A simple model established by blood markers predicting overall survival after radical resection of type II and III Adenocarcinomas of the Esophagogastric Junction

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Research article

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Abstract

Background. The prognostic prediction after radical resection of Adenocarcinomas of the esophagogastric junction (AEG) has not been well established. We aimed to establish a prognostic model for AEG(type II and III) based on routine markers.

Methods. 355 patients who underwent curative AEG at the first affiliated Hospital of Anhui Medical University from January 2010 to January 2011 were included in this study. Univariate and multivariate analysis were used to screen for risk factors. The construction of the nomogram was based on Cox proportional hazard regression models. The new score models was analyzed by C index and Calibration curves.

Results. Multivariate analysis showed that TNM stage, NLR and BMI were independent prognostic factors. The new score system had a higher C-index, and the Calibration curves of the nomogram were reliable.

Conclusions. Based on the serum markers and other clinical indicators, we developed a precise model to predict the prognosis of patients with AEG(type II and III). This score system can provide effective help for surgeons and patients.

1. Background

Adenocarcinomas of the esophagogastric junction (AEG) which located within 5 cm from esophagogastric junction(EGJ), was classified into 3 subgroups, type I AEG (adenocarcinoma of the distal esophagus) is the most prevalent type in Western countries, types II and III AEG are commoner than type I in Asia and are mostly treated as gastric cancer[1,2]. In recent years, the incidence of AEG is increasing rapidly in the world[3,4], surgery is considered the only means of curative treatment of AEG patients[5], however, the cancer recurrence rate and prognosis are still not optimistic even after radical resection.

Electronic gastroscope and Digestive tract angiography are important methods to diagnose AEG and judge the disease progression, however these techniques are inconvenient. At present, many studies are looking for noninvasive and sensitive biomarkers that can accurately predict the prognosis of AEG patients. Among them, commonly used serum marker for gastric cancer is carcinoembryonic antigen (CEA), which has been utilized for the early diagnosis of cancer [6]. Additionally, there are also other serum index which can evaluate the prognosis of cancer, cancer-related systemic inflammatory response plays an important role in the progression and outcome of tumors [7,8], such as neutrophils to lymphocytes ratio (NLR), platelets to lymphocytes ratio (PLR). The presence of malnutrition can cause postoperative complications and poor prognosis [9], and nutritional marker also have significant value for predicting survival. However, the relationship between these blood indexes and prognosis of AEG patients remains unclear.

To our best knowledge, there are few studies that had republished to access the prediction of inflammatory markers, nutritional markers and blood tumor markers for overall survival (OS) in AEG patients(type II and III). Nomograms was a statistic model with a high reliability. In this study, we established a nomogram to explore the value of blood markers and then built a reliable model to predict overall survival after radical resection of AEG(type II and type III).

2. Methods

2.1 Patients.

We collected blood and clinical data from AEG(type II and type III) patients who were hospitalized in the First Affiliated Hospital of Anhui Medical University from January 2010 to January 2011. According the inclusion and exclusion criteria, patients were analyzed retrospectively during the research. The inclusion criteria included: 1) All patients were confirmed AEG(type II and III) by pathological diagnosis; 2) the surgery is definite and complete resection of cancer 3) these patients didn't have heart sickness or any important organs failures; 4) their peripheral blood tests were obtained within one week before surgery. The exclusion criteria included; 1) they had previous malignant tumors or various primary tumors; 2) they had accepted radiation treatment or chemo treatment previously before the treatment; 3) they had certain disease that could influences the counting of peripheral blood cells, such as infection; 4) the patients who died within 30 days after surgery. According to the inclusion criteria, 440 patients with AEG were included in this study, in the end, a cohort of 355 patients were analyzed by conducted the exclusion standard.

2.2 Data collection and follow-up.

The data of patients' demographic and clinicopathological features was gathered through the medical record room of our hospital, including age, gender, BMI, tumor size, differentiation grade and so on. The pathological tumor stage was categorized according to the AJCC 7th TNM staging system. The routine laboratory data were listed below: neutrophil, lymphocyte, platelet, prealbumin, albumin, hemoglobin and so on.

