Prognostic Value of Various Nutritional Assessment Indicators on Long Term and Short Term Outcomes for Patients with High Grade Osteosarcoma Receiving Surgical Resection

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Abstract

Background: Many researchers have focused on exploring the association between patients' nutritional status and clinical outcomes with some easy-to-reach indicators, especially in some carcinoma with high incidence. However, there was little attention on sarcomas and the objective of this study was to evaluate the prognostic value of some innovative nutrition associated indexes on patients with high grade osteosarcoma receiving surgical excision.

Method: We retrospectively included patients' clinical characteristics diagnosed as high grade osteosarcomas histologically receiving surgical excision from January 2008 to June 2018. Body mass index (BMI), Glasgow prognostic score (GPS), systematic inflammatory index (SII), and controlling nutritional (CONUT) score were calculated as nutritional associated factors to evaluate their prognostic value. The primary outcome was overall survival (OS) while the secondary outcome was the postoperative length of hospitalization. The relationship between clinical features and outcomes were performed by Cox and logistic regression analysis, respectively. The independent prognostic factors were chosen to construct predicted model whose internal and external accuracy were validated by concordance index (C-index), Brier score, and calibration plots.

Results: High score of GPS predicted worse OS [HR (95% CI): 3.122 (1.982-4.918) versus 2.208 (1.014-4.804)] and higher rank of CONUT predicted poorer prognosis [HR (95% CI): 2.573 (1.616-4.097)] independently. The CONUT score was selected as the only prognostic factor on the length of hospitalization [HR (95% CI): 2.137 (1.270-3.596)]. The nomogram plots were used to visualize the results of predicted models whose performance was evaluated from the aspects of calibration and discrimination.

Conclusion: Our study suggested prognostic value of nutritional assessment indexes including GPS and CONUT score that appropriate preoperative intervention which could optimize patients' nutrition associated indicators may improve prognosis on patients with high grade osteosarcoma receiving surgical excision.

Level of evidence: Level Ⅲ, prognostic study

Background

Osteosarcoma is the most common primary bone malignancies except some hematological tumor. The classification of osteosarcoma is based on both histology pattern and histologic grade due to the various extracellular matrix it produces and different degrees of differentiation[1]. The high grade osteosarcoma represents higher incident compared with low grade osteosarcoma because of its typical characteristics to improve the diagnostic rates. The most common high-grade subtypes contained conventional, telangiectatic and small cell osteosarcomas which take up more than half of new cases per year[2].

The increasing frequency of morbidity in children and young adults has promoted the research process to identify potential prognostic features to improve patients' outcomes[3]. The amplification of FGFR 1 has demonstrated to associate with the response to chemotherapy and predict the long term prognosis[4]. Patients clinical features about tumors may be more practicable than gene tests[5]. The tumor characteristics including larger size, axial location, and histology patterns have been found associated with poor prognosis[6–8]. Patients' pre-existing diseases have been proven its value to influence the 3- and 5-year survival rates[9]. Age is also a potential prognostic factor that geriatric patients (≥ 65 years old) may have less capacity to tolerate subsequent therapy such as chemotherapy and radiotherapy than the younger[10]. However the tendency of incidence coincides with the growth rates of bone. It is not sufficient to claim the relationship between age and prognosis after comparing the overall survival of patients ≥ 65 and < 65 years old.

The development of malignancies usually depends on patients' nutritional situations. The expansion of tumors may induce patients' malnutrition[11] which links to the poor prognosis. Osteosarcoma performs higher risk in children with abnormal growth of height compared with the peer[1]. The growing and developing demands of young patients during adolescence may interfere the actual nutritional condition that excessive energy consumption of lesions brings. Therefore we need various examining tools to assess the patients' nutrition comprehensively. Besides the body mass index (BMI) and other fundamental indicators, some innovative indexes could also be applied. The Glasgow prognostic score (GPS) has been generated to predict long-term outcomes based on the biochemical indicators from peripheral blood[12]. The systematic inflammatory index (SII) constructed based on a set of inflammation associated indexes including neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR) and monocyte–lymphocyte ratio (MLR) has been built up to indicate patients' prognosis according to the systematic inflammatory response affected by patients' nutritional situations and applied in many kinds of malignancies[13–16]. The prognostic nutritional index (PNI) was calculated by serum albumin and the count of lymphocyte which may be explicit to reflect the patients' conditions[17–19]. Compared with PNI, the additional inclusion of platelet in the controlling nutritional score (CONUT) has been identified the association with the entire nutritional degrees of patients[20–22].

To make up inadequate effects which these nutritional assessment tools used alone brought, we combined various indicators representing nutritional status to evaluate their value of prognosis for overall survival (OS) and postoperative length of hospitalization the predicted models on which were constructed and visualized by nomogram plots on patients with high grade osteosarcoma receiving surgical resection.

Methods

Patients

We retrospectively collected patients' clinical data who received surgical resection of osteosarcoma lesions at West China Hospital, Sichuan University, China from January 2008 to June 2018. All patients were diagnosed as high grade osteosarcoma from needle biopsy or histologic slice examinations during operation. We collected detailed clinical information including age at diagnosis, gender, weight, height, Enneking stage of musculoskeletal system, histologic subtypes, location and size of primary lesions, therapeutic regimen, and indexes from peripheral blood obtained from the last preoperative test. The size of tumor was represented by the maximum diameter of primary lesions. The patients whose essential information was not complete were excluded. The primary outcome was OS as a long term outcome defined as the duration from the date of procedures to the date of death or the last follow-up time, December 2018. The survival status was determined by the follow-up which was accomplished every three months since discharge through telephone calls, e-mails or readmission. The secondary outcome was the postoperative length of hospitalization as a short term outcome defined as the duration from the date of procedures to the date of discharge. All processes were completed under the ethics of West China Hospital, Sichuan University.

Nutritional assessment indicators

There were several nutritional assessment tools obtained from the easy-to-reach clinical features. The body mass index (BMI) was defined as weight (kg) / height^2 (m^2) and was categorized into four groups, underweight/normal/overweight/obese, according to individual standards for different ages. The SII as the reflection of inflammatory reaction was calculated as the ratio of neutrophil and lymphocyte to platelet from the peripheral blood test. The GPS was acquired by the degree of serum albumin and C reactive protein (CRP) that patients would get one score if CRP > 10 mg/L or albumin < 3.5 mg/L. The final score was the sum of the score of CRP and albumin including 0, 1 and 2. The CONUT score was calculated from the serum albumin concentration, total blood cholesterol level, and total peripheral lymphocyte count and was divided into four degrees: normal, light, moderate and severe, as the previous studies reporting[23]. The first degree was considered as a group (CONUT score ≤ 1) and the last three degrees were summarized into the other group (CONUT score > 1).

