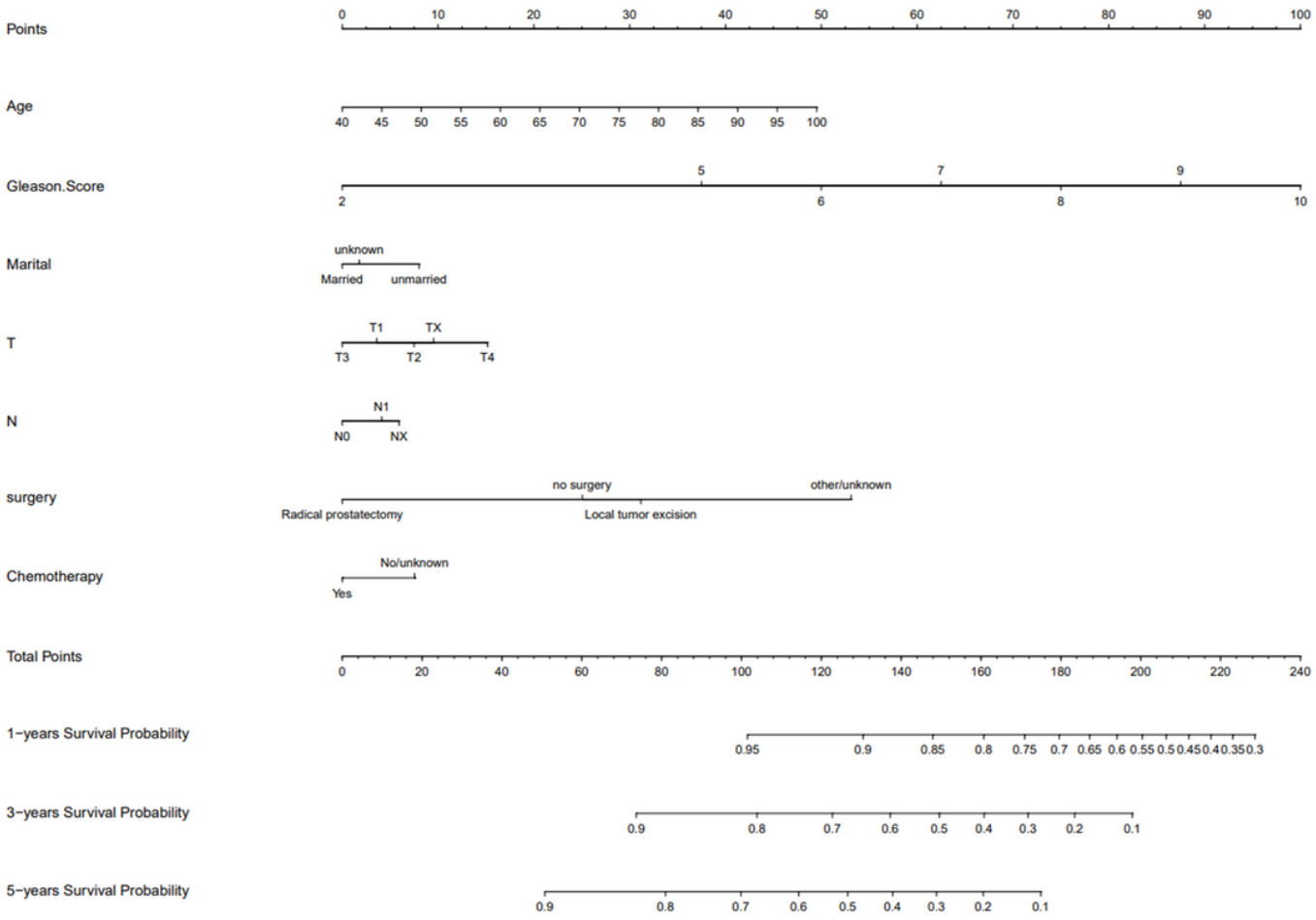

Figure 1

Predictive nomogram for predicting 1-, 3- and 5-year OS.