Peripheral blood tests were obtained within 1 week before surgery, we determine the following indexes (NLR, PLR, PNI). NLR got counted with the means of dividing the strict neutrophil counting with the strict lymphocyte counting, PLR was counted by dividing the strict platelet count by the strict lymphocyte count. PNI（prognostic nutritional index）was calculated using the following formula: serum albumin (g/L)+5×total lymphocyte count (10^9/L)[10]. NLR, PLR and PNI were grouped into low group and high group according to the Youden index [maximum (sensitivity+specificity-1)][11]. BMI was divided into 3 groups: <18.5 (low group), 18.5 to 24.9 (normal group), and ≥25 (high group). CEA, CA199, albumin and prealbumin was grouped based on the normal value.

All Siewert type II/III of AEG patients underwent radical surgery with celiac and mediastinal lymphadenectomy. All patients underwent radical D2 lymphadenectomy. They accepted 4 to 6 cycles of

first-line adjuvant combination chemotherapy after surgery with oxaliplatin plus 5-fluorouracil/leucovorin or a prodrug of 5-fluorouracil (capecitabine; CapeOX). The patients which were enrolled got prospective follow-up. Their follow-up date was obtained through telephones and outpatient visit. This behavior got carried out in normal intervals (each 3 months within two years after the surgery, each 180 days within the years of three-five, and once a year after five years). We followed up all the patients, the median follow up time is 52 months. 85 patients were excluded from the research, among them, 59 lost contact, 16 died of traffic accident or other non-cancer related reasons and 10 died within 30 days after surgery, in the end, 355 AEG patients were included in the final analysis of this study.

2.3 Statistical analysis.

The multivariate and univariate surviving analysis were carried out using the Cox appropriate hazard pattern. Harrell's concordance index(C-index) was used in the nomogram for evaluating the model performance for prognosis of AEG patients. The Calibration curves and receiver operating characteristic (ROC) curve were used to verify the accuracy of new score system in the nomogram. The whole data explanations got carried out applying SPSS app (16.0 version) and RStudio software (version 1.1.447-2009–2018; RStudio, Inc.) .

3. Results

3.1 Baseline characteristics

The baseline characteristics analysis of the 355 patients was expressed in the Table 1. Overall, 281 (79.1%) patients were males and 74 (20.9%) were females. The median age of patients was 65 years old (range, 29-85). The median follow-up month was 52 (range, 1.5-72).

3.2 Prognostic factors of the training cohort

Univariate risk factors of OS are shown in Table 2. The result showed that age, prealbumin, TNM, tumor size, histological type, CEA, PNI, PLR, NLR, BMI, hemoglobin and cancerous node were significant indicators, P values of variables less than 0.05 in univariate analysis were includes in the multivariate analysis. The results showed that TNM, BMI and NLR were independent prognostic factors for OS (Table 3).

3.3 Prognostic nomogram for survival

Based on the cox regression model, nomogram was constructed to predict overall survival of AEG(Figure 1). Each subgroup variable was assigned a corresponding score, a point system was used to

assign a score ranging from 0 to 100 to each subgroup variable and the corresponding 3-, and 5-year OS rates were predicted, the nomogram scoring system was placed in Table 4.

3.4 Validation of the nomogram

Calibration curves were used to verify the performance of the model in predicting overall survival of AEG patients (Figure 2, and Figure 3). The C-index of the model was 0.697, indicating this model is reliable. To further validate the performance of the new score system, the ROC curve was plotted for the nomogram (Figures 4, 5), and the area under the curve (AUC) of the nomogram was large, which indicated that the constructed nomogram was a reliable score system.

3.5 Kaplan–Meier Curves

In addition, we divided the patients into two groups according to the total score of the nomogram (low risk: <58 and high risk: >58) (Figure 6). The Kaplan–Meier curves show excellent prediction results in the nomogram predicting survival.