Statistical analysis

The continuous characteristics were performed as median and its interquartile range (IQR) because of its non-normal distribution. All eligible subjects were distributed into the training and testing cohorts with the ratio of 7:3 randomly. The comparison between the training and testing sets was completed by non-parametric Mann-Whitney tests for continuous parameters and Chi-square tests or Fisher's exact tests for categorical parameters. The SII was dichotomized by its optimal cut-off point which was determined by receiver operating characteristic (ROC) curve on the training cohort. The Cox regression analysis on OS in the training group was applied to explore the association between variables and prognosis the p values of which were less than 0.10 in univariate analysis could enter the multivariate proportional hazards model. The variables with p value less than 0.05 in this Cox regression model would be considered as independent prognostic factors. The postoperative length of hospitalization dichotomized by 7 days was considered as the dependent variable in binary logistic regression analysis. The binary logistic regression

analysis on postoperative length of hospitalization with p values less than 0.10 in univariate analysis could enter the multivariate model. The variables with p values less than 0.05 in this logistic regression model would be considered as independent prognostic factors. These factors were collected to construct predicted models respectively visualized by nomogram plots. The predictive performance was examined by concordance index (C-index), Brier score, and calibration plots for the accuracy of discrimination and calibration. To evaluate the clinical practicability of different models constructed with the features from different analysis, the net benefits were calculated based on decision curve analysis compared with the full-size model including all parameters P value less than 0.05 was considered as significant. All statistical processes were thought as two-sided and completed by R version 3.6.1.

Results

Demographic characteristics

A total of 487 patients was included for final statistical analysis and the detailed clinical features were listed in Table 1. There were 341 patients in the training group and 146 patients in the testing group. The distributions of the location of primary lesions, tumor size, neoadjuvant chemotherapy, peripheral blood indexes including hemoglobin, platelet, white blood cell (WBC), lymphocyte, alkaline phosphatase (AKP), lactic dehydrogenase (LDH), serum total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-c), and some nutritional assessment indexes including BMI, SII, GPS, and CONUT score were not found significant difference between the training and testing groups which indicated the success of this randomization. The optimal cut-off point of SII was examined by ROC curves and was identified as 869.04.

Table 1
Demographic features of patients with high grade osteosarcoma receiving surgical resection

Variable	Clinical characteristics			
	All subjects (N = 487)	Training cohort (N = 341)	Testing cohort (N = 146)	P value
Age at diagnosis, years old, median (IQR)	20 (22)	20 (23)	20 (17)	0.369
Age at diagnosis, years old, n (%)				0.634
0 ~ 10	30 (6.2)	20 (5.9)	10 (6.8)	
10 ~ 20	221 (45.4)	152 (44.6)	69 (47.3)	
20 ~ 30	89 (18.3)	59 (17.3)	30 (20.5)	
30 ~ 40	43 (8.8)	35 (10.3)	8 (5.5)	
40 ~ 50	45 (9.2)	33 (9.7)	12 (8.2)	
50 ~ 60	34 (7.0)	23 (6.7)	11 (7.5)	
60~	25 (5.1)	19 (5.6)	6 (4.1)	
Gender, n (%)				0.866
Male	283 (58.1)	199 (58.4)	84 (57.5)	
Female	204 (41.9)	142 (41.6)	62 (42.5)	
Location of primary tumor, n (%)				0.141
Upper limbs	78 (16.0)	48 (14.1)	30 (20.5)	
Lower limbs	346 (71.0)	245 (71.8)	101 (69.2)	
Trunk	63 (12.9)	48 (14.1)	15 (10.3)	
Histological type, n (%)				0.134
Conventional	458 (94.0)	319 (93.5)	139 (95.2)	
Telangiectatic	21 (4.3)	18 (5.3)	3 (2.1)	
Small-cell	8 (1.6)	4 (1.2)	4 (2.7)	

*IQR: Interquartile range describing the range between the first quartile and the third quartile for variables with non-normal distribution.

SII: systematic inflammatory index; WBC: white blood cell; AKP: alkaline phosphatase; LDH: lactic dehydrogenase; TC: serum total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; BMI: body mass index; CONUT: controlling nutritional tool.

Variable	Clinical characteristics			
	All subjects (N = 487)	Training cohort (N = 341)	Testing cohort (N = 146)	P value
Enneking stage, n (%)				0.400
B	417 (85.6)	289 (84.8)	128 (87.7)	
	70 (14.4)	52 (15.2)	18 (12.3)	
Tumor size, cm, median (IQR)	10.0 (6.3)	10.0 (7.0)	10.0 (5.5)	0.434
Tumor size, cm, n (%)				0.987
≤ 10.0	350 (71.9)	245 (71.8)	105 (71.9)	
> 10.0	137 (28.1)	96 (28.2)	41 (28.1)	
Neoadjuvant chemotherapy, n (%)				0.851
No	363 (74.5)	255 (74.8)	108 (74.0)	
Yes	124 (25.5)	86 (25.2)	38 (26.0)	
Surgery type, n (%)				0.680
Amputation	116 (23.8)	83 (24.3)	33 (22.6)	
Limb-salvage	371 (76.2)	258 (75.7)	113 (77.4)	
BMI rank, n (%)				0.628
Underweight	115 (23.6)	81 (23.8)	34 (23.3)	
Normal	286 (58.7)	204 (59.8)	82 (56.2)	
Overweight	64 (13.1)	43 (12.6)	21 (14.4)	
Obese	22 (4.5)	13 (3.8)	9 (6.2)	
Glasgow Prognostic Score, n (%)				0.503
0	364 (74.7)	260 (76.2)	104 (71.2)	
1	106 (21.8)	70 (20.5)	36 (24.7)	

*IQR: Interquartile range describing the range between the first quartile and the third quartile for variables with non-normal distribution.

SII: systematic inflammatory index; WBC: white blood cell; AKP: alkaline phosphatase; LDH: lactic dehydrogenase; TC: serum total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; BMI: body mass index; CONUT: controlling nutritional tool.

