A nomogram established by inflammatory markers predicting overall survival after radical resection of gastric cancer

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Research

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Abstract

Background The prognostic value of inflammatory markers have been confirmed in some tumors, this research was to explore more clinical markers and then build a reliable nomogram to predict overall survival after radical resection of gastric cancer.

Methods 904 patients who underwent surgery at the First Affiliated Hospital of Anhui Medical University from January 2010 to January 2013 were included. Univariate and multivariate analyses were used to screen for prognostic risk factors. The construction of the nomogram is based on the Cox proportional hazard regression model. The construction of the new scoring model is analyzed by the receiver operator characteristic (ROC) curve and then compared with other clinical indicators.

Results Multivariate analysis showed that TNM stage, CEA, the systemic immune-inflammation index (SII) and age were independent prognostic factors. The value of SII was better than other inflammatory markers. The new nomogram had a higher AUC value than TNM and other risk factors, and the C-index of the nomogram was highly consistent for evaluating survival of gastric cancer patients in the validation groups and training group.

Conclusions Based on the serum markers and other clinical indicators, we developed a precise nomogram to predict the prognosis of gastric cancer patients after radical surgery. This new score system can provide effective help for surgeons and patients.

1 Introduction

Gastric cancer(GC) is the second highest mortality cancer [1], almost with 66% of cases happen in the developing countries [1, 2]. Radical gastrectomy with D2 lymph node cleaning is considered the only means of curative treatment of patients, which provides a chance of cure and longer survival for patients, however, the cancer recurrence rate and prognosis are still not optimistic even after radical resection, the 5-years survival rate remains poor [3]. The TNM stage and other tumor pathological characteristics are related to the diagnosis of gastric cancer patients; however it's hard to get tumor pathological characteristics before surgery. At present, studies indicated that serum markers correlated with the cancer-specific survival time [4, 5, 6], among them, widely used serum markers related to gastric cancer is carcinoembryonic antigen (CEA). CEA have been used as the diagnosis of cancer and was used to detect for recurrences after surgery [4]. Additionally, there are also other serum index which can evaluate the prognosis of cancer, neutrophils to lymphocytes ratio (NLR) and platelets to lymphocytes ratio (PLR) as markers have been researched widely[5, 6, 7]. Besides, the level of hemoglobin which is associated the prognosis of patients [8]. In this study, we are trying to find more clinical serum markers which can help assess the prognosis of gastric cancer patients and then build a reliable new score system.

The relationship between the tumor and inflammation has been studied widely, tumors can lead to inflammation, which can cause the damage of DNA and micro-metastasis lesions[9], the systemic inflammatory response (SIR) can weaken the immune function of body and promote the progression of

tumor. Related research found that neutrophils, lymphocytes and platelets can play a significant role in the SIR which are related the development of tumor[10, 11], based on peripheral lymphocytes, neutrophils, and platelet count, Several systemic inflammation-based scores such as the combination of NLR and PLR(NLR-PLR)[12], the combination of platelet count (PLT) and NLR (PLT-NLR)[13], the systemic immune-inflammation index (SII) can reflect the inflammation and immune status of human body[14, 15], their prognostic value have been confirmed in some tumors. There is little clinical research had been published to compare the prognostic value of these inflammatory markers. In this research, we aimed to explore more clinical serum markers and then built a reliable nomogram to predict overall survival after radical resection of gastric cancer.

2. Patients And Methods

2.1 Patients

We collected blood data and clinical data from gastric cancer patients who were hospitalized in the First Affiliated Hospital of Anhui Medical University from January 2010 to January 2013. We define the pathological types of GC as follows: adenocarcinoma, signet-ring cell carcinoma, adenosquamous carcinoma, squamous carcinoma, mucinous cell carcinoma; Pathological staging according to seventh AJCC TNM staging system classification. In the final analysis of this study, all selected subjects were randomized into training (n = 543) and validation (n = 361) cohorts. This research has been approved by the Ethical Committee and Institutional Review Board of our hospital.

2.2 Inclusion and exclusion criteria

According the inclusion and exclusion criteria, patients have been analyzed retrospectively during the research. The inclusion standards included: 1) All of the patients were confirmed gastric cancer by pathological diagnosis; 2) the surgery is definite and complete resection of cancer 3) all of the patients didn’t have any heart sickness or any important organs failures; 4) all peripheral blood tests have been acquired in one week before the surgery. The exclusion criteria included; 1) the patients had any previous malignant tumors or other primary tumors; 2) the patients had accepted any radiotherapy and chemotherapy before surgery; 3) there were some diseases that could interference peripheral blood cells, just like infection; 4) the patients died in thirty days after the operation during follow-up. A cohort of 904 patients with gastric cancer has been included in this research.

2.3 Data collection and follow-up.

Patient demographic and clinical pathology data was gathered through our hospital's medical record room, including age, gender, tumor location, tumor size, differentiation grade, pathological type and so on. The laboratory data were listed below: neutrophil, lymphocyte, platelet, hemoglobulin and so on.

Peripheral blood examination was performed within 1 week before surgery, the cutoff value of CEA and hemoglobin was got according to the normal level, the cutoff value of neutrophil, lymphocyte, and platelet was acquired by the median. We detected the some indexes (NLR, PLR, and SII). NLR is counted

by dividing the strict neutrophil count by the stringent lymphocyte count, which is counted by dividing the stringent platelet count by the stringent lymphocyte count. SII = platelet count × neutrophil count/ lymphocyte count. These three variables was grouped into low group and high group according to the optimal cut-off values which was calculated based on the Youden index [maximum (sensitivity + specificity-1)][16]. The NLR-PLT was assigned as follows: the patients with high PLT and high NLR group were assigned a score of 2; the patients with one high group were assigned a score of 1; and the patients with low PLT group and low NLR group were assigned a score of 0. The NLR–PLR was calculated as follows: the patients with high NLR and PLR group were assigned a score of 2; the patients with one high group were assigned a score of 1; the patients with low NLR group and low PLR group were assigned a score of 0.

The patients who were enrolled got prospective follow-up. Their follow-up date was acquired by the phones and the outpatient visits. This behavior is performed at regular intervals (every 90 days in the two years after surgery, once every 180 days in three or five years, once and a year after five years).

2.3 Statistical analysis.

We expressed the continuous variables as mean ± standard deviation and analyzed they by Student's T test; Categorical values were identified by counting(percent)and they were counted by Chi-square test or Fisher exact test. Multivariate and univariate survival analyses were performed through the Cox appropriate hazard model. The Harrell Consistency Index (C-index) was used in the nomogram to evaluate the prognostic model of gastric cancer patients. Receiver operating characteristics curve (ROC) was used to verify the accuracy of new score system in the nomogram. The larger C-index and the area under the ROC curve (AUC), the more precise of the prediction. The entire data description was performed using SPSS app (version 16.0) and RStudio software (1.1.447–2009–2018; RStudio, Inc.).

3 Results

3.1 The cutoff value of NLR, PLR and SII

We define the pre-operative NLR, PLR and SII critical points by the ROC curve of the largest Youden index [13]. The cutoff value of PLR was estimated to be 160 (sensitivity, 59.3; specificity, 51.8; P = 0.001), and the cutoff value of NLR was 2 (sensitivity, 52.6; specificity, 54.4; $P \leq 0.001$), and the cutoff value of SII was 475.6 (sensitivity, 47.8; specificity, 70.0; $P \leq 0.001$), according to the Youden index.

3.2 Baseline characteristics

Baseline characterization of 904 patients (543 from the training analysis and 361 from the validation) showed that there were no statistically significant differences between the training and validation groups ($p > 0.05$) (Table 1).