4.discussion

Surgery is considered the only means of curative treatment of AEG patients. Due to the limitation of diagnostic techniques, it is often difficult to detect early AEG and lead to poor prognosis. At present, 5 years of survival rate is low. Therefore, in order to improve the prognosis of AEG, many scholars have made a lot of contributions. Studies have shown that elevated levels of markers may be associated with prognosis of AEG patients. Lymph node metastasis, tumor size, differentiation grade and TNM stage are defined as prognostic factors. However, these prognostic factors are difficult to judge before surgery, so the research on prognostic serum markers has been explored widely in recent years. To the best of our knowledge, this study is the first attempt to develop a prognostic nomogram which combined serum markers (including inflammatory markers, nutritional indexes and tumor markers) and clinicopathology characteristics for estimating the probability of 3-year and 5-year OS and showed a high accurate prediction for the prognosis of AEG(type II and III).

Based on multivariate analysis, the results showed that TNM stage, NLR and BMI were independent prognostic factors for OS. So, we developed a nomogram of these markers, and the C-index was 0.697, which indicated our new model is highly accurate in predicting the prognosis of AEG patients. Moreover, the Calibration curves and ROC curve of the nomogram are reliable. The Kaplan–Meier curves show excellent prediction results in the nomogram predicting survival.

In recent years, nomogram have better value for predicting prognosis in many cancer [12,13], this model has been identified as a new standard, and our study had got the same conclusion, the AUC of nomogram is larger than TNM, this nomogram can be applied in the clinic, which can help surgeon to evaluate the prognosis of patients and take appropriate treatment.

Our nomogram contains three variables in which NLR and BMI are consistent with previous studies [14,15]. Studies have suggested that systemic inflammation is an important factor which can affect the progression and long-term survival of cancer patients [16]. As simple and inexpensive clinical markers, NLR and PLR can reflect the state of inflammation, and they are associated with poor prognosis of some cancer patients, but less reported in AEG. In this study, NLR was an independent risk factors, while PLR was not. The possible mechanism is that the systemic inflammation caused by malignant tumors can releases a large number of pro-inflammatory mediators, such as CRP, fibrinogen, VEGF, TGF-a, and so on. These factors stimulate tumor growth and metastasis [17], meanwhile the anti-tumor immune response of T cells and natural killer cells in the system may are surrounded by a number of neutrophils, this may decrease the opportunity to contact with tumor cells and have adverse effect on the prognosis of patients [18,19], so NLR should be included in the regular assessment index of AEG patients.

As an independent prognostic indicator of tumor-related diseases, BMI has got more and more concern by researchers in recent years. BMI was related with the prognosis of breast carcinoma, non-small-cell lung cancer, and so on[20,21]. In this paper, we found that BMI was significantly correlated with the prognosis of AEG patients. The mechanism remains unclear. The AEG patients with low level of BMI may suffer poor nutritional status and immune function[22], this will have an adverse effect on the progression of the disease, so these patients may have short overall survival.

Our research has several potential limitations: Firstly, this is a single-centered study, which has not enough cases to verify the results; secondly, the included patients who had undergone surgical resection for AEG could not behalf all AEG patients.

Conclusion In summary, TNM stage, NLR and BMI levels were risk factors for the prognosis of AEG patients, and the novel nomogram had reliable prognostic value for AEG patients(type II and III).

Abbreviations

NLR: neutrophils to lymphocytes ratio PLR: platelets to lymphocytes ratio

BMI: body mass index AEG: Adenocarcinomas of the esophagogastric junction EGJ: esophagogastric junction OS: overall survival

PNI: prognostic nutritional index CEA carcinoembryonic antigen

Declarations

Ethics approval and consent to participate

This study was approved by the Institute Research Ethics Committee of The First Affiliated Hospital of Anhui Medical University, Hefei, China. Each patients signed the informed consent.

