A simple model established by blood markers predicting overall survival after radical resection of gastric cancer

Li-xiang Zhang
Department of Gastrointestinal Surgery, The First Affiliated Hospital of Anhui Medical
Zhi-jian Wei
Department of Gasrointestinal Surgery, The First Affiliated Hospital of Anhui Medical University
Wen-xiu Han
Department of Gastrointestinal Surgery, The First Affiliated Hospital of Anhui Medical University
A-Man Xu (jinhyq@163.com)
Department of Gastrointestinal Surgery, The Affiliated Hospotal of Anhui Medical University
https://orcid.org/0000-0002-7171-5295

Research article

Keywords: NLR, PLR SII, prognosis

Posted Date: November 25th, 2019

DOI: https://doi.org/10.21203/rs.2.17763/v1

Abstract

The prognostic prediction after radical resection of gastric cancer patients has not been well established. We aimed to establish a prognostic model based on a new score system, which included another clinical routine serum marker. Methods 904 patients who underwent surgery at the First Affiliated Hospital of Anhui Medical University from January 2010 to January 2011 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 curve (ROC curve) and then compared with other clinical indicators. Results Multivariate analysis showed that TNM stage, CEA, SII and age were independent prognostic factors. The new score system had a higher AUC value than 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 model to predict the prognosis of gastric cancer patients after radical surgery. This score system can provide effective help for surgeons and patients.

Background

Gastric cancer 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, however, the cancer recurrence rate and prognosis are still not optimistic even after radical resection, the 5-years survival rate remain poor [3]. The TNM stage and other tumor pathological characteristics are related to the diagnosis of gastric cancer patients, however they are hard to get 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) , which have been used as the diagnosis of cancer and 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 are 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 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, the immune function of body can promote progression of tumor. Related research found that neutrophils, lymphocytes and platelets can play a significant role in the SIR induced tumor[10,11], based on peripheral lymphocytes, neutrophils, and platelet count, the systemic immune-inflammation index (SII) can better reflect the immune and inflammation status of human body[12,13]. There few clinical research had been published, how to access the prediction of SII and other serum markers together for overall survival in gastric cancer

patients is a big problem. Nomograms was a statistic model with a high reliability. In this research, we have established a new nomogram to explore the value of blood markers and then built a reliable model to predict overall survival after radical resection of gastric cancer.

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 2011. We define the pathological types of GC as follows: adenocarcinoma, signet-ring cell carcinoma, adenosquamous carcinoma, squamous carcinoma, mucinous cell carcinoma; We define the differentiation level of cancer as: high differentiation grade, middle and high differentiation grade, medium differentiation, middle and low differentiation grade, poor differentiation grade, undifferentiated adenocarcinoma, signet ring cell or mucinous carcinoma. We define the location of the tumor as follows: card gate, heart and fundus, fundus, fundus and corpus, stomach, antrum, stomach and antrum, the entire stomach.

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 thr 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; 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 have 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. Pathological staging according to AJCC seventh phase TNM staging system classification. 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. we detected the some indexes (NLR, PLR, 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)][14].

The patients which 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 a year after five years). We followed all patients and excluded 1004 patients, of whom 804 lost contact, 120 died of non-cancer-related deaths, and 80 died within 30 days of surgery. Finally, 904 patients with gastric cancer were included in the study. 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.

2.3 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.).

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 Judden 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).

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).

3.4 Prognostic nomogram for survival

Based on the cox regression model, a nomogram was constructed to predict the overall survival of the PADC (Figure 1). For constructing the nomogram, every subgroup variable is assigned a corresponding score. According the unique situation of each PADC, a point system is used to assign each subgroup variable and corresponding 1-, 3- to a range of 0 to 0. The score between 100 and the 5-year OS rate is predicted, and the nomogram scoring system is located in Table 4.

3.5 Validation of the nomogram

We used calibration curves to testify the model in the prediction of the overall survival of PADC patients (Fig. 2, Fig.3, Fig. 4 and Fig.5). 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 (Figure 6) and the area under the receiver-related operational characteristic curve (AUC) of the nomogram. . Very large, indicating that the constructed nomogram is a reliable scoring system.

3.6 Decision curve analysis (DCA) of the nomogram

DCA graphically showed the new model for predicting 3-, 5-year survival (Fig. 7-10) to verify its clinical utilization in the training group and validation group.

3.7 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) (Figure 11). The excellent results were showed by Kaplan–Meier curve.