Table 1
Baseline demographics and clinical characteristics of patients in training cohort and Validation Cohort

Variables	**Training cohort (n = 543)**	**Validation Cohort (n = 361)**	***P***
The pathological types			0.369
Adenocarcinoma	496(91.3)	336(93.1)	
Signet-ring cell	25(4.6)	14(3.9)	
Adenosquamous	1(0.2)	2(0.6)	
Squamous carcinoma	4(0.7)	4(1.1)	
Mucinous cell	17(3.1)	5(1.4)	
Macroscopic type			0.932
Borrmann I	22(4.1)	15(4.2)	
Borrmann II	391(72)	260(72)	
Borrmann III	113(20.8)	72(19.9)	
Borrmann IV	17(3.1)	14(3.9)	
Tumor location			0.415
Upper	250 (46.1)	156 (43.3)	
middle	123 (22.7)	85(23.6)	
lower	169(31.2)	119(33.1)	
Surgery selection			0.344
Distal gastrectomy	117(21.5)	88(24.4)	
Total gastrectomy	401(73.8)	261(72.6)	
Proximal gastric resection	25(4.6)	11(3.0)	
Differentiated grade			0.662
High	25(4.6)	16(4.4)	
Middle	268(49.5)	181(50.2)	
Poor	248(45.9.3)	164(45.4)	
gender			0.669
male			

Variables	Training cohort (n = 543)	Validation Cohort (n = 361)	*P*
female	142(26.2)	89(24.7)	
Age			0.925
< 60			
≥ 60	334(61.5)	224(62)	
neutrophil count	3.17±4.49	2.89±4.06	0.326
platelet count	196.5±71.70	205.48±84.35	0.086
Lymphocyte count	1.64±1.68	1.58±0.59	0.491

3.3 Prognostic factors of the training cohort

Univariate risk factors of overall survival are shown in Table 2. The result showed that gender, age, CEA, NLR, PLR, SII, tumor size, TNM and hemoglobin 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, CEA, SII and age were independent prognostic factors for OS (Table 3).

Table 2
Univariate analysis of the training cohort.

Characteristics	β	HR(95%CI)	P value
Gender(men/women)	-0.3053	0.737(0.546,0.995)	0.046
age (< 60 / ≥ 60 year)	0.333	1.395(1.071,1.818)	0.014*
NLR (< 2 / ≥2)	0.406	1.502(1.163,1.940)	0.001*
Tumor size (< 5 / ≥ 5 cm)	0.810	2.248(1.746,2.894)	< 0.001*
TNM stage	1.062	2.892(1.897,4.409)	< 0.001*
Histologic type	-0.788	0.455(0.140, 1.478)	0.190
neutrophil count	0.007	0.992(0.963, 1.023)	0.622
platelet count	0.001	0.999 (0.997, 1.000)	0.247
Lymphocyte count	0.048	1.0489 (0.966, 1.139)	0.259
PLR (< 120 / >120)	0.482	1.619(1.251, 2.096)	< 0.001*
The pathological types	-6.144e-01	5.410e-01(0.255,1.148)	1.148
Macroscopic type	-0.1138	0.893(0.486,1.640)	0.714
Tumor location	-0.102	0.903(0.543,1.502)	0.695
Surgery selection	0.098	0.903(0.806,1.508)	0.540
CEA(5ug/L)	1.238	3.449 (2.679, 4.440)	< 0.001*
SII(< 475.6/ >475.6)	0.632	1.881(1.464,2.417)	< 0.001*
NLR-PLR	0.286	1.331(1.194, 1.483)	< 0.001*
NLR-PLT	0.269	1.308(1.158,1.477)	< 0.001*
hemoglobin	-0.350	0.705(0.549,0.905)	0.006

Table 3
Multivariate analysis of the training cohort.

Characteristic	beta	HR(95%CI)	P value
TNM	0.888	2.429(1.588,3.716)	< 0.001*
CEA	0.839	2.313(1.774,3.015)	< 0.001*
SII	0.405	1.499 (1.165, 1.930)	0.002*
Age	0.303	1.354(1.034,1.771)	0.028

3.4 the prognostic value of blood markers

The receiver operating characteristic curve (ROC) was used to compare the value of blood markers for predicting the overall survival of gastric cancer patients, the results was expressed in the Fig. 1, the area under the ROC of SII was larger than NLR, PLR, NLR-PLR and NLR-PLT.

3.5 Prognostic nomogram for survival

Based on the multivariate analysis, a nomogram was constructed to predict the overall survival of the gastric cancer(Fig. 2), and the 1-year, 3 year, 5- year survival rate was predicted. For constructing the nomogram, every subgroup variable is assigned a corresponding score, and the nomogram scoring system is located in Table 4.

Table 4
Nomogram Scoring System

SII	points	age	points	CEA	points	TNM	points
low	0	low	0	low	0	I	0
high	26	high	20	high	55	II	58
						III	100

3.6 Validation of the nomogram

We used calibration curves to testify the model in the prediction of the overall survival of GC patients (Fig. 3, Fig. 4, Fig. 5 and Fig. 6). The C-index of the model in training group was 0.736, and this value was 0.651 in the validation group. To further testify the model's performance in the diagnosis of patients with gastric cancer; we plotted the receiver operating characteristic curve (ROC) of the nomogram (Fig. 7) and the area under the receiver-related operational characteristic curve (AUC) of the nomogram is large, indicating that the constructed nomogram is a reliable score system.

3.7 Decision curve analysis (DCA) of the nomogram

DCA graphically showed the new model for predicting 3-, 5-year survival (Fig. 8–11) to verify its clinical utilization in the training group and validation group.

3.8 The Kaplan–Meier curves

In addition, we divided the training team into three sub-groups based on the following: The total number of points in the nomogram (low risk: <60; medium risk: 60–120; high risk: > 120) (Fig. 12). The excellent results were showed by Kaplan–Meier curve.

4. Discussion

Surgery is considered the only means of curative treatment of gastric cancer. Because of the limit of techniques, early gastric cancer is usually difficult to detect. The current 5-year survival rate is very low. Therefore, many researchers have made many efforts to improve the prognosis of patients with gastric cancer. Lymph node metastasis, tumor size, degree of differentiation, and TNM staging were defined as prognostic factors. Because these prognostic factors are difficult to assess before surgery, the study of serum prognostic markers has been extensively studied in recent years. To our knowledge, this study is the first attempt to establish a prognostic model that combines serum markers (including inflammatory markers, nutritional markers, and tumor markers) and clinicopathological features to estimate 1 year, 3 years and 5-year survival rate. Based on multivariate analysis, the results showed that TNM stage, CEA, SII and age were independent prognostic factors for OS. And the AUC of SII was larger than NLR-PLR and NLR-PLT indicating that SII was a better inflammatory marker for predicting OS of GC patients. Besides, we developed a nomogram based on independent risk factors, the C-index was 0.736, which indicated our new model is highly accurate in predicting the prognosis of gastric cancer patients. Moreover, the AUC of the nomogram is larger than the AUC of TNM and other factors; the DCA also verified its clinical utilization. Therefore, this nomogram is an reliable score system.

In recent years, Nomograms showed high reliability for predicting tumor prognosis as a statistic model. Nomogram have better value for predicting prognosis than TNM stage in many cancer [17, 18], nomogram has been identified as a new standard, and our study had got the same conclusion, the AUC of the nomogram is larger than the AUC of TNM, this score system can be applied to the clinic, which can helps the surgeon to better judge the patient's prognosis, and thus take more scientific and appropriate treatment.

Our nomogram contains four variables in which SII was an significant factor. Studies have suggested that systemic inflammation is an important factor affected the progression and long-term survival of cancer patients [19]. As simple and inexpensive clinical markers, NLR and PLR can reflect the state of inflammation, and are associated with poor prognosis of some cancer patients, but SII was less reported which can combine neutrophil count, platelet count and lymphocyte count. NLR, PLR, NLR-PLR, NLR-PLT were related to the prognosis of gastric cancer patients, while SII was an independent risk factor, SII had a better predictive ability. 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 [23], 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 [20, 21], besides, platelets can also promote tumor growth by increasing angiogenesis via VEGF [22]. So SII should be included in the regular assessment index of gastric cancer patients.