Consent for publication

Not applicable.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests: All authors declare no conflict of interest.

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Authors' contributions: LXZ designed this study, drafted this manuscript and revised this work. AMX and ZJW performed the study and participated in this work. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of the recruited patients

characteristics	N(percentage) or Median(25%-75%)
gender	
male	281（79.1）
female	74（20.9）
Age(year)	
< 60	246（69.3）
≥ 60	168（30.7）
Tumor size	
<5 cm	164（69.1）
≥ 5 cm	191（30.9）
TNM stage	
I- II	154（43.4）
III	201（56.6）
Differentiation grade	
low	226（63.7）
high	129（36.3）
BMI(kg/m 2)	

<18.5	39（11.0）
≥18.5 and<25	232(65.4)
≥25	84（23.7）
Tumor location	
Siewert II	202(56.90)
Siewert III	153(43.10)
NLR	2.28（1.57-3.12）
PLR	118.44（83.87-169.70）
CEA	3.20（1.60-8.20）
LT AST	
CA199	9.90（5.72-19.79）
PNI	49.53（45.80-53.25）
albumin	42.10(39.00-44.40)
prealbumin	209.00（165.00-255.00）
neutrophil	3.37（2.57-4.51）
platelet	181.5（145-231）
lymphocyte	1.52（1.16-1.88）

(Categorical values were identified by N(percentage), and continuous variable were expressed by median(P25, P75).)

Table2 Univariate analysis of the AEG(type II and III) patients

Characteristics	*β*	*HR*（95% *CI*）	*P value*
Gender（men/women）	0.078	1.081（0.765，1.528）	0.660
age	0.019	1.019（1.002，1.037）	0.031*
NLR	0.176	1.193（1.112，1.280）	< 0.001*
Tumor size	0.178	1.195（1.134，1.260）	< 0.001*
TNM stage	1.042	2.836（2.046，3.930）	< 0.001*
Histologic type	0.390	1.477（1.086, 2.009）	0.013
CEA	0.010	1.010（1.002, 1.018）	0.016
CA199	0.000	1.000 (0.998, 1.002)	0.948
PNI	-0.034	0.966 (0.940, 0.993)	0.013
PLR	0.003	1.003（1.001, 1.005）	0.009
fibrinogen	0.010	1.030（0.970,1.095）	0.332
albumin	-0.289	0.479（0.557，1.008）	0.056
prealbumin	-0.102	0.362（0.271，0.484）	< 0.001*
Surgery time	0.017	1.017（0.755，1.369）	0.912
BMI	-0.580	0.560 (0.431, 0.727)	< 0.001*
Cancerous node	0.219	1.245（1.150，1.347）	< 0.001*
hemoglobin	-0.006	0.994（0.988，1.000）	0.033
Tumor location	0.719	1.127(0.855, 1.487)	0.397
smoking	0.006	0.994(0.970, 1.019)	0.624
comorbidities	0.017	0.983(0.953, 1.013)	0.264

Table3 Multivariate analysis of the AEG(type II and III) patients.

Characteristic	beta	*HR*（95% *CI*）	*P value*
TNM	0.827	2.286（1.236，4.227）	0.008*
BMI	-0.470	0.625（0.413，0.946）	0.026*
NLR	1.092	2.979 (1.565, 5.674)	0.001*
CEA	0.008	1.008（0.997，1.019）	0.143
age	0.031	0.970(0.556, 1.691)	0.914
Tumor size	0.143	1.154(0.651, 2.045)	0.624
PNI	0.347	1.415(0.783, 2.557)	0.250
PLR	0.040	1.041(0.567, 1.912)	0.897
hemoglobin	0.197	0.821(0.479, 1.408)	0.474
prealbumin	0.122	0.885(0.496, 1.578)	0.678
Differentiation grade	0.073	1.075(0.630, 1.836)	0.791
Cancerous node	0.084	1.088(0.587, 2.016)	0.789
Tumor location	0.082	0.922(0.695, 1222)	0.571