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 and often causes a bad prognosis. The current 5-year survival rate is very low. Therefore, many researchers have made many contributions to improve the prognosis of patients with gastric cancer. Researches have presented that the elevated levels of markers may be related to the prognosis in patients with gastric cancerLymph 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. As far as we know, this study is the first to develop a prognostic nomogram that combines serum markers (including inflammatory markers, nutritional markers, and

tumor markers) with clinicopathological features to estimate 1 year, 3 years, and A 5-year probabilistic annual OS and a highly accurate prediction of the prognosis of patients with gastric cancer. Based on multivariate analysis, the results showed that TNM stage, CEA, globulin, SII and age were independent prognostic factors for OS. So, we developed a nomogram of these markers, and 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 other independent factors, the DCA also verified its clinical utilization. Therefore, the nomogram based on multiple factors has greater prognostic value of gastric cancer patients.

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 [15,16], this model has been identified as a new standard, and our study had got the same conclusion, the AUC of the nomogram is similar to the AUC of TNM, it can be applied in the clinic, which can help surgeon to evaluate the prognosis of patients and take appropriate treatment.

Our nomogram contains four variables in which SII was an insignificant factor. Studies have suggested that systemic inflammation is an important factor affected the progression and long-term survival of cancer patients [17]. 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 combined neutrophil count, platelet count and lymphocyte count. In this study, NLR and PLR were related to the prognosis of gastric cancer patients, while SII was an independent risk factor, SII had an 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 [21], 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], besides, platelets can also promote tumor growth by increasing angiogenesis via VEGF [20]. So SII should be included in the regular assessment index of gastric cancer patients.

CEA was an 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 insignificant factor, our result was consistent with previous study[21], the old patients has poor body function which can permit loco-regional recurrence, thus it can have an adverse on the prognosis of gastric cancer patients. In order to find early recurrence and metastasis of patients with high level of SII, old age, high CEA level and high TNM stage, they need more follow up and examination, and the surgeon should take comprehensive and make an appropriate treatment plan for these patients.

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, TNM stage, CEA, SII and age were risk factors for the prognosis of gastric cancer patients, and the novel nomogram model 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: Not applicable

from the corresponding author upon request.

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.

Funding: Natural Science Project of Anhui Province(No. KJ2017A829)

Authors' contributions: Conceptualization: A-man Xu and Wen-xiu Han; Methodology: Li-xiang Zhang; Formal analysis and investigation: Li-xiang Zhang, Zhi-jian Wei; Writing - original draft preparation: [Li-xiang Zhang; Writing - review and editing: A-man Xu and Wen-xiu Han; Funding acquisition: A-man Xu; Resources: Zhi-jian Wei; Supervision: A-man Xu and Wen-xiu Han.

Acknowledgements: We thank *Department of Gastrointestinal Surgery, The First Affiliated Hospital of Anhui Medical University* for their contributions to our study. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

[1]. Naghavi M. The global burden of cancer. JAMA Oncol 2015; 1: 505–27.

[2] Liu Y, Zhang Q, Ren C, Ding Y, Jin G, et al. A germline variant N375S in MET and gastric cancer susceptibility in a Chinese population. J Biomed Res 2012; 26: 315–318.

[3] Wang W, Li Y-F., Sun X-W, et al. Prognosis of 980 patients with gastric cancer after surgical resection [J]. Chinese Journal of Cancer. 2010; 29(11): 923–930.

[4] Deng K, Yang L, Hu B, Wu H, Zhu H, Tang C. The prognostic significance of pretreatment serum cea levels in gastric cancer: a meta-analysis including 14,651 patients. PLoS ONE. 2015; 4: e124151.

[5]. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357:539–45.

[6]. Coussens LM, Werb Z. Inflammation and cancer. Nature, 2002;420:860–7.

[7]. Proctor MJ, Talwar D, Balmar SM, et al. The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. Br J Cancer 2010; 103:870–6.

[8] Huang XZ, Yang YC, Chen Y, et al. Preoperative Anemia or Low Hemoglobin Predicts Poor Prognosis in Gastric Cancer Patients: A Meta-Analysis. Dis Markers. 2019;2019:7606128. Published 2019 Jan 2.

[10] Carruthers R, Tho LM, Brown J, Kakumanu S, McCartney E and McDonald AC: Systemic inflammatory response is a predictor of outcome in patients undergoing preoperative chemoradiation for locally advanced rectal cancer. Colorectal Dis 2012; 14: e701-707.