CEA was a regular marker for screening the recurrence of cancer, our study verified that CEA was an independent risk marker; we need to take more attention for the patients with high CEA level. Age was also an significant factor, our result was consistent with previous study [23], the old patients may have poor body function which can permit loco-regional recurrence, and thus it can have an adverse on the

prognosis of gastric cancer patients, so these significant variables need to take more attention in order to make a better prediction, and the nomogram may applied more widely in the clinic.

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

In summary, our study indicated that TNM stage, CEA, SII and age were significant factors for the prognosis of gastric cancer patients, and the novel nomogram had reliable prognostic value for patients.

Abbreviations

CEA: carcinoembryonic antigen NLR: neutrophils to lymphocytes ratio PLR: platelets to lymphocytes ratio SIR: The systemic inflammatory response SII: systemic immune-inflammation index

Declarations

Ethics approval and consent to participate: The studies involving human participants were reviewed and approved by Institutional Review Board and the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Written informed consent for participation was acquired in accordance with the national legislation and the institutional requirements.

Consent for publication: Yes.

Data Availability: The data used to support the findings of this study are available.

Competing interests: All authors declare no conflict of interest.

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Authors' contributions: Conceptualization: A-man Xu; Methodology: Li-xiang Zhang and Ye-zhou Su; Formal analysis and investigation: Li-xiang Zhang, Zhi-jian Wei, Pan-qi Luo, Zhang-ming Chen, Peng Xu, Gang Wang and Hai Zhu; Writing - original draft preparation: [Li-xiang Zhang; Funding acquisition: A-man Xu and Wen-xiu Han;

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Figures

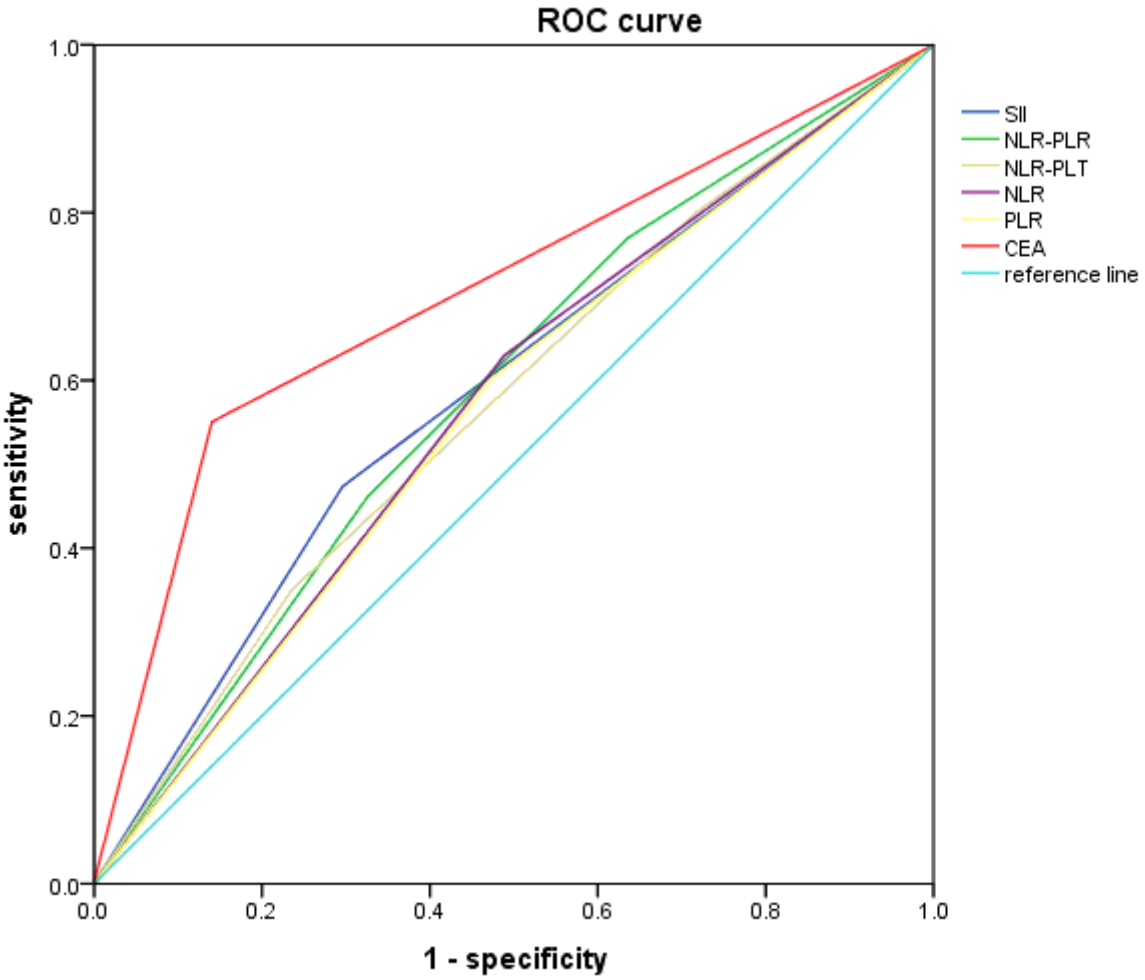

Figure 1

The ROC curve of the blood markers

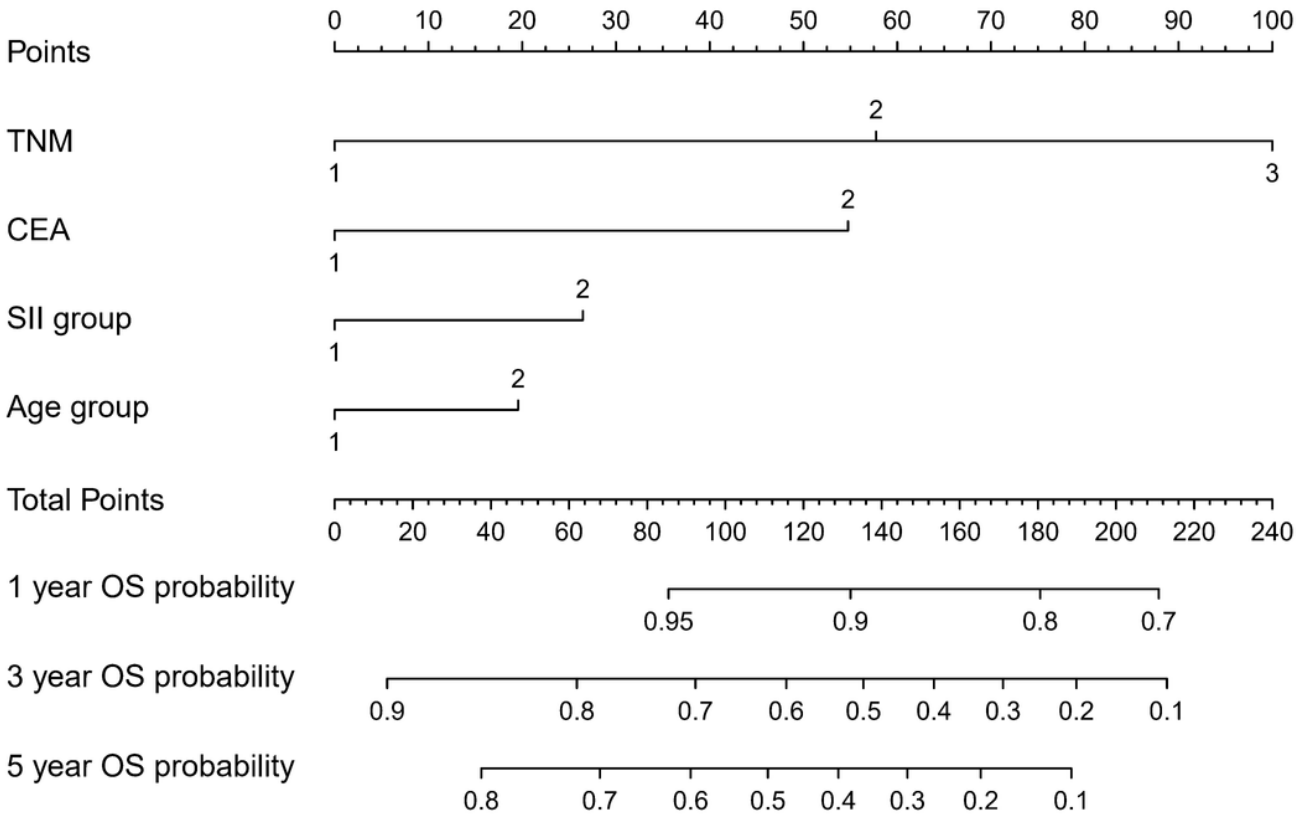

Figure 2

Nomogram for predicting overall survival after curative resection of gastric cancer