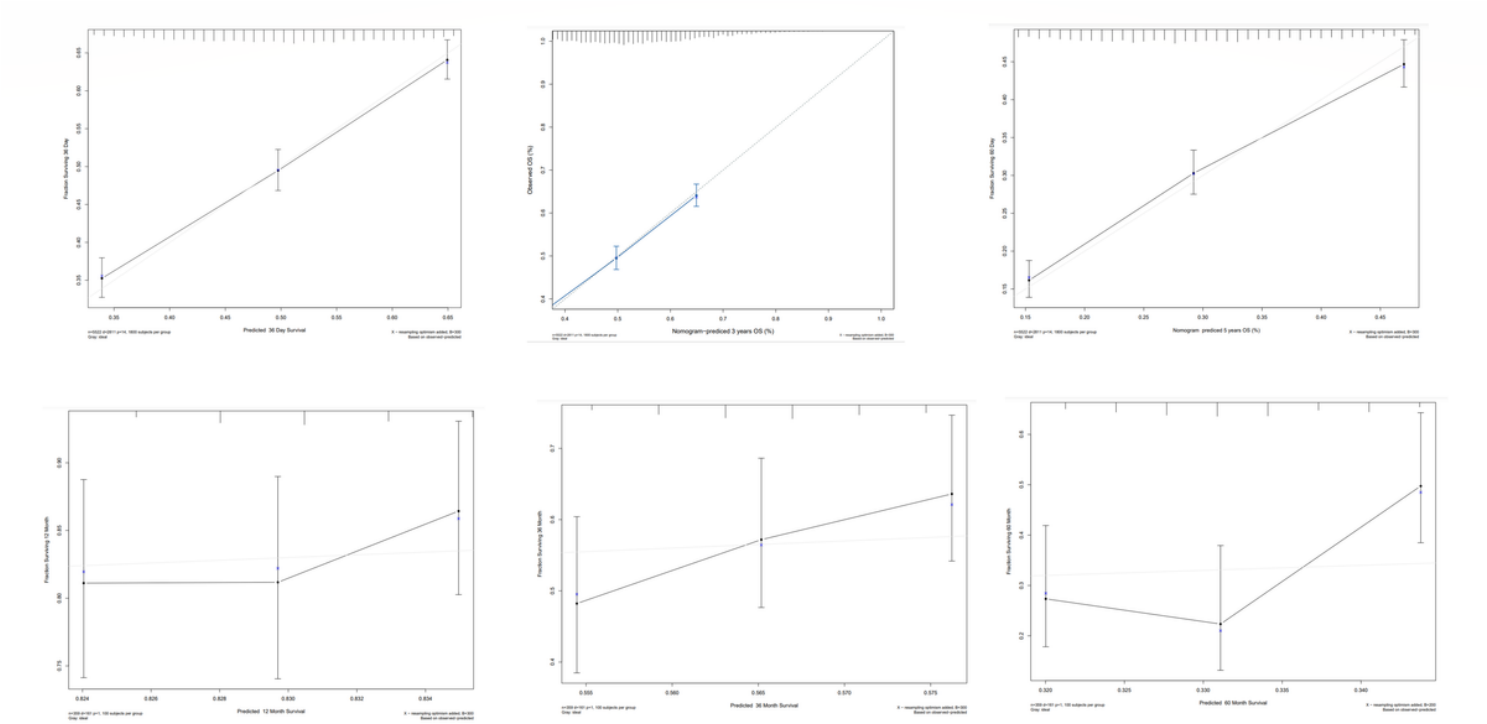

Figure 2

(A–C) The calibration curves of nomogram for predicting 1-, 3-, and 5-year survival in the training cohort. (D–F) The calibration curves of nomogram for predicting 1-, 3-, and 5-year survival in the external validation cohort.

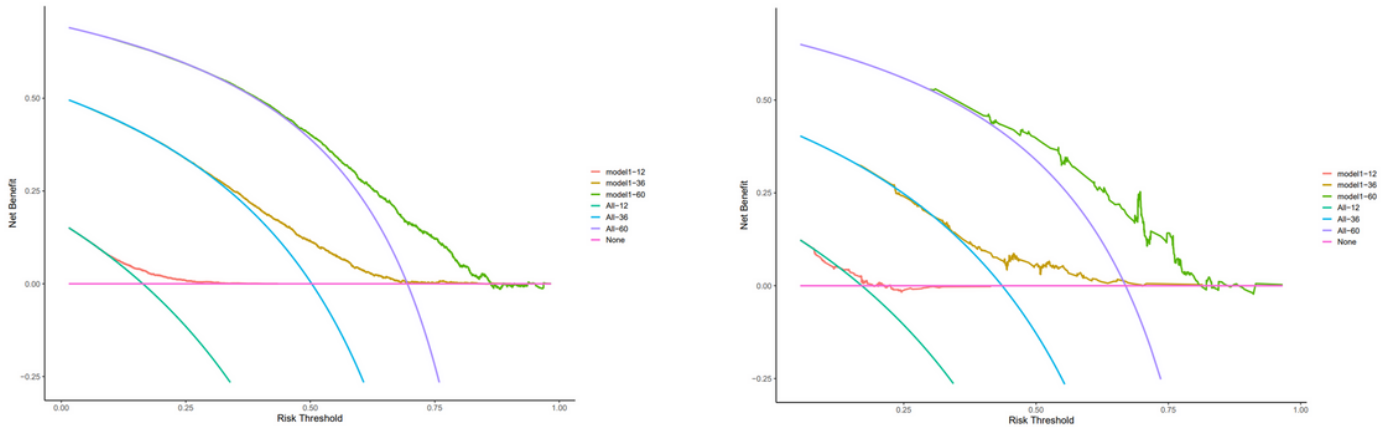

Figure 3

Decision Curve Analysis of the training cohort (A) and validation cohort (B).