Variable	Clinical characteristics			
	All subjects (N = 487)	Training cohort (N = 341)	Testing cohort (N = 146)	P value
2	17 (3.5)	11 (3.2)	6 (4.1)	
SII, median (IQR)	477.29 (515.59)	480.45 (544.10)	468.00 (453.82)	0.596
SII, n (%)				0.297
≤ 869.04	379 (77.8)	261 (76.5)	118 (80.8)	
> 869.04	108 (22.2)	80 (23.5)	28 (19.2)	
CONUT score, median (IQR)	1 (2)	1 (2)	0 (2)	0.499
CONUT score group, n (%)				0.630
≤ 1	353 (72.5)	245 (71.8)	108 (74.0)	
> 1	134 (27.5)	96 (28.2)	38 (26.0)	
Hematological parameters, median (IQR)				
Hemoglobin (g/L)	127 (27)	128 (29)	127 (28)	0.622
Platelet (109/L)	211 (108)	213 (108)	211 (104)	0.489
WBC (109/L)	6.08 (3.15)	6.02 (3.09)	6.25 (3.19)	0.655
AKP (IU/L)	117 (114)	116 (106)	121 (178)	0.066
LDH (IU/L)	180 (87)	175 (74)	189 (125)	0.015
TC (mmol/L)	3.67 (1.18)	3.71 (1.15)	3.59 (1.28)	0.405
TG (mmol/L)	0.95 (0.62)	0.96 (0.62)	0.93 (0.70)	0.397
HDL-c (mmol/L)	1.18 (0.37)	1.19 (0.36)	1.16 (0.41)	0.419
LDL-c (mmol/L)	1.97 (0.92)	2.01 (0.90)	1.92 (0.95)	0.299
Complication, n (%)				0.264
No	428 (87.9)	296 (86.8)	132 (90.4)	

*IQR: Interquartile range describing the range between the first quartile and the third quartile for variables with non-normal distribution.

SII: systematic inflammatory index; WBC: white blood cell; AKP: alkaline phosphatase; LDH: lactic dehydrogenase; TC: serum total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; BMI: body mass index; CONUT: controlling nutritional tool.

Variable	Clinical characteristics			
	All subjects (N = 487)	Training cohort (N = 341)	Testing cohort (N = 146)	P value
Yes	59 (12.1)	45 (13.2)	14 (9.6)	
Length of hospitalization, median (IQR)	8 (5)	8 (6)	8 (5)	0.929
Length of hospitalization, n (%)				0.748
0 ~ 7	204 (41.9)	140 (41.1)	64 (43.8)	
7 ~ 30	266 (54.6)	188 (55.1)	78 (53.4)	
30~	17 (3.5)	13 (3.8)	4 (2.7)	
Overall survival, median (IQR)	31 (42)	29 (42)	34 (45)	0.765
*IQR: Interquartile range describing the range between the first quartile and the third quartile for variables with non-normal distribution.				
SII: systematic inflammatory index; WBC: white blood cell; AKP: alkaline phosphatase; LDH: lactic dehydrogenase; TC: serum total cholesterol; TG: triglyceride; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; BMI: body mass index; CONUT: controlling nutritional tool.				

Cox regression analysis

The nutritional assessment tools and other demographic features were included in the univariate Cox regression analysis successively. The histological subtypes, GPS, SII, and CONUT score entered the multivariate Cox proportional hazard model with $p < 0.10$ (Table 2). Higher scores of GPS and CONUT score were found as independent risk factors for OS significantly compared with the lower scores [GPS: HR (95% CI): 3.122 (1.982–4.918) versus 2.208 (1.014–4.804); CONUT score: HR (95% CI): 2.573 (1.616–4.097)]. These two factors were taken into the ultimate predicted model based on survival analysis.

Table 2
Results of univariate and multivariate Cox regression analysis on OS for patients with high grade osteosarcoma receiving surgical resection.

Variable	Cox regression analysis			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age at diagnosis, years old				
0 ~ 10	Reference	0.499		
10 ~ 20	1.498 (0.461–4.866)	0.502		
20 ~ 30	2.134 (0.631–7.219)	0.223		
30 ~ 40	1.998 (0.557–7.164)	0.288		
40 ~ 50	2.425 (0.676–8.695)	0.174		
50 ~ 60	2.291 (0.607–8.644)	0.221		
60~	1.089 (0.243–4.875)	0.911		
Gender				
Male	Reference			
Female	1.175 (0.778–1.774)	0.443		
Location of primary tumor				
Upper limbs	Reference	0.357		
Lower limbs	0.869 (0.468–1.614)	0.657		
Trunk	1.274 (0.611–2.653)	0.518		
Histological type				
Conventional	Reference	0.045	Reference	0.381
Telangiectatic	1.005 (0.407–2.480)	0.991	0.979 (0.395–2.425)	0.964
Small-cell	4.352 (1.364–13.882)	0.013	2.346 (0.703–7.826)	0.165
Enneking stage				
B	Reference			
	1.081 (0.621–1.881)	0.783		
Tumor size, cm				

* OS: overall survival; CI: confidential interval; BMI: body mass index; Hb: hemoglobin; LLN: lower limit of normal; SII: systematic inflammatory index; CONUT: controlling nutritional tool.

Variable	Cox regression analysis			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
≤ 10.0	Reference			
> 10.0	1.000 (0.638–1.567)	0.999		
Neoadjuvant chemotherapy				
No	Reference			
Yes	0.950 (0.592–1.524)	0.832		
Surgery type				
Amputation	Reference			
Limb-salvage	1.124 (0.691–1.830)	0.638		
BMI rank				
Underweight	Reference	0.984		
Normal	0.943 (0.569–1.562)	0.819		
Overweight	1.054 (0.518–2.145)	0.885		
Obese	1.021 (0.350–2.978)	0.969		
Hb, g/L				
<LLN	Reference			
≥LLN	1.412 (0.823–2.422)	0.211		
Glasgow Prognostic Score				
0	Reference	< 0.001	Reference	< 0.001
1	4.077 (2.640–6.295)	< 0.001	3.122 (1.982–4.918)	< 0.001
2	5.058 (2.525–10.131)	< 0.001	2.208 (1.014–4.804)	0.046
SII				
≤ 869.04	Reference		Reference	
> 869.04	1.969 (1.292–3.001)	0.002	1.140 (0.723–1.798)	0.573
CONUT group				

* OS: overall survival; CI: confidential interval; BMI: body mass index; Hb: hemoglobin; LLN: lower limit of normal; SII: systematic inflammatory index; CONUT: controlling nutritional tool.

Variable	Cox regression analysis			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
≤ 1	Reference		Reference	
> 1	3.787 (2.499–5.737)	< 0.001	2.573 (1.616–4.097)	< 0.001
Complication				
No	Reference			
Yes	1.498 (0.893–2.511)	0.126		
Length of hospitalization, day				
0 ~ 7	Reference	0.826		
7 ~ 30	1.144 (0.746–1.755)	0.536		
30~	1.092 (0.335–3.561)	0.884		

* OS: overall survival; CI: confidential interval; BMI: body mass index; Hb: hemoglobin; LLN: lower limit of normal; SII: systematic inflammatory index; CONUT: controlling nutritional tool.