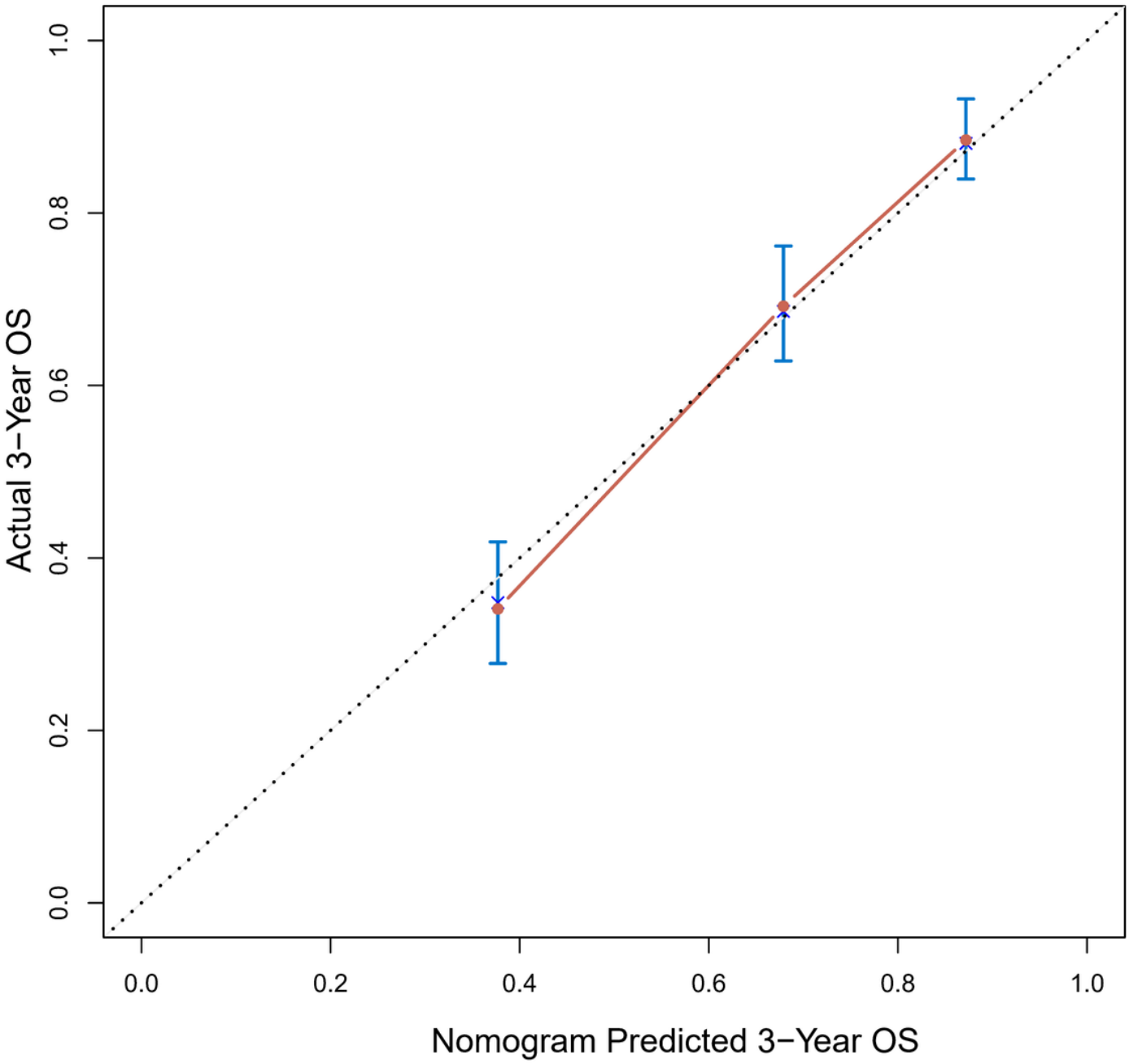

Figure 3

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

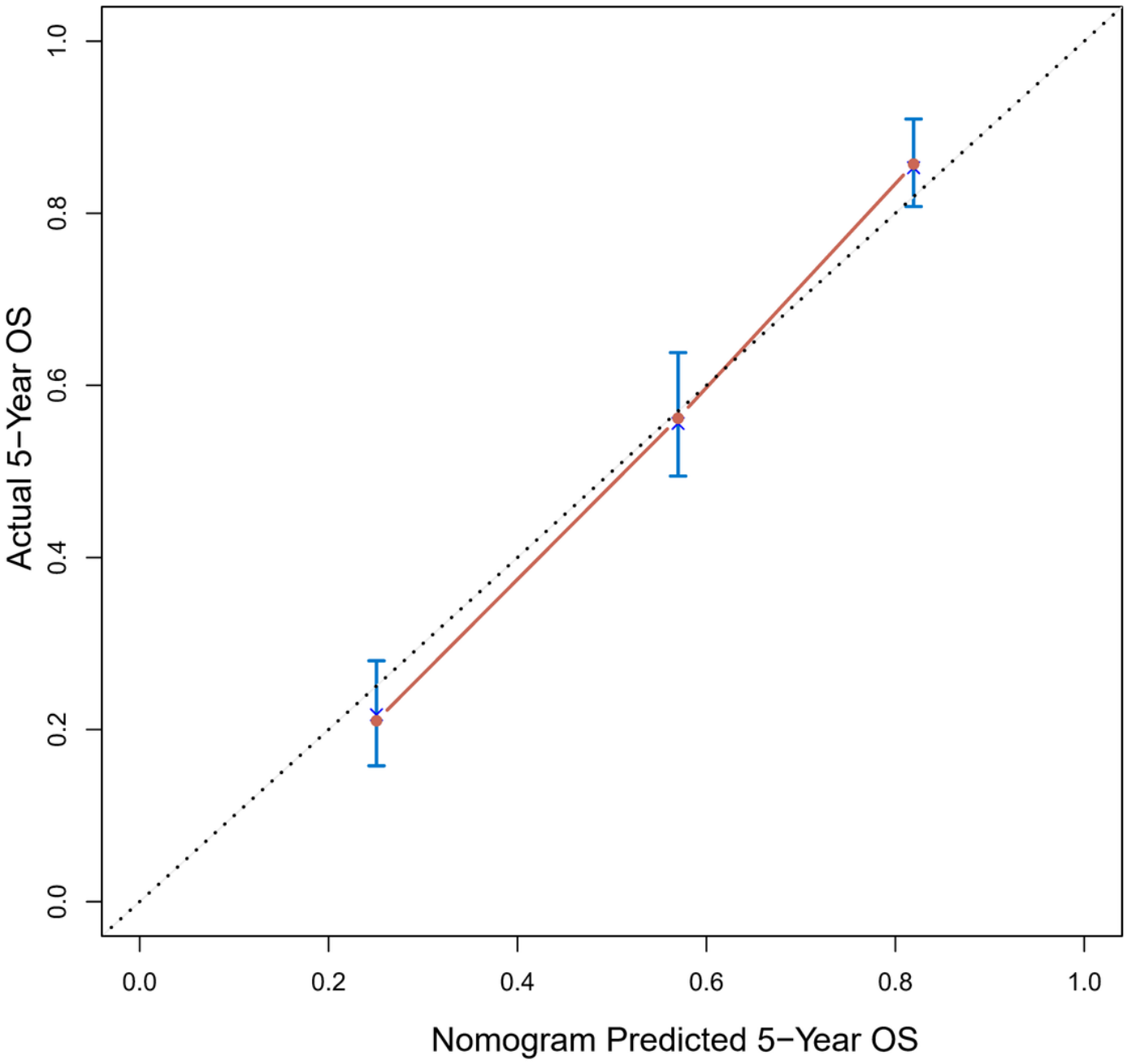

Figure 4

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

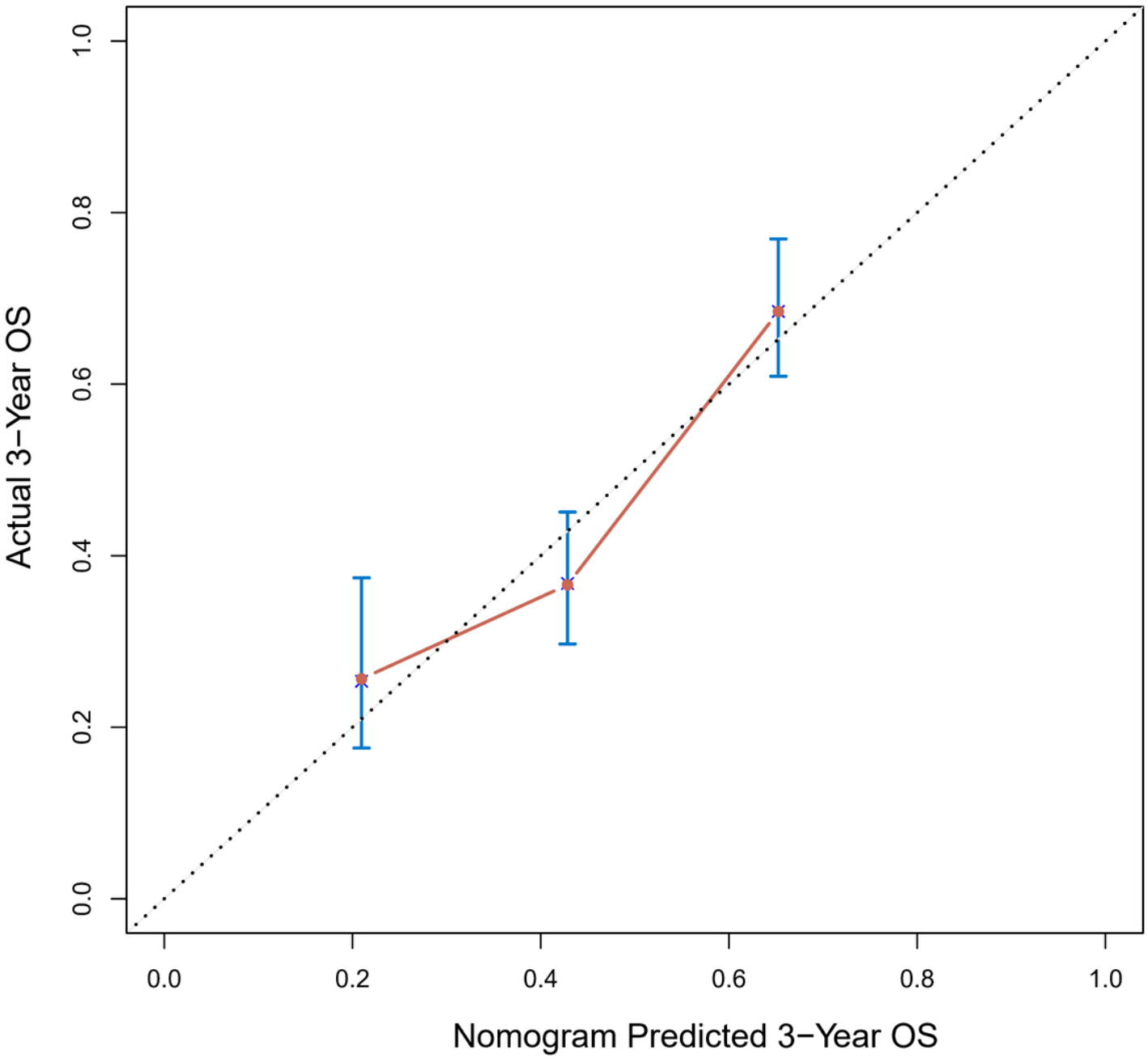

