Construction of a nomogram prediction model for opportunistic sarcopenia in patients with malignant tumors

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Liting Li MSc[1†], Ying Wang MPH[2,3†], Chunhua Bian MPH[4], Hongmei Xue PhD[3,5], Cong Wang[6], Jialu Hao[6], Zengning Li PhD[3,5]

[1]Department of Radiology, The First Hospital of Hebei Medical University, Shijiazhuang, China
[2]Department of Nutrition，Affiliated Hospital of Hebei University of Engineering, Handan, China
[3]Department of Clinical Nutrition, The First Hospital of Hebei Medical University, Shijiazhuang, China
[4]Department of Nutrition, Tianjin Kanghui Hospital, TianJin, China
[5]Hebei Key Laboratory of Nutrition and Health, Shijiazhuang, China
[6]Department of Oncology, The First Hospital of Hebei Medical University, Shijiazhuang, China
[†]Both authors contributed equally to this manuscript

Authors' email addresses and contributions:
Liting Li: liliting2023@163.com ORCID: 0009-0003-6777-2478
Contribution: Participate in software development, formal analysis, first draft writing and visualization

Ying Wang: wy1596wnyy1596@163.com ORCID:0009-0004-4752-3930
Contribution: Participate in software development, verification, formal analysis, original manuscript writing and visualization

Chunhua Bian: chunhuabian0@163.com ORCID:0000-0003-0451-9718
Contribution: Participate in verification, data organization and the drafting of the original draft

Hongmei Xue: 58603548@hebmu.edu.cn ORCID:0000-0002-8627-9609
Contribution: Participate in the conceptualization, methodology, review and editing supervision, as well as project management

Cong Wang: 21833279@qq.com ORCID: 0009-0003-3165-0081
Contribution: Participate in data collection and the writing of the original manuscript

Jialu Hao: 1051033486@qq.com ORCID: 0009-0005-4645-5945
Contribution: Participate in data organization

Zengning Li: zengningli@hebmu.edu.cn ORCID:0000-0002-0915-6541
Contribution: Participate in the conceptualization, methodology, review and editorial supervision

Corresponding Author: Dr Zengning Li, Department of Clinical Nutrition, The First Hospital of Hebei Medical University, Shijiazhuang, China; Hebei Key Laboratory of Nutrition and Health, Shijiazhuang, China. Tel: 18633889888. Email: zengningli@hebmu.edu.cn

ABSTRACT

Background and Objectives: The aim of this study was to establish a predictive model for opportunistic sarcopenia applicable to Chinese cancer patients, so as to quickly detect the occurrence of this condition and provide a basis for early clinical intervention. **Methods and Study Design:** A total of 522 malignant tumor patients admitted to the First Hospital of Hebei Medical University from October 2017 to March 2022 were retrospectively analyzed. Opportunistic sarcopenia was diagnosed by L3 SMI. Twelve variables were collected; risk factors were screened and modeled via univariate and multivariate regression in R Studio, and continuous variable cutoff points were determined by SPSS. A nomogram was constructed and validated with clinical decision and calibration curves. **Results:** The prevalence of opportunistic sarcopenia in the study population was 66.1% (345/522). The final predictive model included six key variables: gender, body mass index (BMI), C-reactive protein (CRP) level, systemic immune-inflammation index (SII), prognostic nutritional index (PNI), and SII-PNI. The area under the curve (AUC) of the model was 0.890 (95% CI: 0.854-0.926), indicating high discriminative ability. The calibration curve showed good consistency between the model's predictions and the actual diagnostic results. Clinical net benefit analysis showed that when the threshold range was greater than 0.6, the clinical benefit rate of the predictive model was higher than those of relative appendicular skeletal muscle mass (RASM) and appendicular skeletal muscle mass index (ASMI). **Conclusions:** The constructed nomogram model can accurately estimate the probability of opportunistic sarcopenia in cancer patients, facilitating its early screening and targeted prevention.

Key Words: malignant tumors, opportunistic sarcopenia, nomogram prediction model, screening, inflammatory index

INTRODUCTION

Sarcopenia is a progressive and systemic skeletal muscle illness defined by muscle mass and function loss.1 It is a common manifestation of cancer-related cachexia and may be associated with increased poor outcomes such as falls, fractures, physical impairment, and death.2 Although sarcopenia is a relatively novel syndrome, with only a 10% to 27% global prevalence in elderly persons (⩾ 60 years of age), it is a serious concern for those afflicted.3