Binary logistic regression analysis

The postoperative length of hospitalization as the dependent variable was dichotomized into two groups on the median length of hospital day (0 ~ 7 day versus 7 ~ day). Various nutritional assessment tools and other clinical characteristics were included in the univariate logistic regression analysis successively. The location of primary tumor, preoperative intervention, and CONUT score entered the multivariate logistic model with $p < 0.10$ (Table 3). The CONUT score was identified as the only independent prognostic factor for the postoperative length of hospitalization [OR (95% CI): 2.137 (1.270–3.596)]. The ultimate predicted model contained CONUT score and additional two variables, the location of primary tumor and preoperative chemotherapy.

Table 3
Results of univariate and multivariate binary logistic regression analysis on postoperative length of hospitalization for patients with high grade osteosarcoma receiving surgical resection.

Variable	Binary logistic analysis			
	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Age at diagnosis, years old				
0 ~ 10	Reference	0.275		
10 ~ 20	2.238 (0.864–5.795)	0.097		
20 ~ 30	1.904 (0.679–5.342)	0.221		
30 ~ 40	3.273 (1.042–10.278)	0.042		
40 ~ 50	2.036 (0.658–6.302)	0.218		
50 ~ 60	4.250 (1.169–15.454)	0.028		
60~	1.350 (0.379–4.804)	0.643		
Gender				
Male	Reference			
Female	0.919 (0.593–1.423)	0.704		
Location of primary tumor				
Upper limbs	Reference	0.074	Reference	0.077
Lower limbs	2.030 (1.086–3.795)	0.027	2.037 (1.075–3.858)	0.029
Trunk	2.143 (0.947–4.848)	0.067	2.198 (0.952–5.706)	0.065
Histological type				
Conventional	Reference	0.372		
Telangiectatic	0.543 (0.209–1.413)	0.211		
Small-cell	2.037 (0.210-19.798)	0.540		
Enneking stage				
□B	Reference			
□	1.526 (0.817–2.849)	0.185		
Tumor size, cm				

* CI: confidential interval; BMI: body mass index; Hb: hemoglobin; LLN: lower limit of normal; SII: systematic inflammatory index; CONUT: controlling nutritional tool.

Variable	Binary logistic analysis			
	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
≤ 10.0	Reference			
> 10.0	1.229 (0.757–1.996)	0.404		
Neoadjuvant chemotherapy				
No	Reference		Reference	
Yes	1.739 (1.036–2.919)	0.036	1.680 (0.983–2.871)	0.058
Surgery type				
Amputation	Reference			
Limb-salvage	0.931 (0.562–1.543)	0.783		
BMI rank				
Underweight	Reference	0.613		
Normal	1.099 (0.651–1.853)	0.725		
Overweight	0.758 (0.360–1.593)	0.465		
Obese	0.707 (0.463–5.725)	0.448		
Hb, g/L				
<LLN	Reference			
≥LLN	1.430 (0.850–2.406)	0.178		
Glasgow Prognostic Score				
0	Reference	0.554		
1	1.168 (0.680–2.005)	0.574		
2	1.956 (0.507–7.540)	0.330		
SII				
≤ 869.04	Reference			
> 869.04	1.059 (0.635–1.764)	0.826		
CONUT group				

* CI: confidential interval; BMI: body mass index; Hb: hemoglobin; LLN: lower limit of normal; SII: systematic inflammatory index; CONUT: controlling nutritional tool.

Variable	Binary logistic analysis			
	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
≤ 1	Reference		Reference	
> 1	2.188 (1.312–3.647)	0.003	2.137 (1.270–3.596)	0.004
Complication				
No	Reference			
Yes	1.641 (0.838–3.213)	0.148		

* CI: confidential interval; BMI: body mass index; Hb: hemoglobin; LLN: lower limit of normal; SII: systematic inflammatory index; CONUT: controlling nutritional tool.

Nomogram visualization and validation

The construction of nomogram on OS was performed by collecting independent prognostic factors, GPS and CONUT score, identified by Cox regression analysis which showed the 3- and 5-year survival rates for patients with high grade osteosarcoma receiving surgical resection in the training cohort (Fig. 1). The C-index was 0.583 (95%CI: 0.518–0.648) in the training set and 0.634 (95%CI: 0.534–0.733) in the testing cohort which indicated discrimination between the predicted survival probability and actual KM curves, while the Brier score representing the accuracy of both discrimination and calibration was 21.4 (95%CI: 18.9–23.8) in the training set and 20.6 (95%CI: 17.3–23.9) in the testing cohort. The calibration curves showed strong consistency of 3- and 5-year survival probabilities between predicted results and actual observations both in training and testing sets (Fig. 2).

The nomogram plot on postoperative length of hospitalization was constructed by independent prognostic factors, CONUT score, and additional two additional two variables, the location of primary tumor and preoperative chemotherapy from binary logistic regression analysis indicating risk for patients with high grade osteosarcoma receiving surgical resection in the training cohort (Fig. 3). The C-index was 0.639 (95%CI: 0.582–0.696) in the training set and 0.559 (95%CI: 0.467–0.651) in the testing cohort, while the Brier score was 22.9 (95%CI: 21.5–24.3) in the training set and 25.0 (95%CI: 22.8–27.3) in the testing cohort. The calibration curves showed moderate consistency between predicted and actual risk both in training and testing sets (Fig. 4).

Decision curve

The decision curve of several risking models, the full model, the model with features from Cox regression analysis, and the model with features from binary logistic regression analysis was depicted in comparison with all-screening and non-screening scenarios in the training cohort (Fig. 5). The line y = 0 revealed the risk threshold probability while the line x = 0 provided a threshold probability for net benefit.

These three models performed clearly larger net benefit than the strategies for screening all subjects and no subject, whereas little difference was shown between these three models.

Discussion

In this study, we included nearly five hundred patients with high grade osteosarcoma receiving surgical excision and collected their clinical features for calculating nutritional assessment indicators to explore the relationship between these indexes and different clinical outcomes. The GPS and CONUT score were evaluated as independent prognostic factors that high score on them indicated poor outcomes for OS significantly. The CONUT score was found significant association with duration of postoperative length of hospitalization from results of binary logistic regression analysis. A nomogram model on OS was built up to predict 3- and 5-year survival probability whose accuracy was evaluated by C-index, Brier score, and calibration curves. The calibration curves showed fitness between predicted and actual survival probability.