Figure 5

Calibration curves of the prognostic nomogram for 3-year overall survival in the validation set.

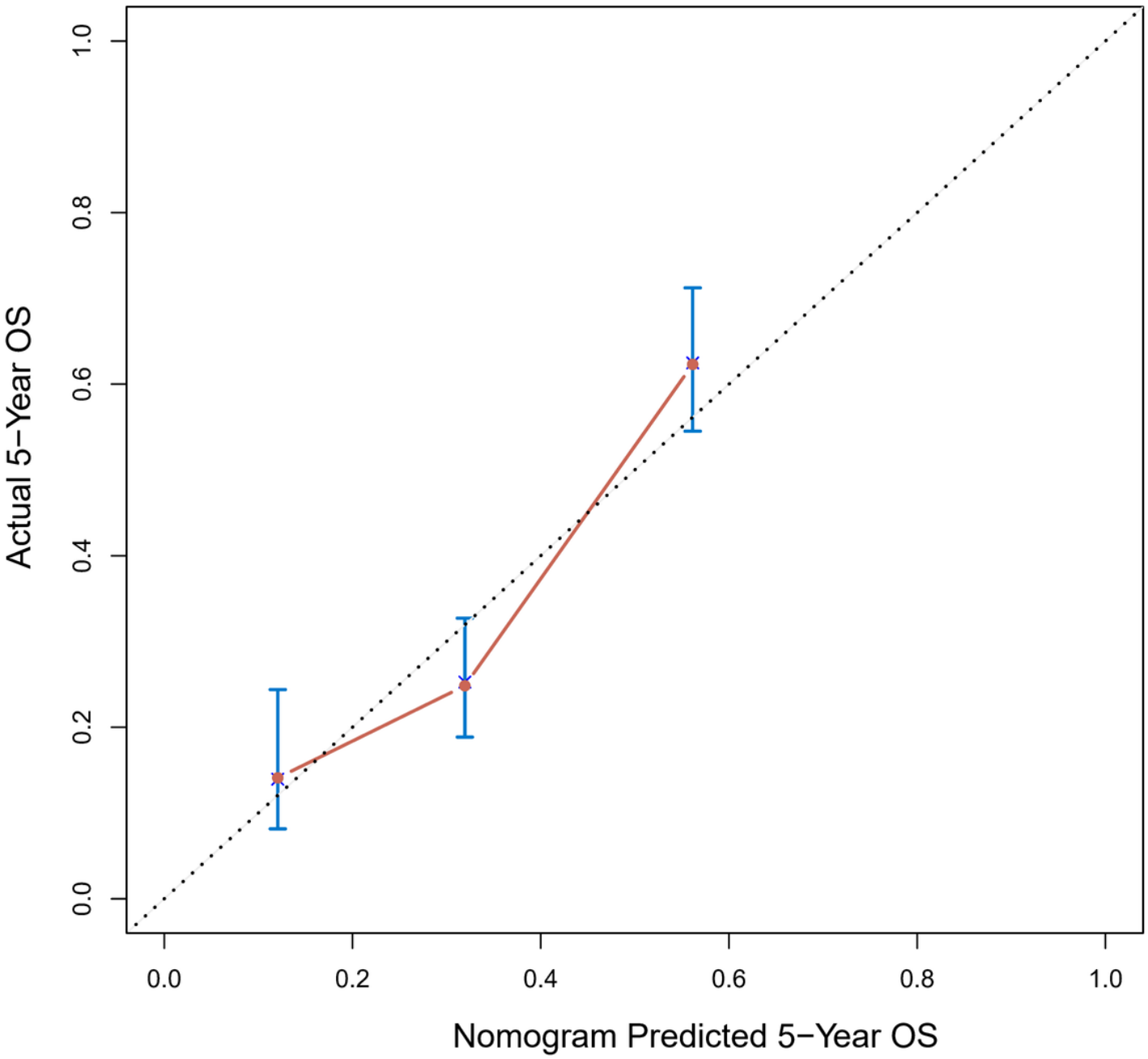

Figure 6

Calibration curves of the prognostic nomogram for 5-year overall survival in the validation set.