Many accessible and affordable clinical trials, including grip strength tests, chair standing tests, and gait speed measurements, can be used to assess muscle strength and physical

function, though they are not very reliable. The International Consensus on the Definition and Classification of Cancer Malignancy, published in 2010, was the first to include computed tomography (CT) assessment of muscle mass in the assessment system for malignancy, and low muscle mass is considered to be an independent prognostic indicator of morbidity and mortality in oncology patients.4 When evaluating skeletal muscle mass, CT is the most accurate,5,6 and the most commonly used sites are the third lumbar vertebrae level, including the measurement of cross sectional area (CSA), and the third lumbar vertebrae skeletal muscle index (L3 SMI).4,7 Semi-automatic contour outlining can also be performed by third-party software based on CT values. The skeletal muscle edges can be manually trimmed by the investigator, and the area within the contour can then be calculated by the software.4 Muscle Imaging Assessments in Sarcopenia: A Statement from China National Center for Orthopedics (NCO) and the East Meets West Action Group of the European Calcified Tissue Society (ECTS) also indicates that CT can be used for the diagnosis of opportunistic sarcopenia.8

L3 SMI is a widely accepted indicator for the evaluation of skeletal muscle mass in patients with malignant tumors worldwide, yet its clinical application in China remains limited. Measurement of L3 SMI relies on abdominal CT, which is not routinely performed across all tumor types. For instance, patients with lung cancer, head and neck cancer, or other non-abdominal malignancies do not typically undergo abdominal CT during routine staging, thus requiring additional abdominal CT scans for muscle assessment. Moreover, CT based skeletal muscle analysis often necessitates specialized post-processing software and manual segmentation, which are time-consuming and not widely available in general clinical settings. Accordingly, the present study aimed to develop a predictive model for opportunistic sarcopenia in patients with malignant tumors using admission laboratory parameters and routine clinical data, in order to establish a simple, convenient, and efficient screening approach that does not require dedicated imaging processing or additional CT examinations.

MATERIALS AND METHODS

This study was performed in line with the principles of the Declaration of Helsinki. The Biomedical Ethics Committee of The First Hospital of Hebei Medical University approved this study (Approval No. 2024-067).

Data sources and research objects

This retrospective cross-sectional study was conducted at the Department of Oncology, the First Hospital of Hebei Medical University, enrolling patients admitted between October 2017 and March 2022. A total of 522 patients were initially screened for eligibility. The inclusion criteria were defined as follows: (1) completion of an abdominal CT scan; (2) pathological and/or cytological confirmation of stage III or IV malignant tumors; and (3) age ≥18 years. Patients were excluded if they were receiving treatment for mental disorders or had significant cardiovascular diseases, including New York Heart Association (NYHA) functional class III-IV heart failure, uncontrolled coronary heart disease, cardiomyopathy, uncontrolled arrhythmia, uncontrolled hypertension, or a history of myocardial infarction within the prior 12 months. Ultimately, all 522 initially screened patients met the predefined inclusion criteria, with no patients excluded; thus, all were included in the final analysis.

Sample size calculation

Using the events per variable (10EPV) technique, the sample size for the clinical prediction model was determined to be 10 samples size for each common variable and 20 samples size for each ordered multi-categorical variable. This study contained a total of 12 variables, with the body mass index (BMI) and SII-PNI index being ordered multi-categorical variables. Therefore, 140 samples size are required, and the data set in this study meets the requirements.

Index calculations

L3 SMI = skeletal muscle cross-sectional area (cm2) ÷ height (m)2. Slice Omatic software was used to analyze the skeletal muscle scans of the third lumbar vertebrae in CT images of the study subjects. After plotting the skeletal muscle cross-sectional area of the third lumbar spine (Figure 1), the diagnostic criteria for opportunistic sarcopenia could be evaluated: L3 SMI $\leq 52.4 cm^2/m^2$ for men and L3 SMI $\leq 38.5 cm^2/m^2$ for women.[8,9]

Systemic immune-inflammation index (SII) = platelet count (×109/L) × neutrophil count ($\times 10^9$/L) ÷ lymphocyte count ($\times 10^9$/L).[10] Neutrophil-to-lymphocyte ratio (NLR) = neutrophil count ($\times 10^9$/L) ÷ lymphocyte count ($\times 10^9$/L).[10] Prognostic nutritional index (PNI) = 10 × serum albumin level (g/L) + 5 × lymphocyte count ($\times 10^9$/L).[10] Platelet lymphocyte ratio (PLR) = platelet count ($\times 10^9$/L) ÷ lymphocyte count ($\times 10^9$/L).[11] SII-PNI was classified according to the following scores: 0 points, high SII low PNI; 1 point: high SII high PNI or low SII low PNI; 2 points: low SII high PNI.[11]

Data processing and statistical analysis

Statistical analyses were performed using SPSS (version 26) and R software. Normality of continuous variables was assessed using the Shapiro-Wilk test. As variables such as age were not normally distributed in certain subgroups, all descriptive statistics were presented as medians with the 25th and 75th percentiles. Group comparisons for continuous variables were conducted using the Kruskal-Wallis test. Categorical variables were expressed as frequencies and percentages, and compared using the chi-square test. The significance level for all statistical tests was set at $\alpha = 0.05$.