Osteosarcoma as a mesenchymal originated tumor represents the difference on peak incidence compared with other malignancies that geriatric population is not the only high-risk group but also the pediatric. The distributions of some patients' demographic characteristics were different within two groups significantly. The location of primary malignancies was different that the tumors preferred to locate at axial line and its surrounds as age grows[24]. The standards of underweight, normal, overweight and obese depending on BMI were totally different between children and adult[25, 26], so the pure comparison of value of BMI was lack of clinical practicability. Therefore, we categorized patients into different group depending on standards of the World Health Organization for each age range before statistical analysis. The development of the immune system was immature in children[27] so the count of inflammatory indexes may differ from those of adults. Hence, we applied the ratio of correlated variables or adjusted the criteria of scoring for children that the inflammatory response reflects the nutritional situations[28–30].

Our study identified GPS score as an independent prognostic factor that higher score of GPS predicted worse OS [HR (95% CI): 3.122 (1.982–4.918) versus 2.208 (1.014–4.804)]. This result was found in other researches of osteosarcoma base on Chinese population[31]. In that study, the GPS was divided into group, 0 and 1/2 that patients performed shorter survival time if CRP > 10 mg/L or albumin < 3.5 mg/L. In our study, we explored the increasing risk as the score of GPS elevating. There was a retrospective study showing the prognostic value of an innovative factor also based on C-reactive protein and albumin[32] that may eliminate errors. The SII were calculated significantly just in the univariate Cox analysis. Nevertheless, their predicted value has been demonstrated by previous studies[31, 33].

PNI as a continuous variable was the foundation of some innovative nutrition associated indicators like CONUT score. A previous study presented the prognostic value of PNI[34] with the optimal cutoff point of 52.9 that may influence the further clinical practicability. We need a larger sample prospective study to estimate the predicted value of PNI. CONUT score was a modified index integrating serum albumin,

lymphocyte and total cholesterol which was associated with the risk of malnutrition[35, 36]. In case of disturbance from the proportions of TG, HDL-c and LDL-c, we included them as confounding factors to avoid interference from them. The reliability of CONUT score was estimated superior than SII which only included indexes reflecting inflammatory response[37, 38] in some kinds of carcinoma, but there have been no evidence to prove the advantages of CONUT scores compared with other inflammatory indicators. The prognostic value of CONUT score has been demonstrated in soft-tissue sarcoma[39, 40] that the raised score of CONUT indeed improved risk of death.

Nomogram based on potential prognostic factors predicted patients' long term survival probability and risk of duration of hospitalization. Extensive aspects about patients with osteosarcoma have been collected into the construction of nomogram[41–43] including clinical, radiometric and genetic features. The validation for nomogram model was inevitable to assess the agreement between the predicted and actual survival probabilities that calibration curves in our study presented moderate consistency. Nevertheless, as for further practical application, we demand more adjustment of this model to decrease the bias and increase the accuracy.

There are several limitations existing in our study. Firstly, we were a single-center and retrospective study that the presence of recalling bias may decrease the actual efficacy of nutritional assessment tools which need to be assessed in a prospective study. Secondly, the preoperative nutritional status need a comprehensive evaluate with respect to the effects from diet habits, economic conditions and other factors which were omitted by in-hospital examination and inquiry of history easily. Thirdly, the bias existed during the recruitment of patients. Patients with high grade osteosarcomas who obtain alleviation from neoadjuvant chemotherapy may be more positive to receive surgery and other interventions. The different reflection of neoadjuvant chemotherapy may attribute to the individual nutritional status that there was bias in the baseline data which need justify.

Our study suggested prognostic value of nutritional assessment indexes including GPS and CONUT score on OS in patients with high grade osteosarcoma receiving surgical resection. These factors constructed a predicted model which was visualized and validated in this study. Appropriate preoperative interventions which could optimize patients' nutrition associated indicators may improve prognosis on patients with high grade osteosarcoma receiving surgical excision.

Conclusion

Our study suggested prognostic value of nutritional assessment indexes including GPS and CONUT score that appropriate preoperative intervention which could optimize patients' nutrition associated indicators may improve prognosis on patients with high grade osteosarcoma receiving surgical excision.

Abbreviations

BMI: body mass index; GPS: Glasgow prognostic score; SII: systematic inflammatory index; CONUT: controlling nutritional; OS: overall survival; C-index: concordance index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; MLR: monocyte–lymphocyte ratio; PNI: prognostic nutritional index; CRP: C reactive protein.

Declarations

Ethics approval and consent to participate

Each author certified that his or her institution approved the human protocol for this investigation and that all investigations were consistent with ethical principles of research. This work performed by West China Hospital, Sichuan University, Chengdu, Sichuan, China.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and material

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

Competing interests

Each author certified that neither she or he, nor any member of her or his immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might induce conflicts of interest connected with this submitted article.

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Authors' Contributions

XM, YY, and XD made substantial contributions to conception and design, and revised the manuscript critically for important intellectual content. XM revised the manuscript and gave final approval of the version to be published. All authors read and approved the final manuscript.