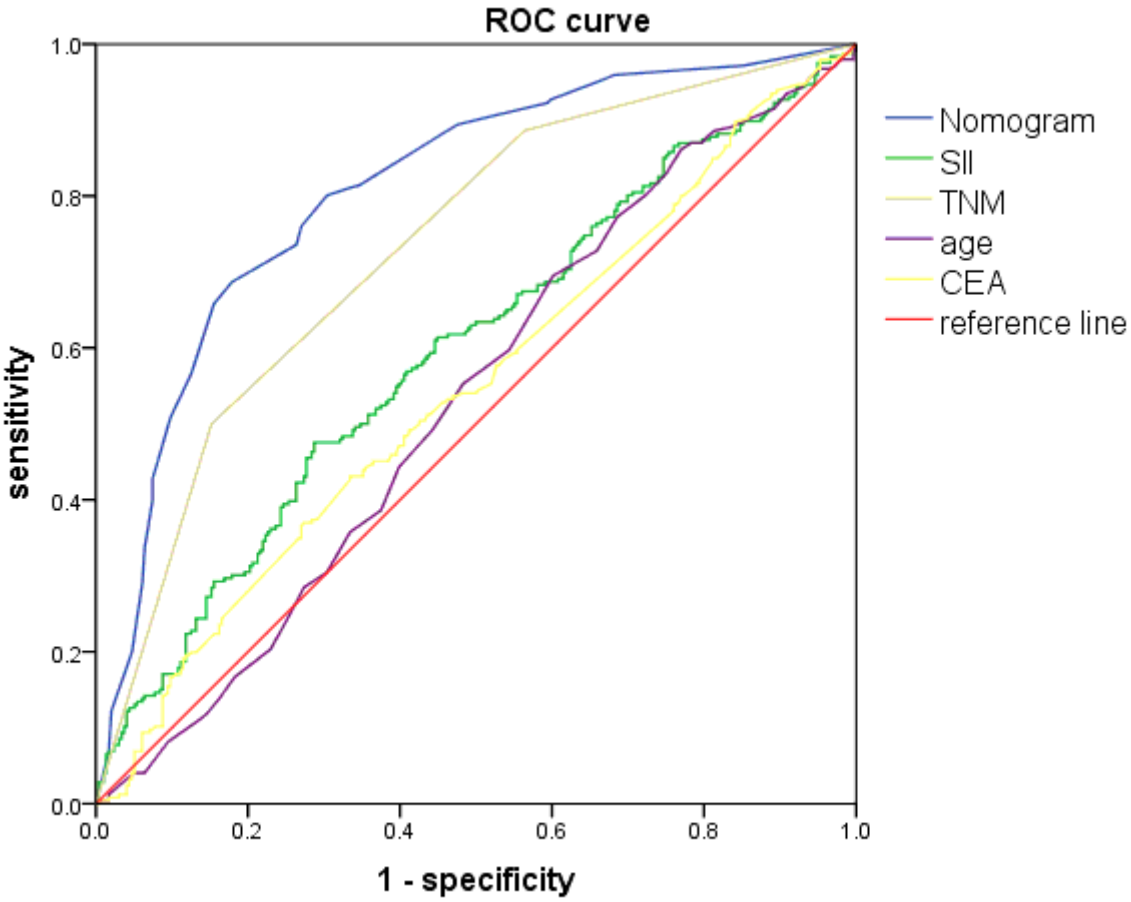

Figure 7

The ROC curve of the prognostic nomogram in the training set.

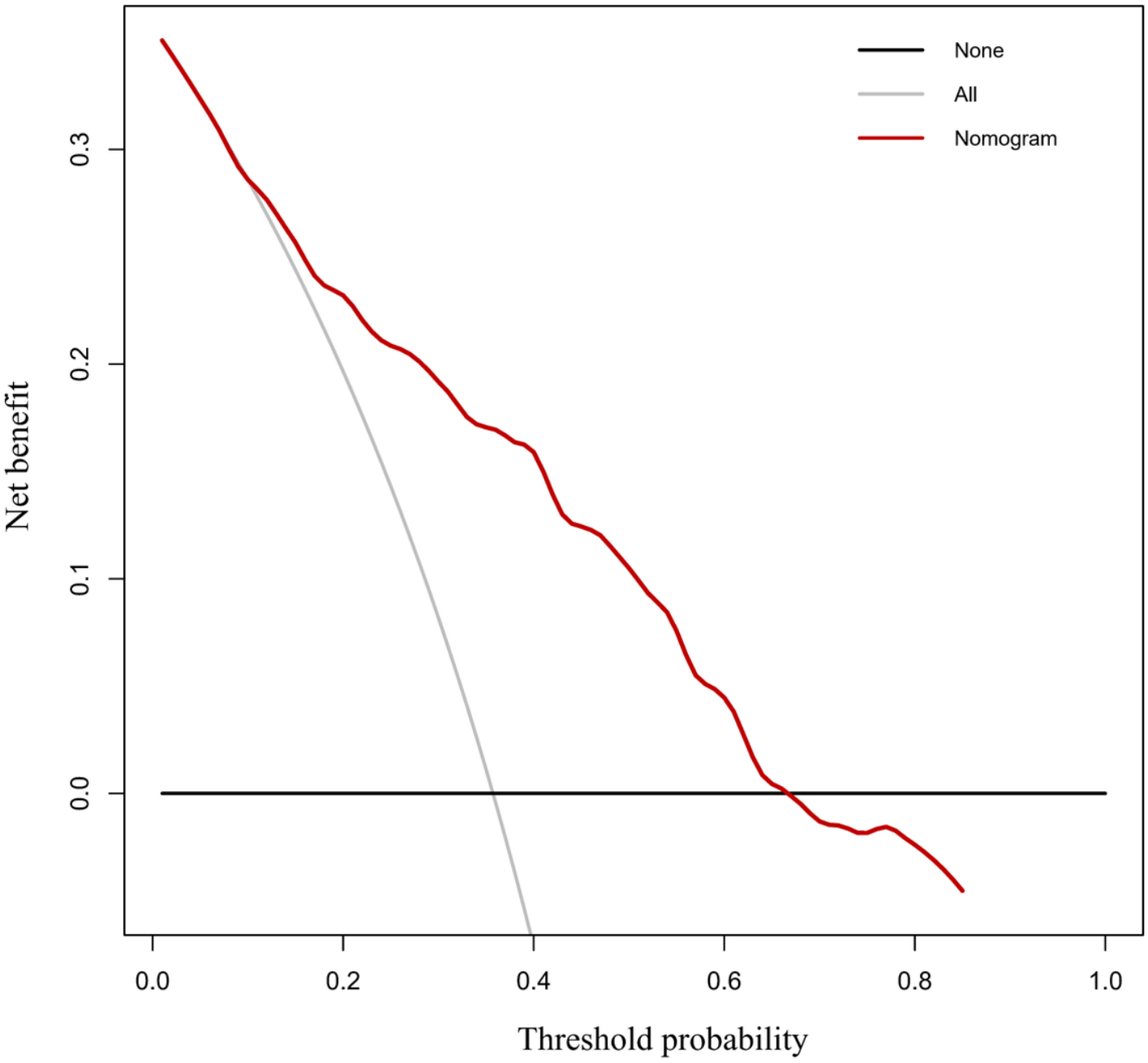

Figure 8

The DCA curve of the prognostic nomogram for predicting 3-year overall survival in the training set.