Subjects were divided into a training set (365 participants) and a validation set (157 participants) according to a ratio of 7:3.

1) Variable classification was performed as follows: the dependent variable was categorized into binary variables based on the third lumbar skeletal muscle mass index; for continuous variables, including the SII, NLR, PNI, and C-reactive protein (CRP) level, the optimal cutoff values were determined by receiver operating characteristic (ROC) curve analysis with reference to the method described in existing literature.12 SPSS 26.0 software was used to plot ROC curves for each indicator. The optimal cutoff value for each indicator was determined according to the principle of the maximum Youden index, and the aforementioned continuous variables were converted into binary variables based on these cutoff values for subsequent model construction and analysis.

2) Nomogram model construction: The independent influencing variables selected by multi-factor analysis were imported into RStudio 3.6.3 software, and the "rms" package was then used to build the nomogram prediction model of opportunistic sarcopenia.

3) Model evaluation: The "pROC" package for Rstudio 3.6.3 software was used to calculate the C-index of the opportunistic sarcopenia nomogram prediction model in order to evaluate the differentiation of the model, and the "pROC" package was also used to make a opportunistic sarcopenia nomogram prediction model calibration curve. Using the "caret" package, the bootstrap method and validation set were used to validate the prediction model of the nomogram internally, including a test of the differentiation and calibration of the prediction model.

RESULTS

Overview of baseline characteristics and group balance

A total of 522 malignant tumor patients were included in this retrospective study, among whom 345 (66.1%) had opportunistic sarcopenia. The cohort was divided into a training set (n

= 365) and a validation set (n = 157). Baseline characteristics including demographics, nutritional status, tumor features, and laboratory parameters were well balanced among the total cohort, training set, and validation set (all p >0.05). The only significant difference was observed in the outcome variable Transform (p <0.001), which was a natural result of grouping and did not compromise baseline comparability. These results verified the representativeness and comparability of the two subgroups. Detailed results are shown in Supplementary Table 1.

Data set description

This study used a 7:3 screening method to screen 365 participants in the training set and 157 participants in the validation set. Twelve variables, including gender, BMI, whether primary cancer metastasis occurred, calcium content, albumin content, creatine kinase content, CRP, red blood cell count, SII, NLR, PNI, and SII-PNI index, had statistical significance in the training set (Supplementary Table 2 and 3).

Determination of cutoff values value

The results of ROC curve analysis showed that the AUC of CRP, SII, PNI, and NLR were all greater than 0.5, indicating that these indicators had certain predictive value. According to the optimal cutoff values determined by ROC curve analysis, the cutoff values for each indicator were as follows: CRP 9.17, SII 938, PNI 11.3, and NLR 2.71. The specific ROC curve characteristics and detailed data of the cutoff values are presented in Table 1 and Figure 2 of the paper.

Regression analysis using both single and multiple factors

SPSS was used to perform univariate and multivariate logistic regression analysis for variables with statistical significance (gender, BMI, whether primary cancer metastasis occurred, calcium content, albumin content, creatine kinase content, CRP, red blood cell count, SII, NLR, PNI, SII-PNI index). The results showed that gender, BMI, CRP, SII, PNI and SII-PNI were significantly different (p <0.05) (Table 2)

Construction of the nomogram prediction model

The "rms" package in RStudio was used to construct a nomogram prediction model for opportunistic sarcopenia in malignant tumor patients according to the variables selected by multivariate analysis, as shown in Figure 3. The vif function was used to diagnose

collinearity, and the vif values of the six variables included in the model were all less than 10, indicating that the amount of collinearity in the model was negligible. The number of points that correspond to the individual prediction indicators can be obtained according to the final nomogram prediction model, and after totaling them, the prediction probability corresponding to the total score is the probability of opportunistic sarcopenia for a given patients with malignant tumors.

Evaluation of the nomogram prediction model

Efficacy of the prediction model: The C-index of the prediction model for opportunistic sarcopenia in patients with malignant tumors was 0.890 (95% CI: 0.854, 0.926), as shown in Figure 4A The calibration curve shows that the prediction model tends to agree with the diagnosis results for the observed values, as shown in Fig.4B. In addition, the clinical decision curve for the component-based diagnosis of opportunistic sarcopenia and prediction model was constructed based on the "rmda" package for R. The results showed that when the threshold range was greater than 0.6, the order of clinical benefit rate was: prediction model > RASM > ASMI, and the predicted model's clinical net benefit rate was always the highest, as shown in Figure 5.

Validation of the predictive model

Using the "caret" package for RStudio, the bootstrap method was implemented to validate the training set internally. The number of resamples was set to 500 times, and the calculated C-index was 0.796 (C-index >0.7). The C-index of the prediction model calculated from the validation set and the calibration curve of the prediction model are shown in Fig.6 (C-index = 0.884, 95% CI: 0.827, 0.942).