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Figures

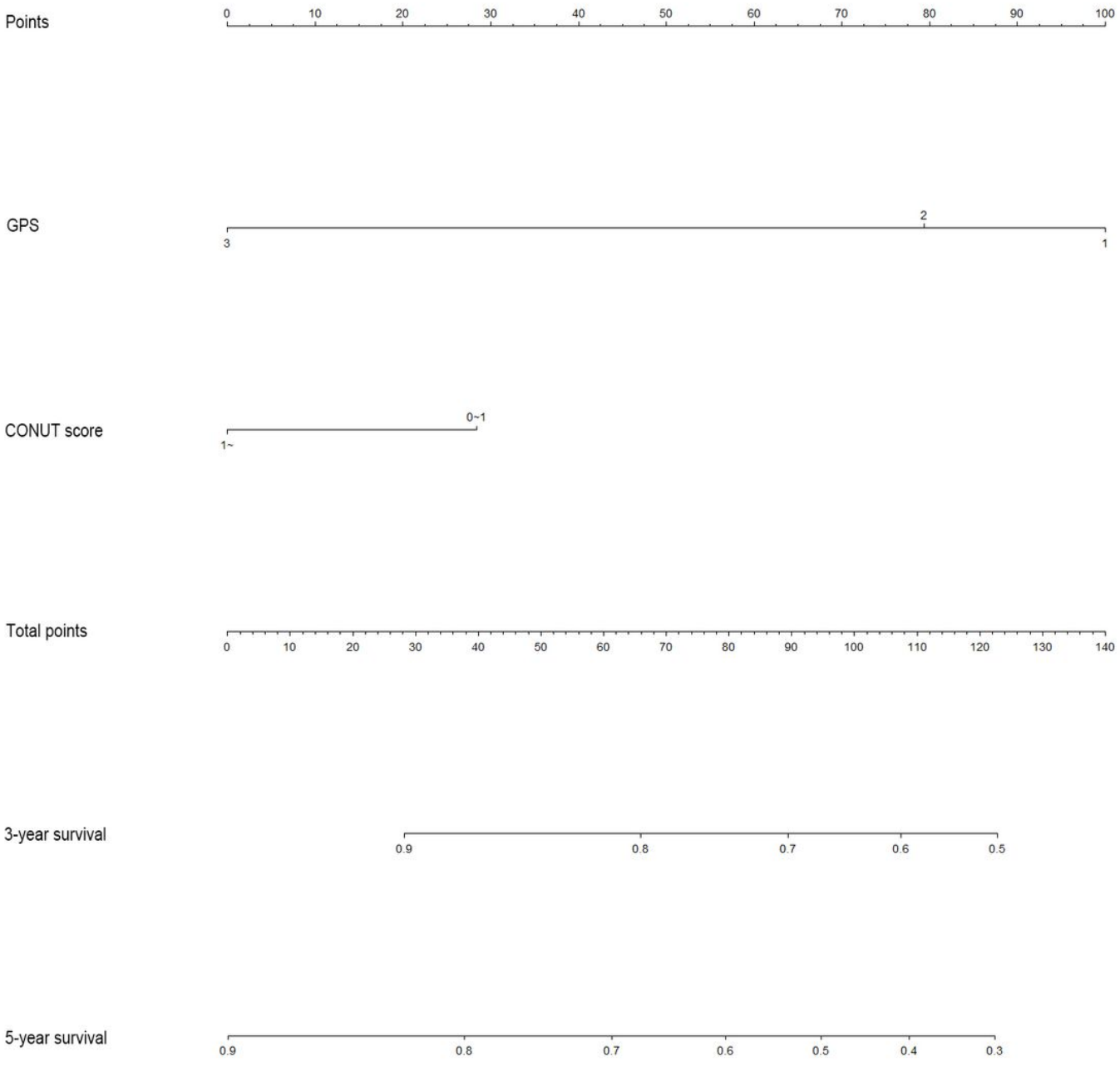

Figure 1

Nomogram on OS constructed for patients with high grade osteosarcoma receiving surgical resection to predict 3- and 5-year survival probabilities*. *The nomogram was developed according to clinical features including GPS and CONUT score identified as independent prognostic factors in multivariate Cox regression analysis.

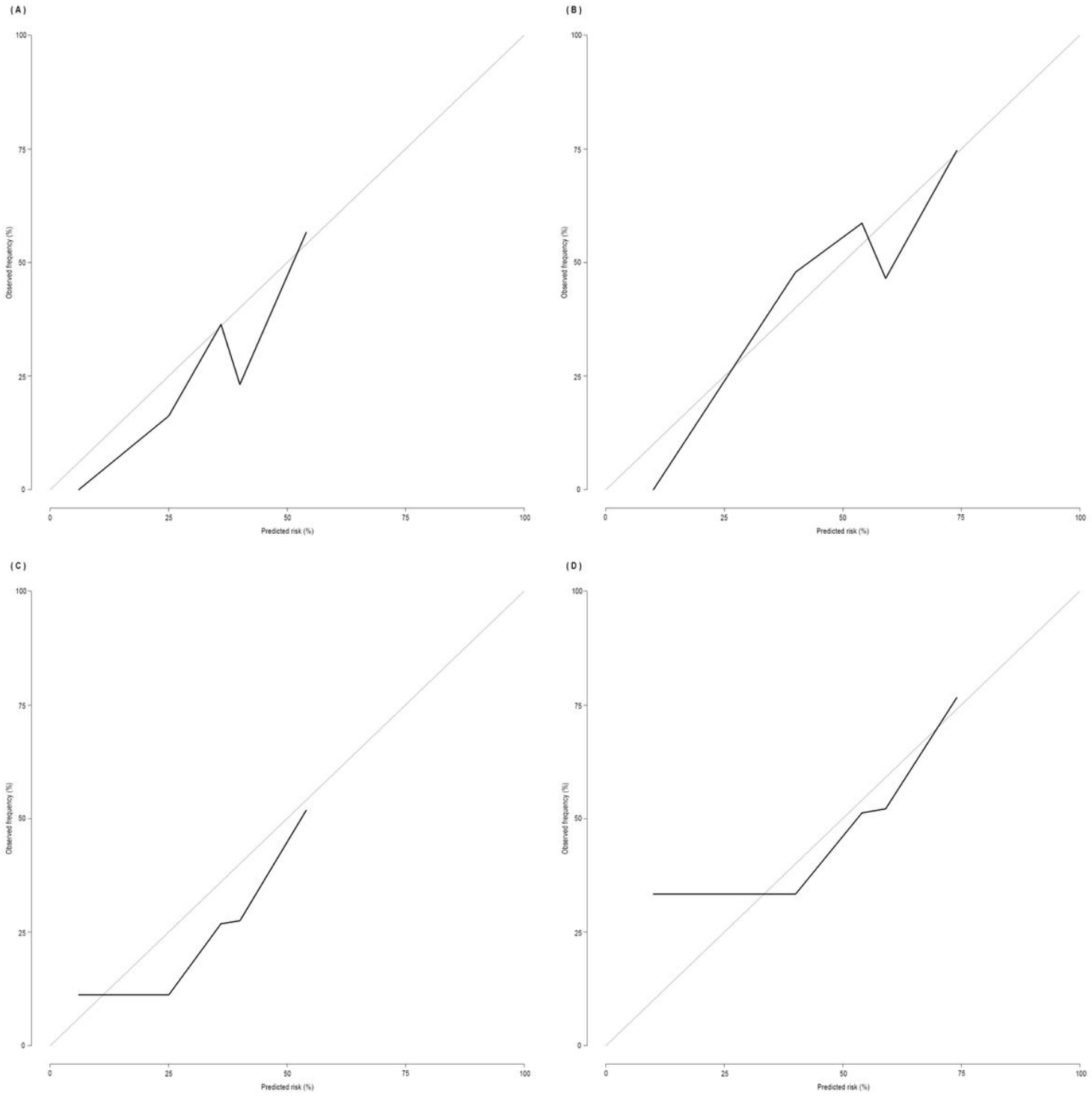

Figure 2

Calibration curves for the nomogram presenting agreement between predicted and observational survival probability of OS for patients with high grade osteosarcoma receiving surgical resection. *(A) Calibration plot for comparison between nomogram predicted 3-year survival rates and actual observation for OS in the training cohort. (B) Calibration plot for comparison between nomogram predicted 5-year survival rates and actual observation for OS in the training cohort. (C) Calibration plot for comparison between nomogram predicted 3-year survival rates and actual observation for OS in the testing cohort. (D)

Calibration plot for comparison between nomogram predicted 5-year survival rates and actual observation for OS in the testing cohort. The gray line of y=x represents a perfect predictive power by an ideal model. The fit goodness with this diagonal line coincided with the accuracy of predicted performance for nomogram model.