[12] B. L. Wang, L. Tian, X. H. Gao et al., “Dynamic change of the systemic immune inflammation index predicts the prognosis of patients with hepatocellular carcinoma after curative resection,”Clinical Chemistry and Laboratory Medicine, vol. 54, no. 12, pp. 1963–1969, 2016.

[13] Y. Geng, Y. Shao, D. Zhu et al., “Systemic immune inflammation index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis,” Scientific Reports, vol. 6, no. 1, article 39482, 2016.

[14] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.

[15] Zivanovic O, Jacks LM, Iasonos A et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. Cancer 2012; 118: 660–9.

[16] Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J. Clin. Oncol. Off. J. Am. Soc. Clin.Oncol. 2008; 26: 1364–70.

[17] Roxburgh CS,Salmond JM,Horgan PG,et al.The relationship between the local and systemic inflammatory responses and survival in patients undergoing curative surgery for colon and rectal cancers[J].J Gastrointest Surg,2009,13:2011-2018.

[18] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell140 (2010) 883–899.

[19] Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity [J]. Adv Immunol, 2006,90:1–50.

[20] D. Schumacher, B. Strilic, K. K. Sivaraj, N. Wettschureck, and S. Offermanns, “Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via

p2y2 receptor,” Cancer Cell, vol. 24, no. 1, pp. 130–137, 2013.

[21] Shu-Bei Wang, Wei-Xiang Qi, Jia-Yi Chen, et al. Competing risk nomogram predicting initial loco-regional recurrence in gastric cancer patients after D2 gastrectomy. Radiation Oncology , 2019, 14(1): 128.