DISCUSSION

Sarcopenia syndrome refers to a series of health problems caused by aging, reduced activity, disease, malnutrition and other factors, and tumor patients have an especially high incidence of opportunistic sarcopenia.[14,15] Due to the high energy consumption of tumors, disease progression, and treatment methods, the digestive system and physical activities are most directly affected by the condition, which results in the relative lack or insufficient intake of essential proteins, vitamins and other nutrients required for muscle synthesis. Moreover, muscle apraxia results in increased loss of muscle protein and decreased synthesis.[16] Therefore, successful screening for opportunistic sarcopenia in patients with malignant tumor

has the potential to benefit numerous patients via early detection and treatment. In this study, L3 SMI was used as the diagnostic criterion for opportunistic sarcopenia in patients with malignant tumor, which exposed a prevalence rate of opportunistic sarcopenia in patients with malignant tumor of 66.09% in our sample, a number that is consistent with the results of Carla M et al.[16]

Although abdominal CT is routinely used for tumor staging in clinical practice, it is not performed in all tumor types and cannot be widely applied specifically for opportunistic sarcopenia screening. In addition, the measurement of L3 SMI relies on specialized image post-processing software and manual segmentation, which are time-consuming and often unavailable in general wards. The major clinical value of the present prediction model is not to replace CT scans, but to provide a rapid and convenient screening tool that bypasses the need for dedicated imaging analysis and complex operations. Using only routine clinical and laboratory indicators at admission, this model is more suitable for widespread use in daily clinical settings and allows for early identification of opportunistic sarcopenia in patients with malignant tumor.

Basic patient data, such as age, gender, BMI, etc., were used as independent variables to determine the factors that influence opportunistic sarcopenia in patients with malignant tumor. SII, PLR, NLR, PNI, SII-PNI, and other inflammatory indicators were also calculated using the admission examination indicators of tumour patients in the study. Using a 7:3 ratio, the individuals were split into training and validation groups. Ultimately, six variables were chosen for inclusion in the column chart: gender, BMI, CRP, SII, PNI, and SII-PNI index. SII and PNI can both be utilized as prognostic variables for cancer patients, according to studies.[17] For example, according to Yong et al., patients with breast cancer who have a high SII also have a lower overall survival rate, and according to a review by Wang et al.,[18] patients with lung cancer who have poor PNI also have lower survival rates. Furthermore, Okadome K et al. showed that the PNI score can be used as a predictive biomarker for patients with esophageal cancer,[19] and a study on the variables that influence surgical resection of medulloblastoma patients, a patient's overall survival rate decreases with decreasing SII-PNI score.[20] However, this is the first study to our knowledge to demonstrate that the SII-PNI score, which measures a patient's immunological, inflammatory, and nutritional status, is an independent risk factor for opportunistic sarcopenia in patients with malignant tumor.

Based on a multi-factor statistical model, the columbaric prediction model is a straightforward visual representation that can be used to determine quantitatively the

likelihood that a research object will occur based on the scores of several indicators of the object.[21] Research has indicated that patients with tumors who are sarcopenic not only have a higher chance of developing complications after surgery but also have a considerably lower quality of life and overall survival rate. In patients with malignant tumor, the loss of skeletal muscle during chemotherapy and radiation therapy is thought to be a predictor of overall survival rate.[22]

The European Working Group on Sarcopenia in Older People (EWGSOP) criteria, which consist of four components, are currently used to diagnose sarcopenia. These components include the SCAR-F scale screening (which includes muscle strength, climbing stairs, assistance in walking, rising from a chair, and falls) as well as tests for muscle strength, muscle strength assessment, and physical fitness. However, it is challenging to apply in a clinical setting, so a straightforward and effective way to estimate the likelihood of sarcopenia in patients with malignant tumor would undoubtedly be of more use. To this end, clinical markers and fundamental data were combined to create the nomogram prediction model used in this investigation, which demonstrated both good differentiation and calibration as indicated by the model's C-index and calibration curve,[22,23] respectively Additionally, the validation results of the model all showed that it had good predictive ability and could be applied in practical clinical setting.