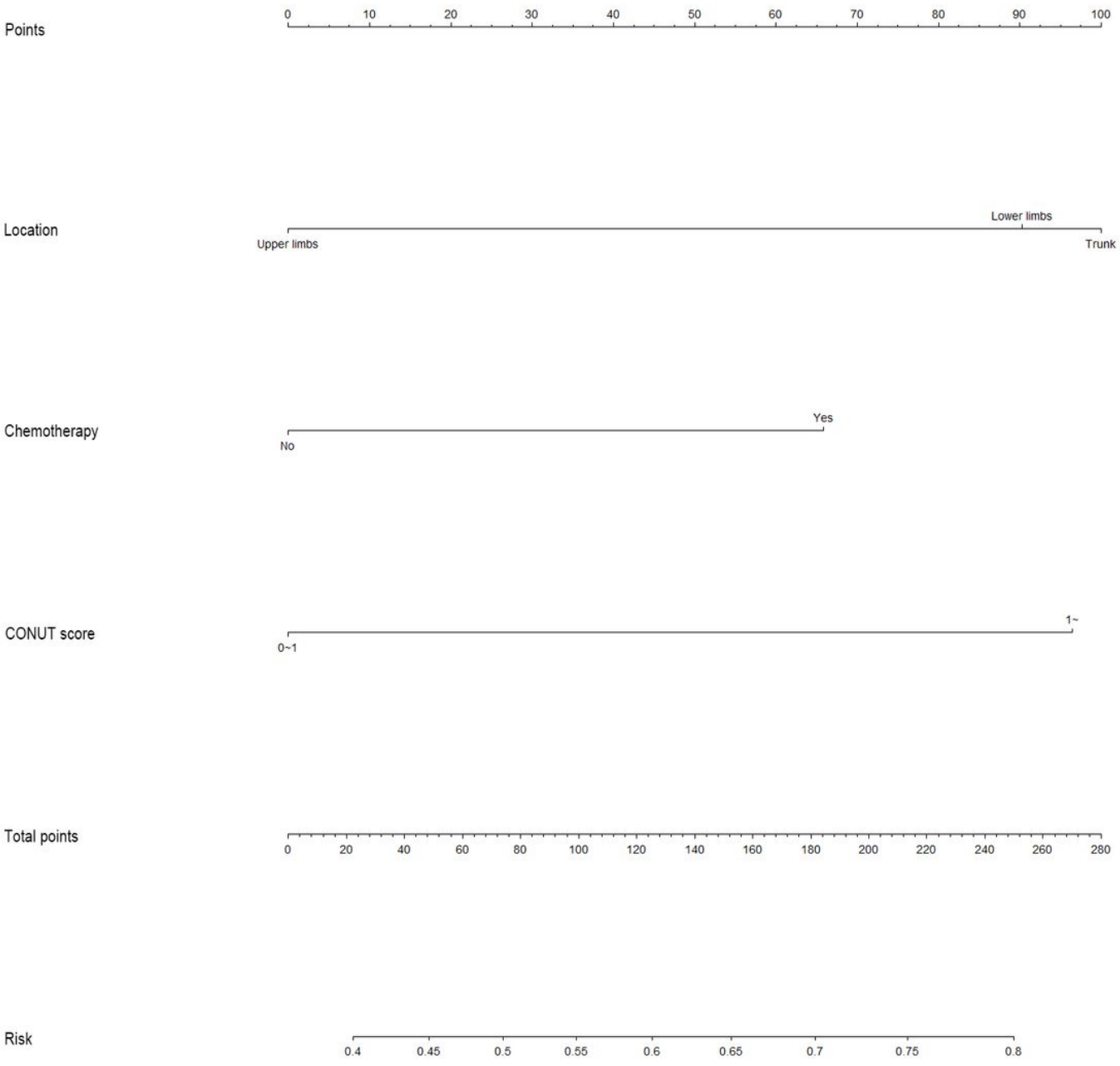

Figure 3

Nomogram on postoperative length of hospitalization constructed for patients with high grade osteosarcoma receiving surgical resection to predict risk of hospitalization*. *The nomogram was

developed according to independent prognostic factors, CONUT score, and additional two additional two variables, the location of primary tumor and preoperative chemotherapy selected from the univariate analysis.