Figures

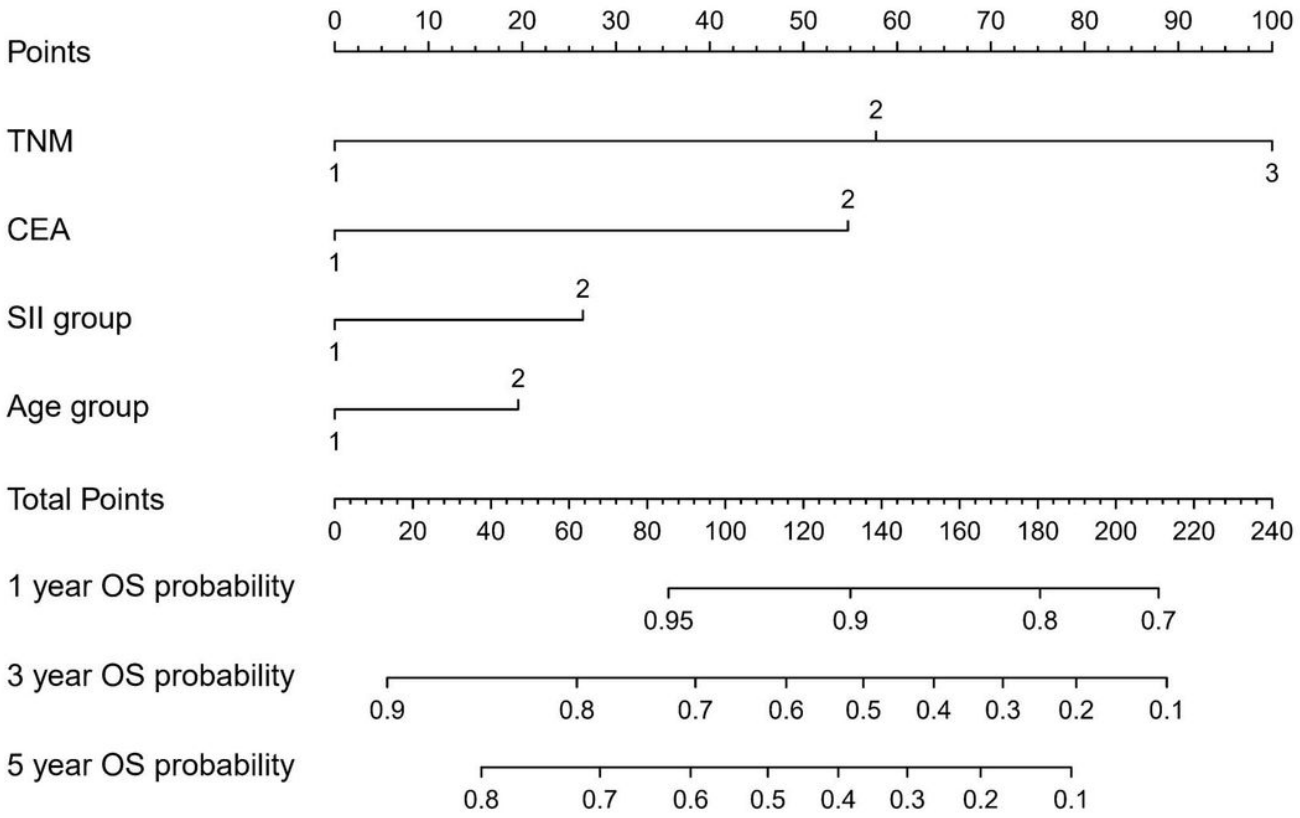

Figure 1

Nomogram for predicting overall survival after curative resection of gastric cancer