Limitations of this study should be noted. First, significant heterogeneity existed among the included patients due to diverse tumor sites. The pathophysiological mechanisms of opportunistic sarcopenia vary by tumor location. For example, gastrointestinal tumors cause obstruction that impairs nutrient absorption, while lung cancer induces opportunistic sarcopenia via systemic cachexia. These differences may potentially confound the nomogram's performance and generalizability. Thus, the model's accuracy may be limited when applied to a single specific tumor type. Second, only logistic regression was used for variable selection, and no comparison with LASSO regression was performed. Different variable selection strategies may identify different variable combinations and generate models with higher C-index, which could affect the final predictive model. Third, most subjects were over 55 years old, with few young patients, which restricts the model's applicability in young cancer cohorts. Fourth, model validation relied on a random split; incorporating multicenter or out-of-sample data could further enhance its efficacy. Fifth, this study only used L3 SMI to diagnose opportunistic sarcopenia, without collecting muscle function data such as handgrip strength, making it impossible to diagnose confirmed sarcopenia in accordance with EWGSOP or AWGS criteria. Future studies should develop tumor-specific nomograms

tailored to different cancer types, use multiple variable selection methods (such as LASSO regression) for comparison and verification, increase the enrollment of young patients to improve the model's predictive accuracy in this population, collect muscle function data to complete the comprehensive assessment of sarcopenia, and conduct multicenter and out-of-sample validation to strengthen the model's stability and clinical applicability, thereby better supporting clinical opportunistic sarcopenia screening and individualized intervention.

Conclusion

The nomogram model in this paper can predict the probability of opportunistic sarcopenia in patients with malignant tumor according to gender, BMI, CRP, SII, PNI, SII-PNI index, and other factors, which is conducive to the screening and early intervention of patients at high risk of sarcopenia.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that there are no conflicts of interest.

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Table 1. Continuous variable ROC curve analysis

Variable	Cutoff value	AUC	Sensitivity	Specificity	95% CI	*p*
Calcium, mmol/L	-	0.340	-	-	0.283, 0.398	<0.001***
Hemoglobin, g/L	-	0.455	-	-	0.394, 0.516	0.2
Albumin, g/L	-	0.397	-	-	0.335, 0.458	0.001**
Creatine kinase, U/L	-	0.432	-	-	0.362, 0.483	0.02*
CRP, mg/dL	9.17	0.639	0.520	0.731	0.578, 0.699	<0.001***
Red blood cell count, $\times 10^9$/L	-	0.401	-	-	0.346, 0.467	0.004**
SII	938	0.568	0.438	0.709	0.506, 0.629	0.04*
PNI	11.3	0.861	0.840	0.840	0.818, 0.904	<0.001***
NLR	2.71	0.606	0.702	0.504	0.546, 0.667	0.001**

CRP: C-reactive protein; SII: systemic immune-inflammation index; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.
*p<0.05, **p<0.01, ***p<0.001.

Table 2. Univariate and multivariate logistic regression analysis for opportunistic sarcopenia

Variable	Univariate	*p*	Multivariate	*p*
	OR (95% CI)		OR (95% CI)	
Gender		<0.001***		<0.001***
Men	1		1	
Women	0.162 (0.100, 0.262)		0.074 (0.035, 0.153)	
BMI group		<0.001***		<0.001***
≤ 18.4 kg/m²	1		1	
18.5 - 23.9 kg/m²	0.624 (0.176, 2.21)		1.52 (0.357, 6.45)	
24.0 - 27.9 kg/m²	0.129 (0.037, 0.452)		0.162 (0.038, 0.695)	
≥ 28 kg/m²	0.036 (0.009, 0.137)		0.077 (0.016, 0.381)	
Whether the primary cancer has metastasized		0.003**		0.3
Yes	2.53 (1.38, 4.67)		-	
CRP		<0.001***		0.02*
Low-level	1		1	
High-level	2.91 (1.82, 4.67)		2.51 (1.17, 5.41)	
SII		0.09		0.001**
Low-level	1		1	
High-level	1.48 (0.941, 2.31)		0.011 (0.001, 0.260)	
PNI		0.5		0.003**
Low-level	1		1	
High-level	0.886 (0.556, 1.35)		0.021 (0.002, 0.262)	
NLR		<0.001***		0.3
Low-level	1		1	
High-level	2.40 (1.53, 3.76)		-	
SII-PNI		<0.001***		0.002**
0	1		1	
1	0.327 (0.160, 0.669)		0.017 (0.001, 0.260)	
2	1.11 (0.544, 2.28)		0.001 (0.001, 0.027)	

BMI: body mass index; CRP: C-reactive protein; SII: systemic immune-inflammation index; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.
The SII-PNI classification was defined as follows: (1) 0 points: high SII and low PNI; (2) 1 point: high SII and high PNI, or low SII and low PNI; (3) 2 points: low SII and high PNI.
*p<0.05, **p<0.01, ***p<0.001