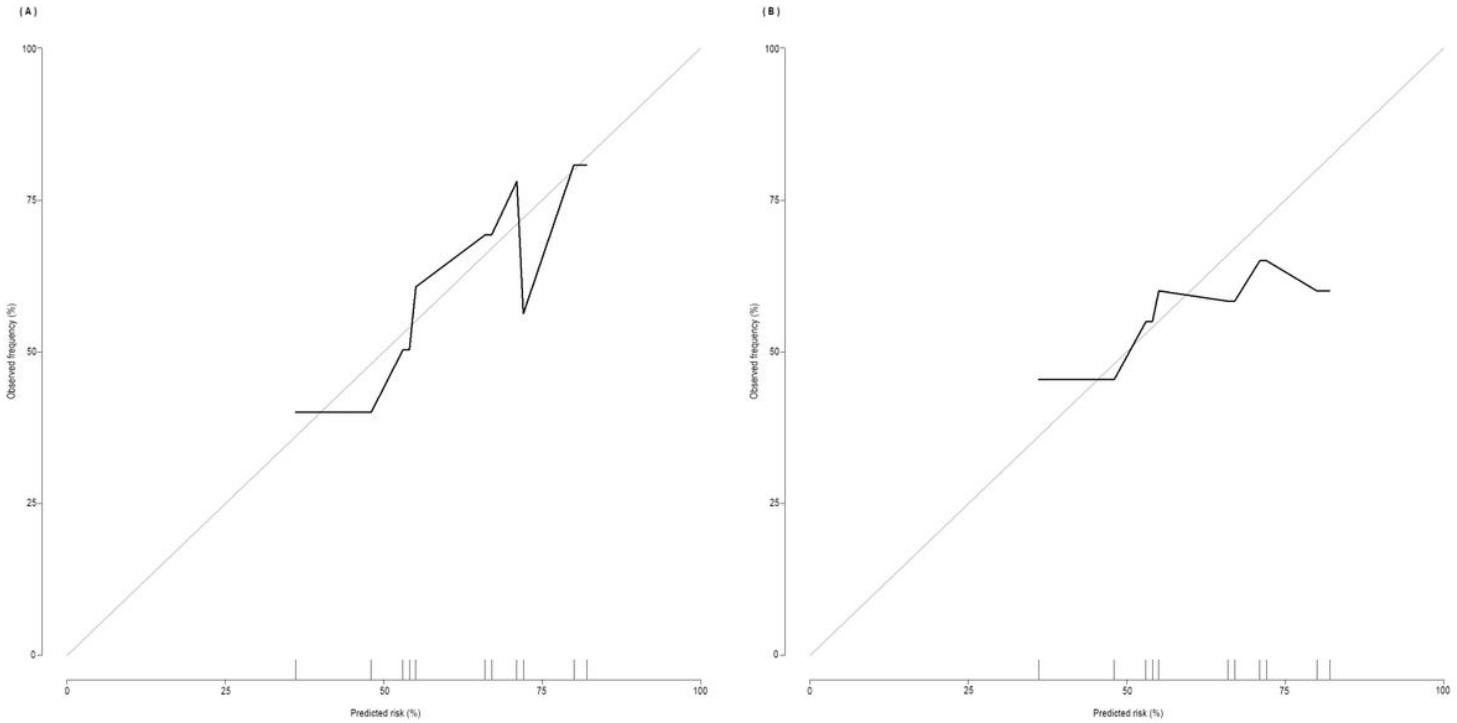

Figure 4

Calibration curves for the nomogram presenting agreement between predicted and observational risk of postoperative hospital day for patients with high grade osteosarcoma receiving surgical resection. * (A) Calibration plot for comparison between predicted and actual risk for postoperative hospital day in the training cohort. (B) Calibration plot for comparison between predicted and actual risk for postoperative hospital day in the testing cohort. The gray line of y=x represents a perfect predictive power by an ideal model. The fit goodness with this diagonal line coincided with the accuracy of predicted performance for selected model.

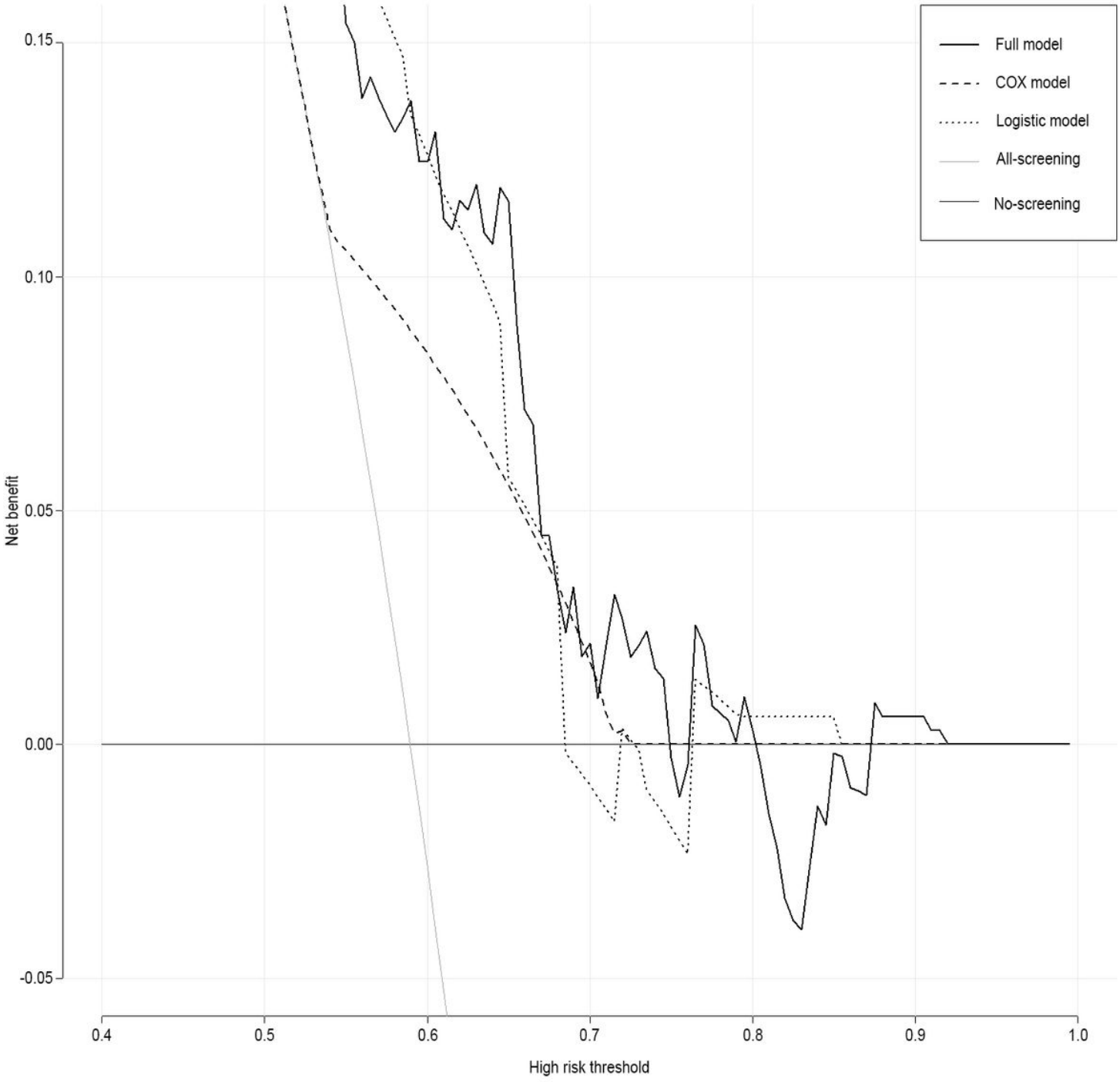

Figure 5

Decision curve analysis for three models, the full model, the model with features from Cox regression analysis, and the model with features from binary logistic regression analysis in the training cohort. * The thin and thick gray lines revealed net benefit of strategies for screening all subjects and no subjects, respectively. The black line with solid, dashed, and dotted types displayed the net benefits of the full model, the model with features from the Cox regression model, and models with features from binary logistic regression model, respectively.