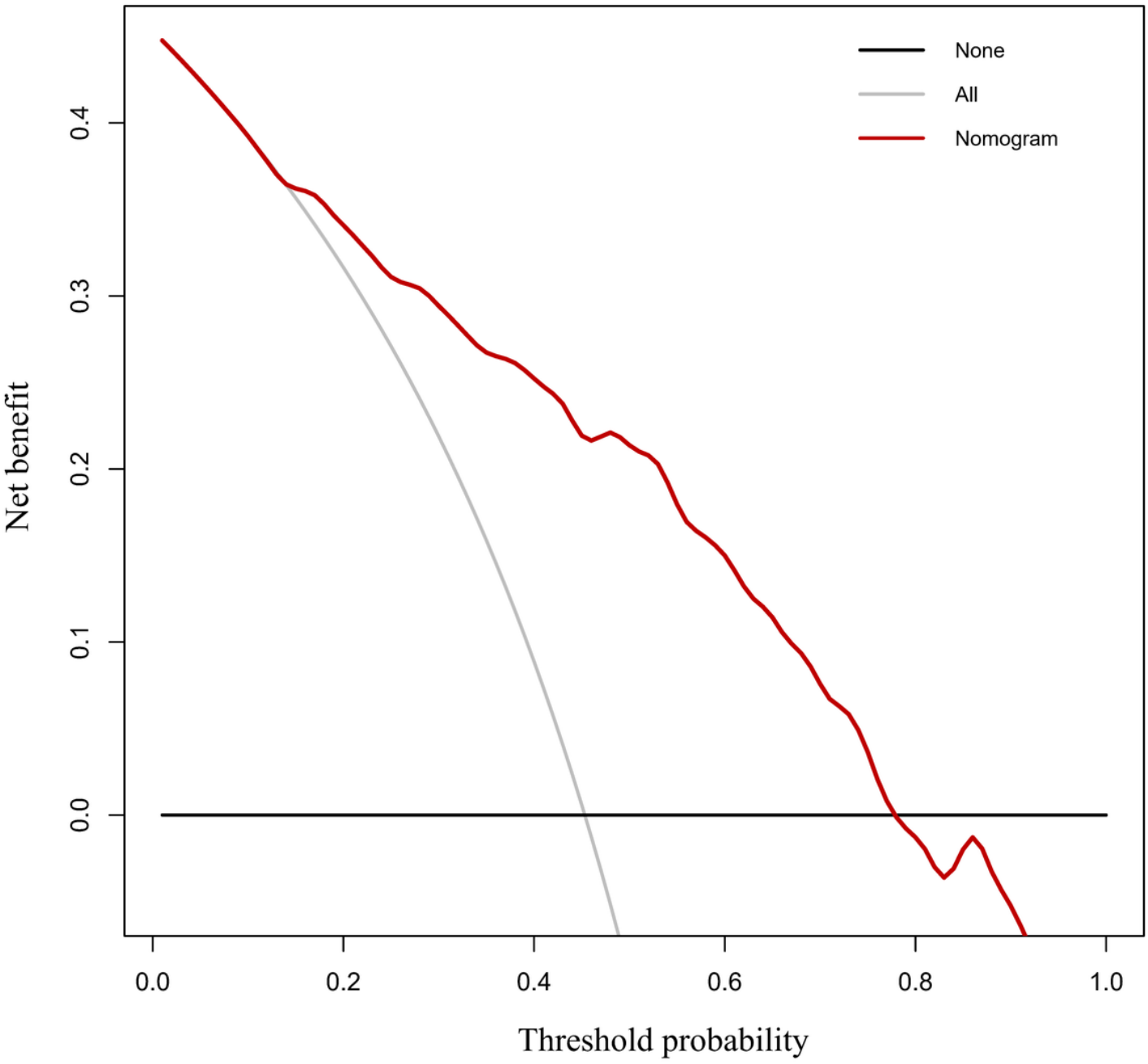

Figure 9

The DCA curve of the prognostic nomogram for 5-year overall survival in the training set

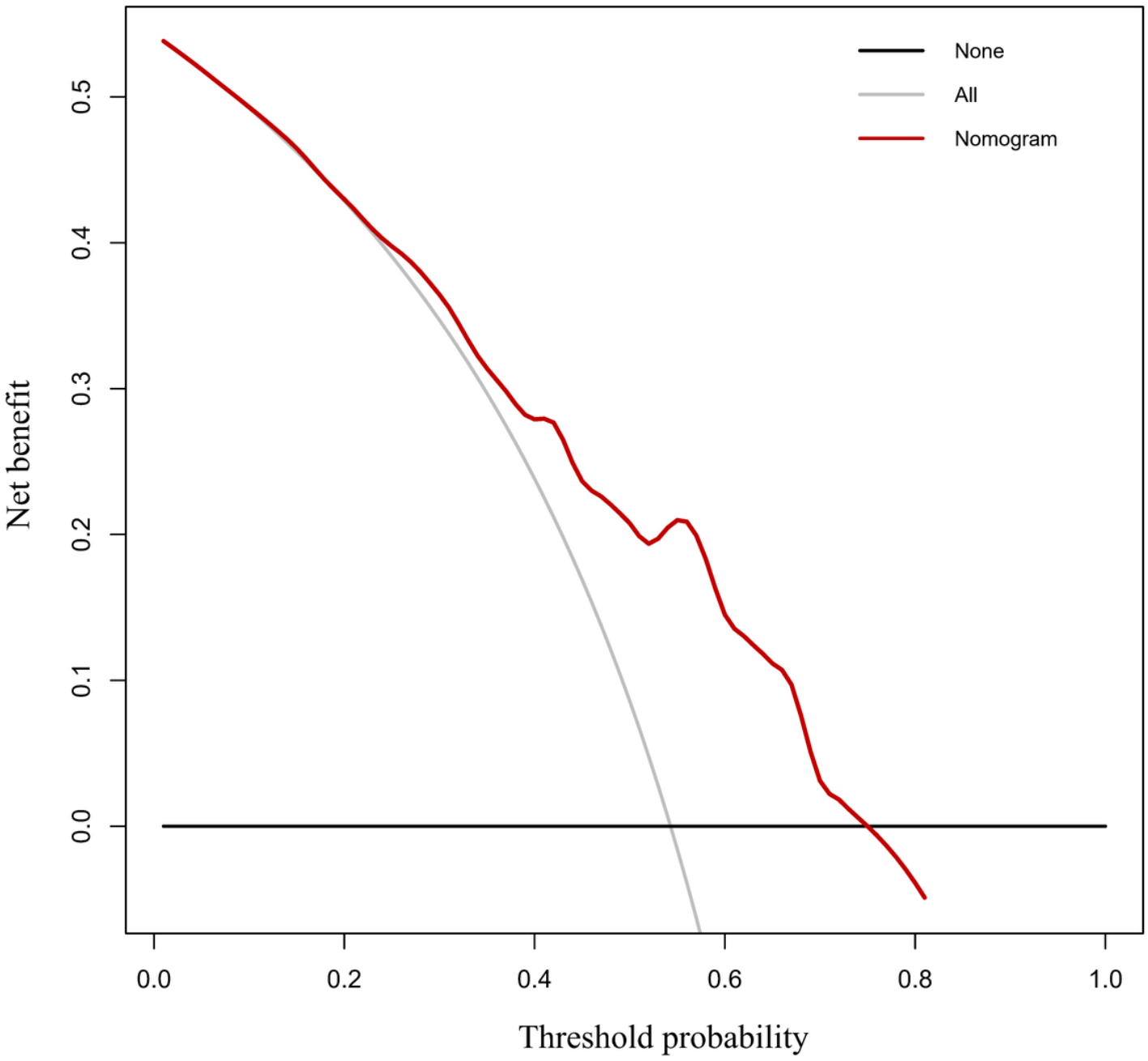

Figure 10

The DCA curve of the prognostic nomogram for 3-year overall survival in the validation set.