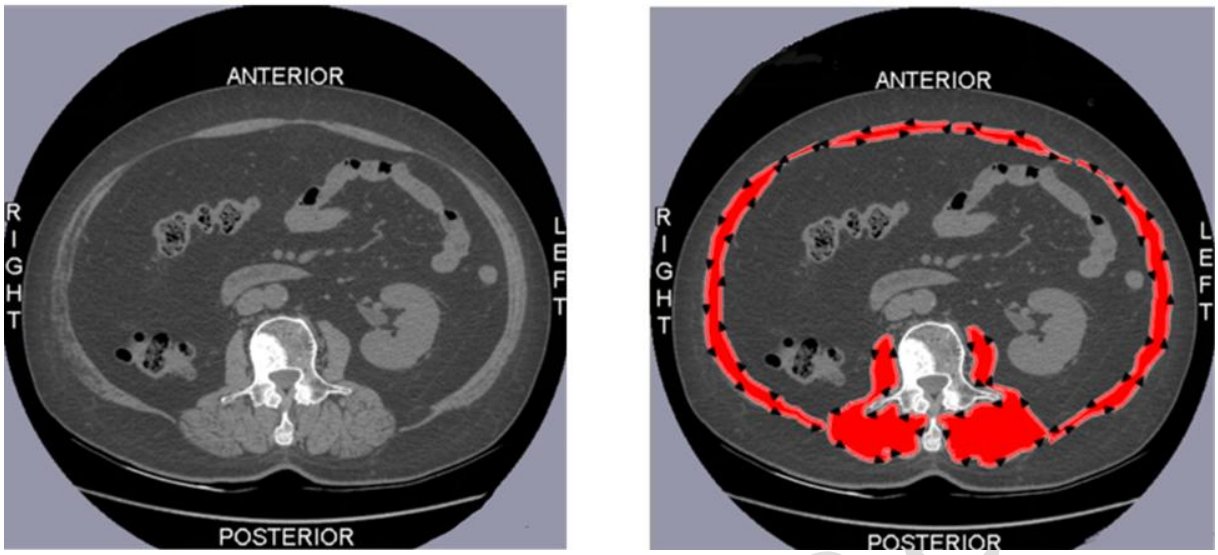


Figure 1. Graphing process using SliceOmatic software. Original image in DCM file format† (left); muscle tissue outlined with black dotted lines, and the segmented region filled in red (right). †The DCM file format is a DICOM® (Digital Imaging and Communications in Medicine) file compliant with the international standard for medical image transmission, storage, and display.