Table 4 Nomogram Scoring System

NLR	points	TNM	points	BMI	points
low	0	low	0	high	0
high	26	high	20	normal	58
				high	100

Figures

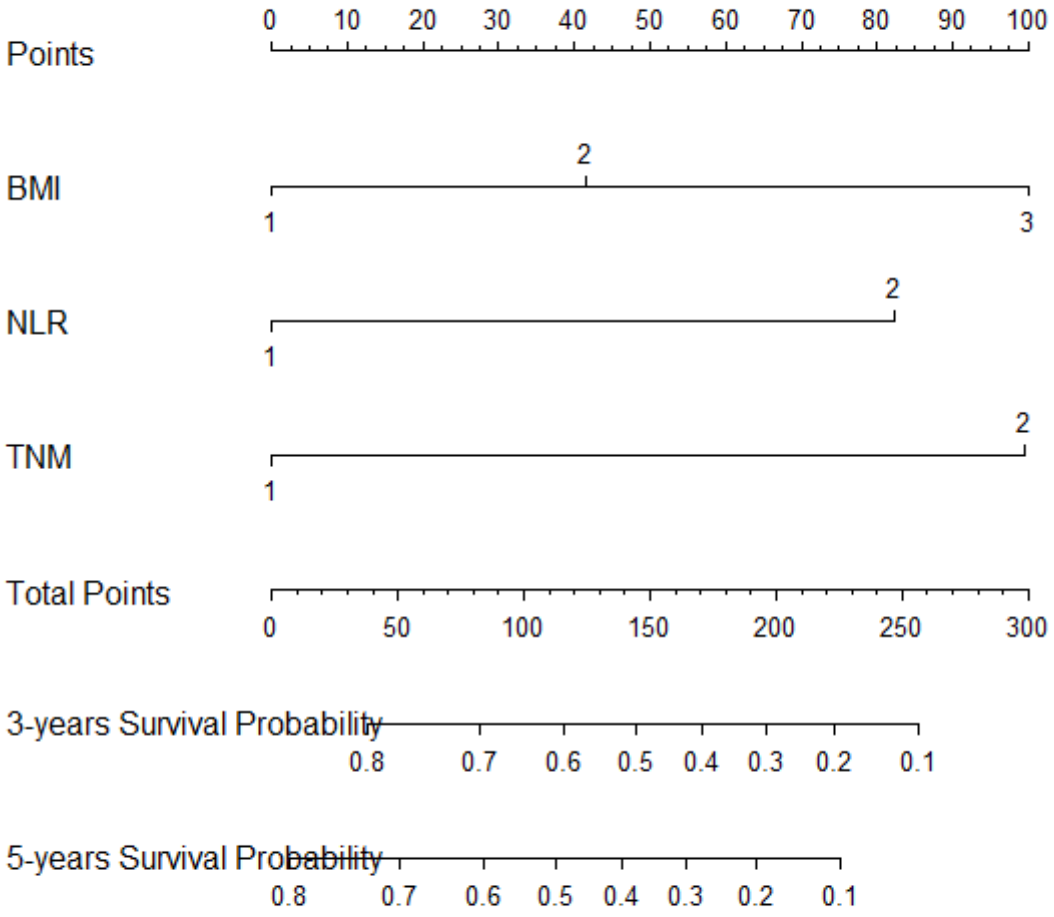

Figure 1

Nomogram for predicting overall survival after curative resection of gastric cancer