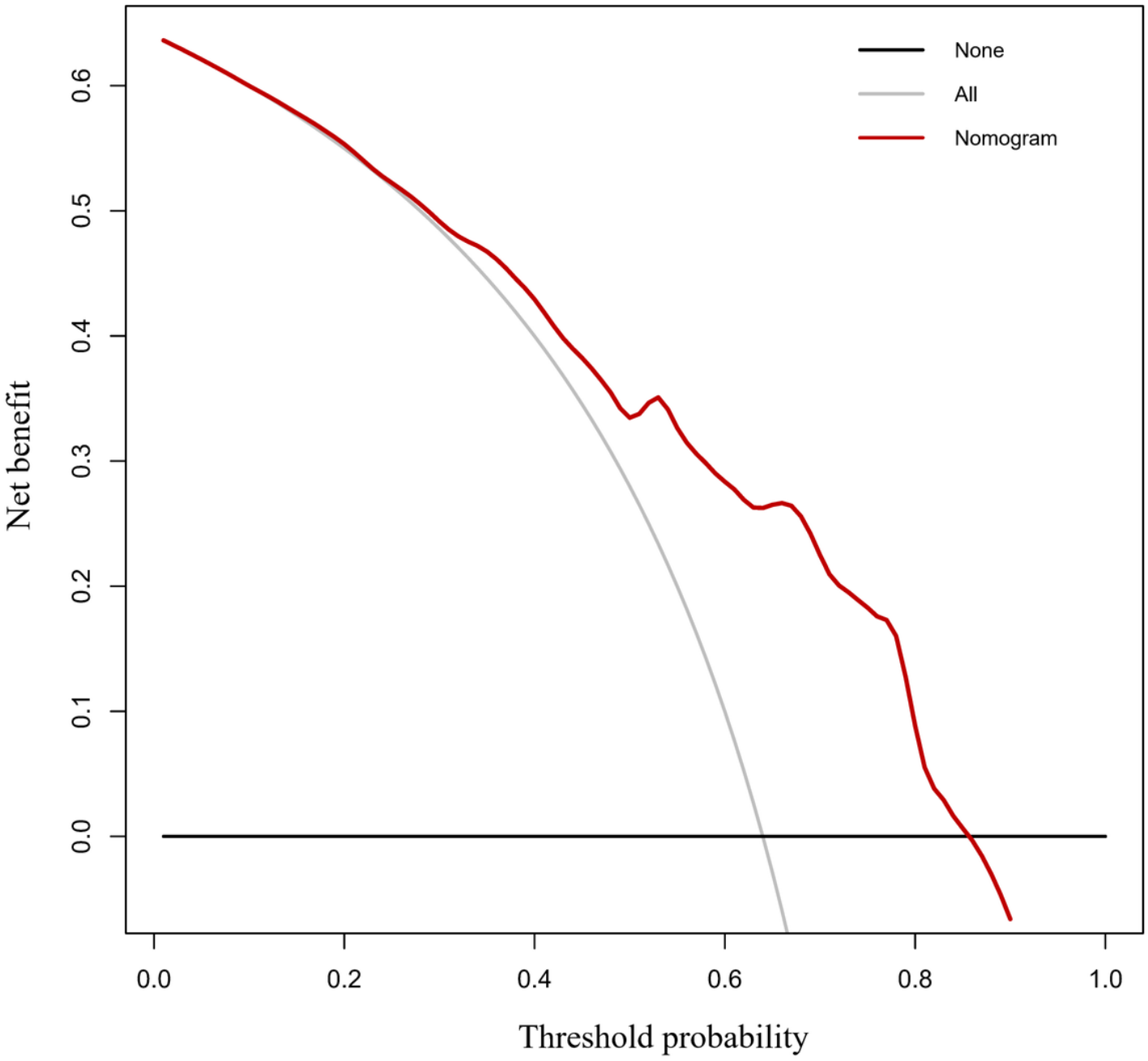

Figure 11

The DCA curve of the prognostic nomogram for 5-year overall survival in the validation set.

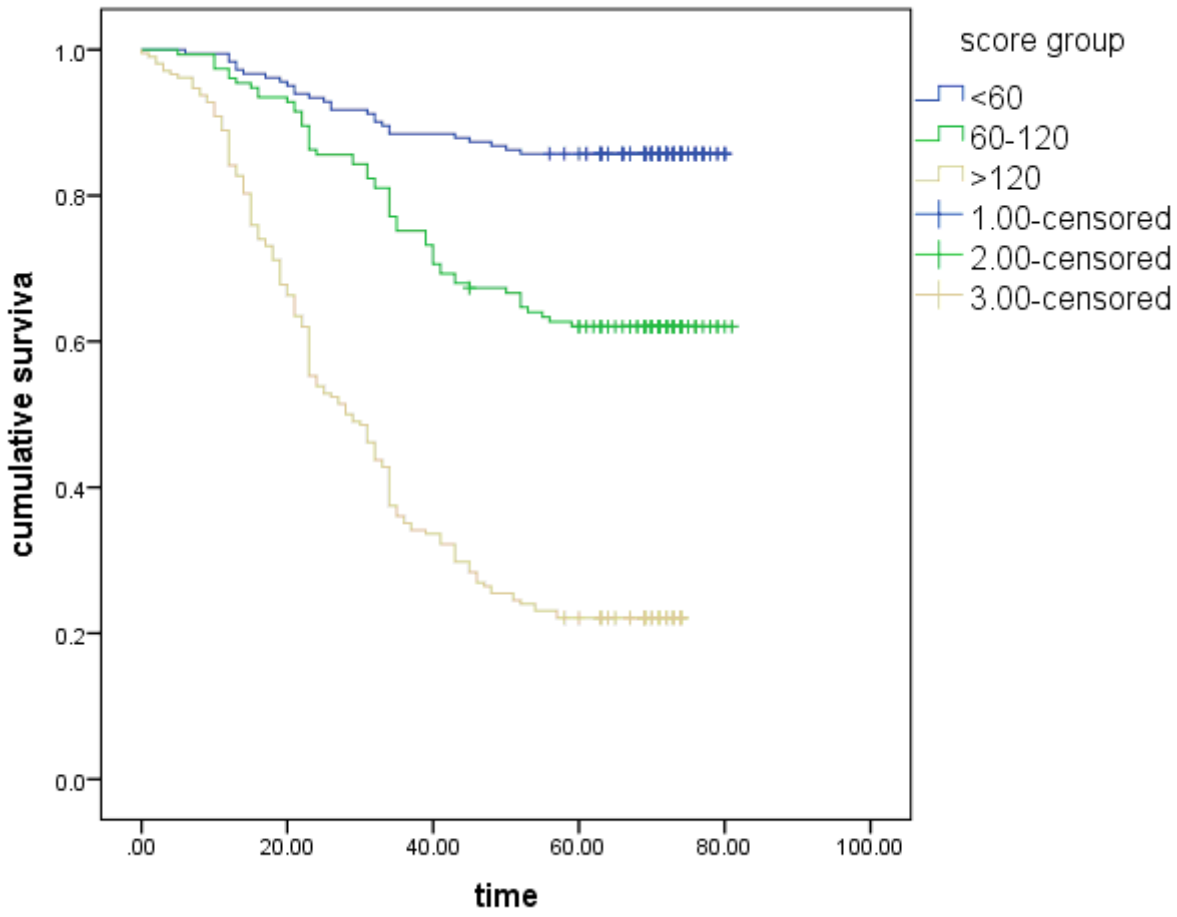

Figure 12

Survival curves stratified by the score calculated by the nomogram in the training cohort (low risk: <60; intermediate risk: 60–120; and high risk: >120).