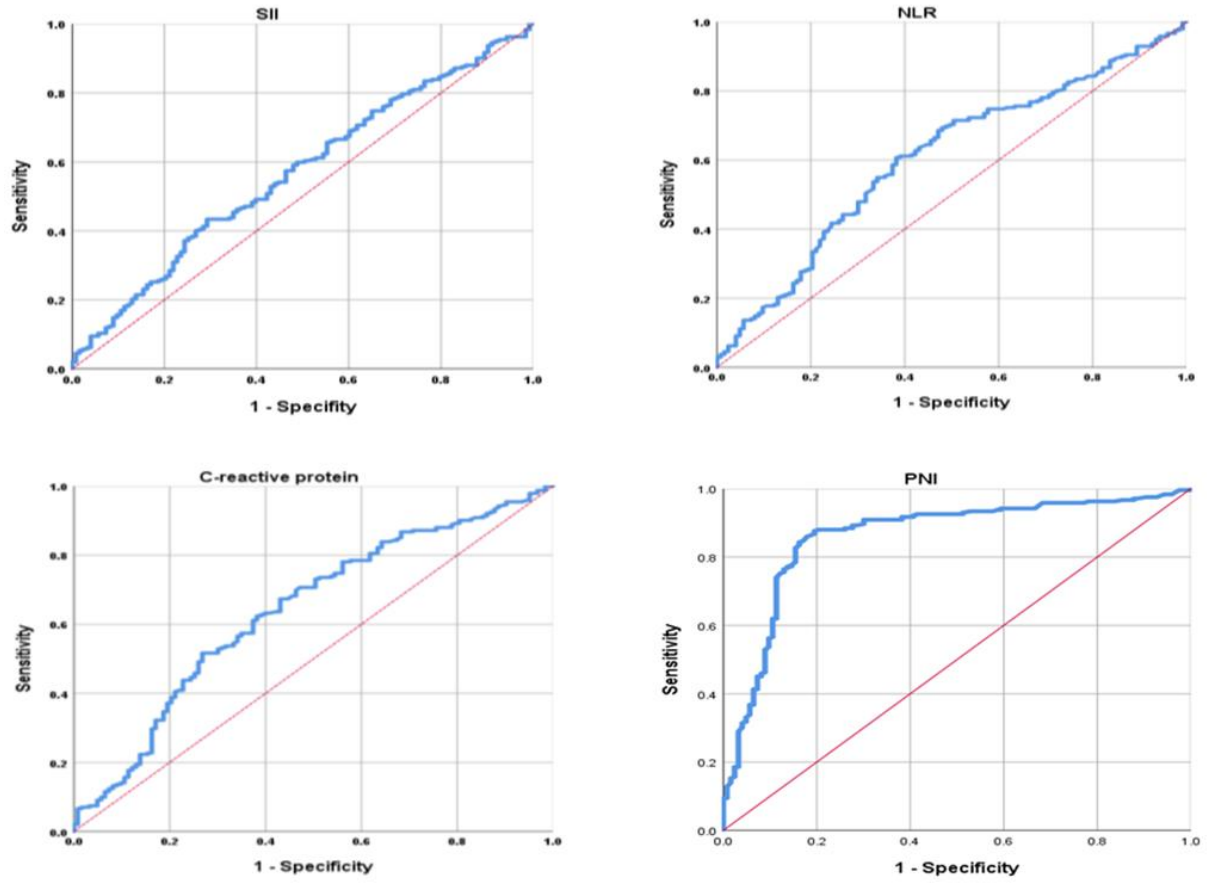


Figure 2. ROC curves for determining optimal cutoff values of continuous variables. SII: systemic immune-inflammation index; NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index

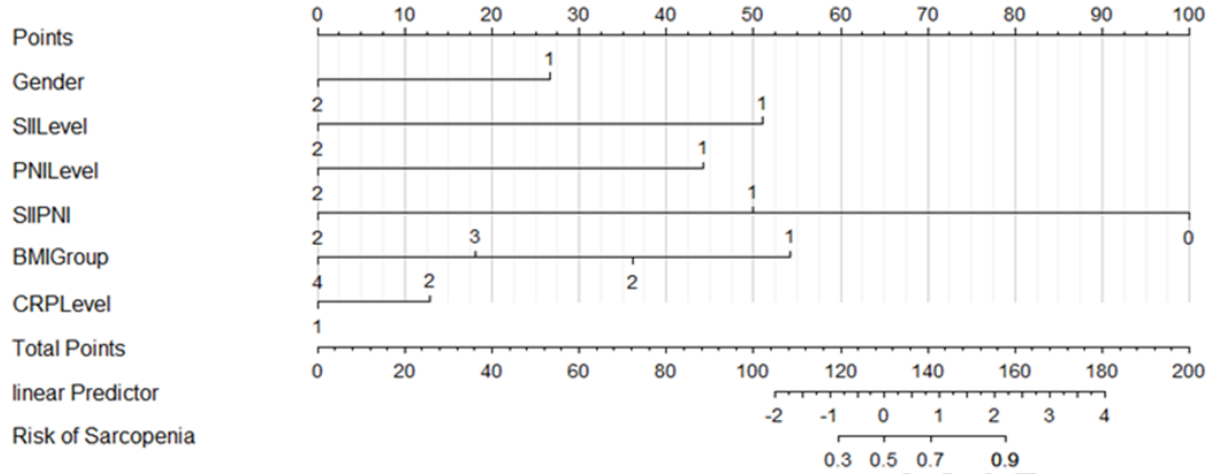


Figure 3. Predictive model for opportunistic sarcopenia column line graphs in patients with malignancy. SII: systemic immune-inflammation index; PNI: prognostic nutritional index; CRP: C-reactive protein. The SII-PNI classification was defined as follows: (1) 0 points: high SII and low PNI; (2) 1 point: high SII and high PNI, or low SII and low PNI; (3) 2 points: low SII and high PNI. The BMI groups were defined as follows: (1) ≤18.4 kg/m²; (2) 18.5-23.9 kg/m² ; (3) 24.0-27.9 kg/m² ; (4) ≥28 kg/m² .