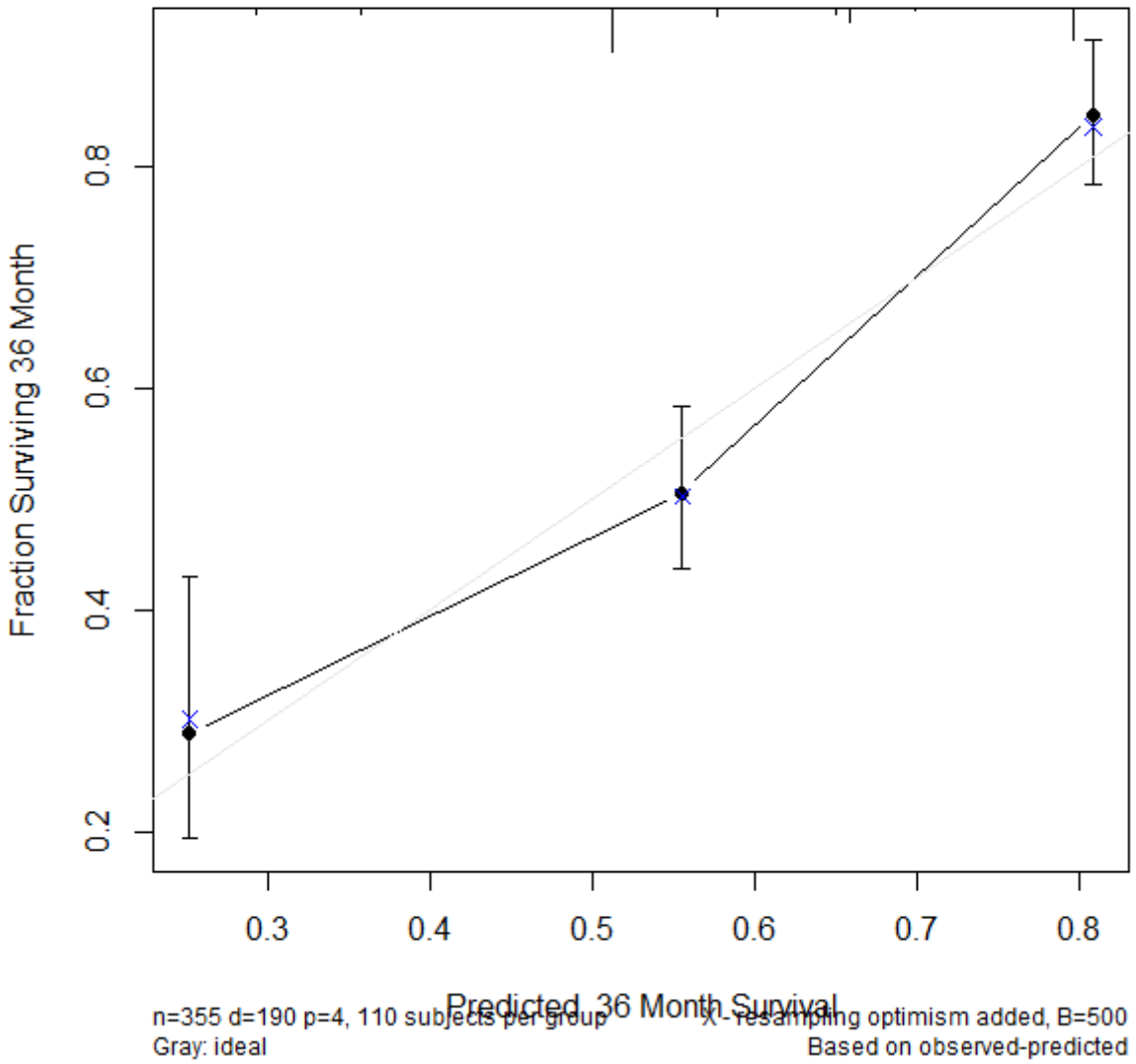

Figure 2

Calibration curves of the prognostic nomogram for 3-year overall survival

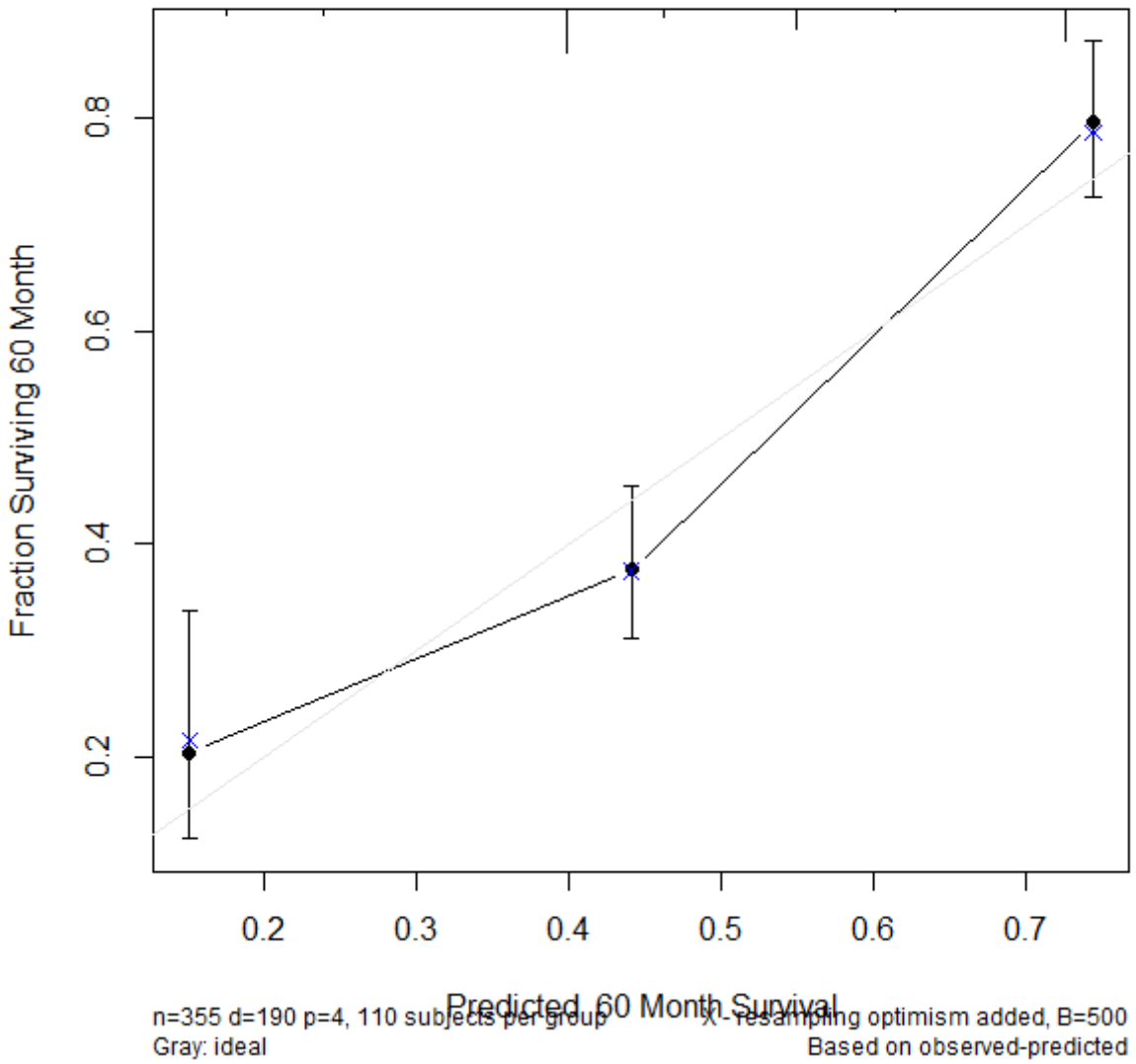

Figure 3

Calibration curves of the prognostic nomogram for 5-year overall survival

Figure 4

The ROC curve of the prognostic nomogram and TNM for 3-year overall survival

Figure 5

The ROC curve of the prognostic nomogram and TNM for 5-year overall survival

Figure 6

Survival curves stratified by the score calculated by the nomogram (low risk: <58 and high risk: >58).