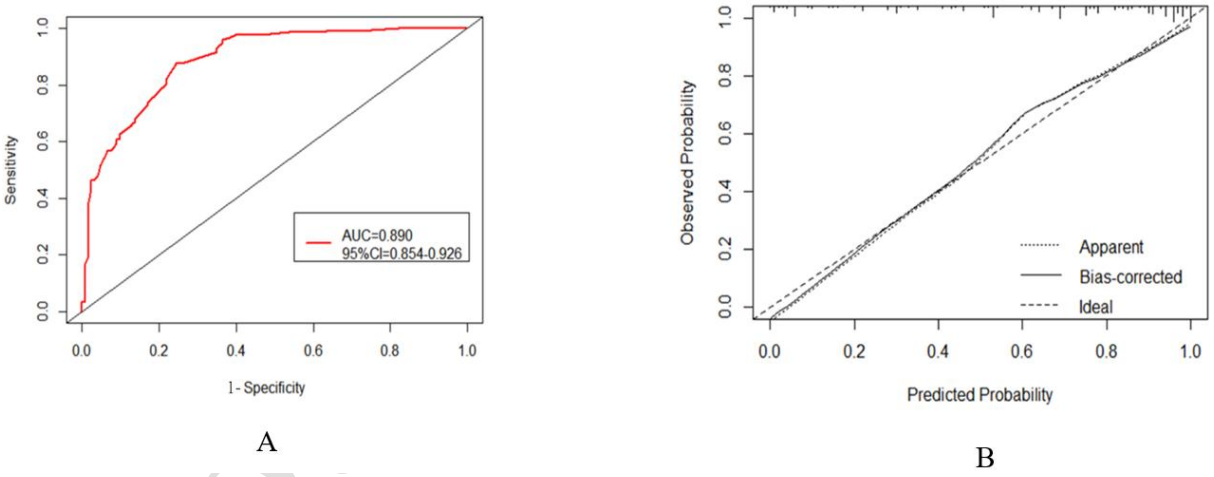


Figure 4. Evaluation of the nomogram prediction model. (A) ROC curves for the column line graph prediction model; (B) Calibration curves for the column line graph prediction model.

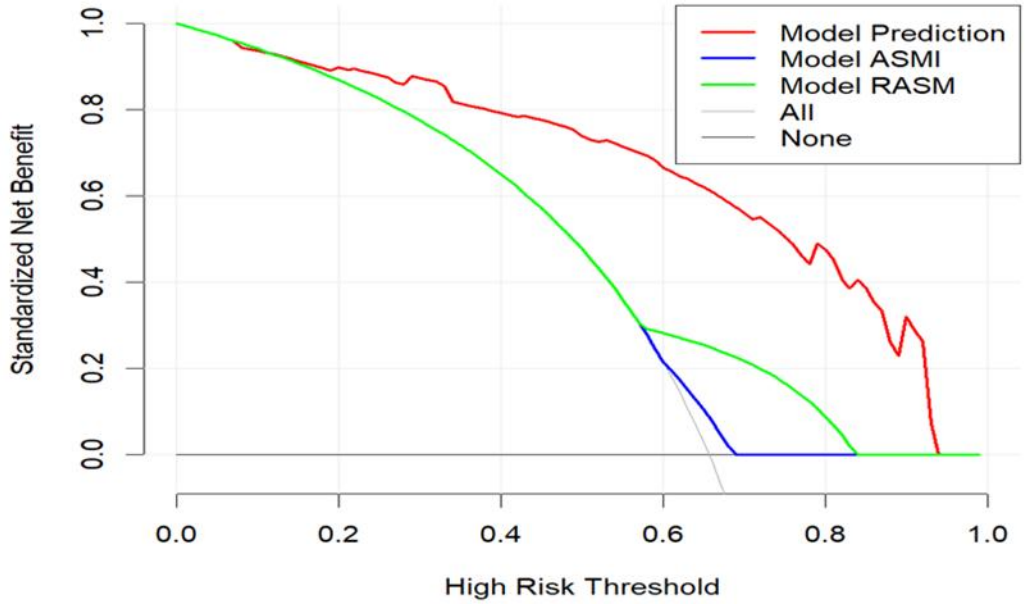
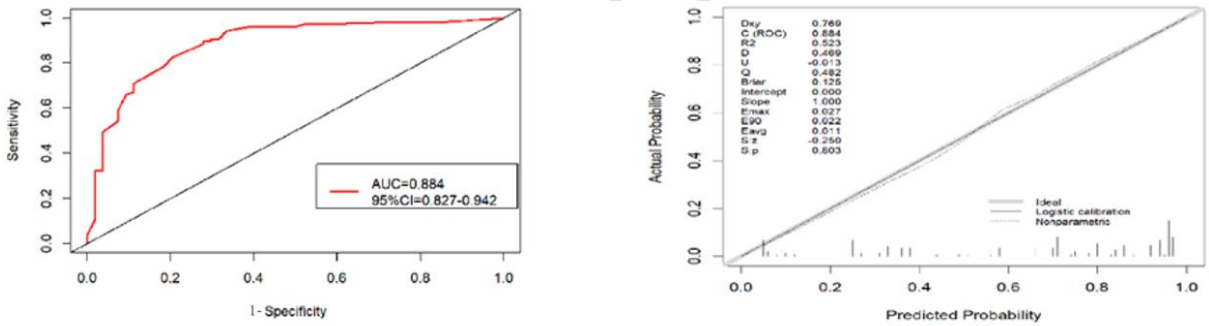


Figure 5. Predictive model clinical decision curve. (1) Red: Prediction model of opportunistic sarcopenia in patients with malignant tumors; (2) Green: RASM = limb muscle mass (kg)/body mass (kg) × 100%, opportunistic sarcopenia: Men <29.53%, Women <23.20%;[13] (3) Blue: ASMI = limb muscle mass (kg)/height (m)2, opportunistic sarcopenia: Men <7.0 kg/m^2, Women < 5.7 kg/m^2.[13]



A ROC curve **B** Calibration curve

Figure 6. The ROC curve and calibration curve for the validation of the prediction model.