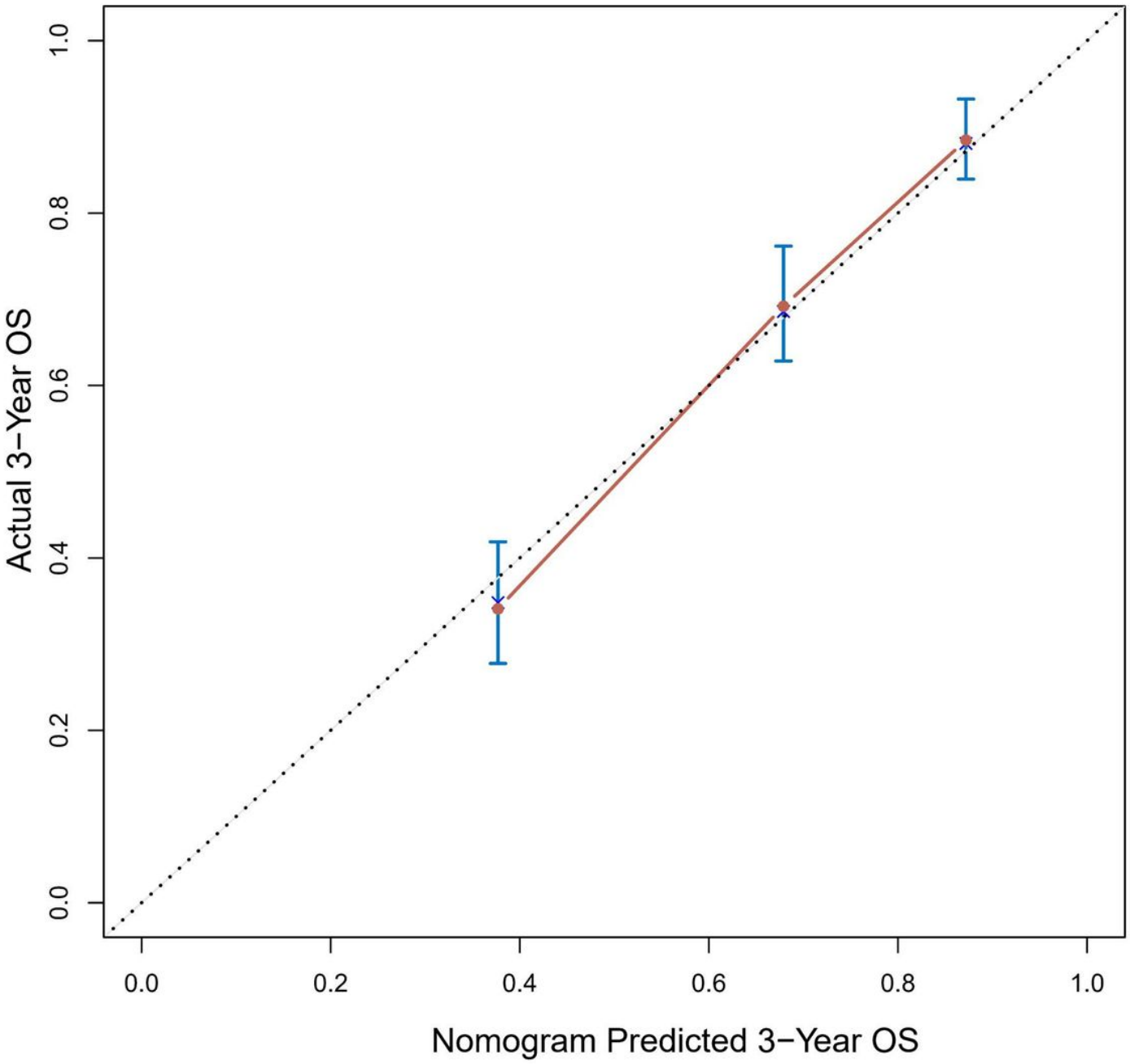

Figure 2

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

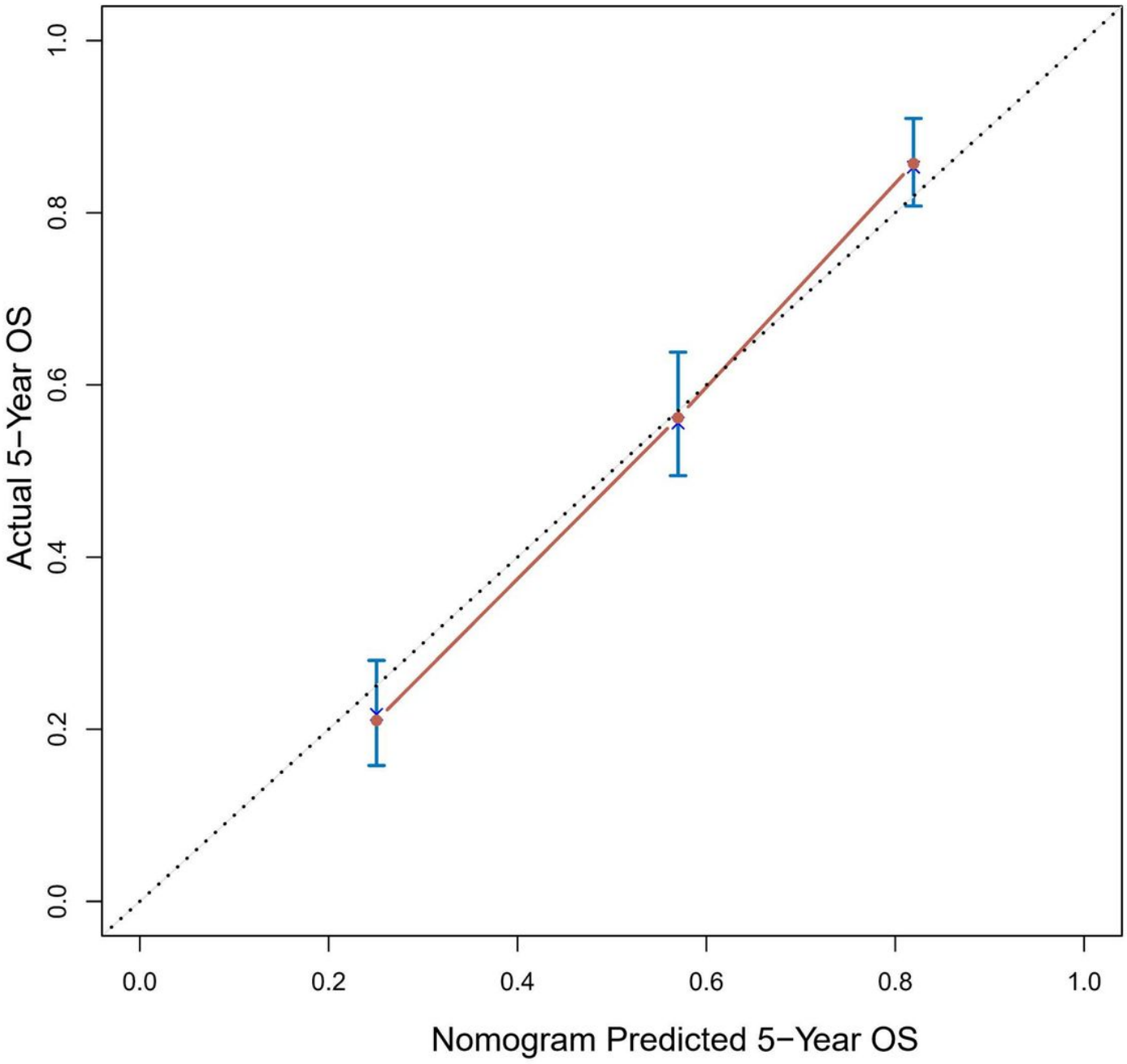

Figure 3

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

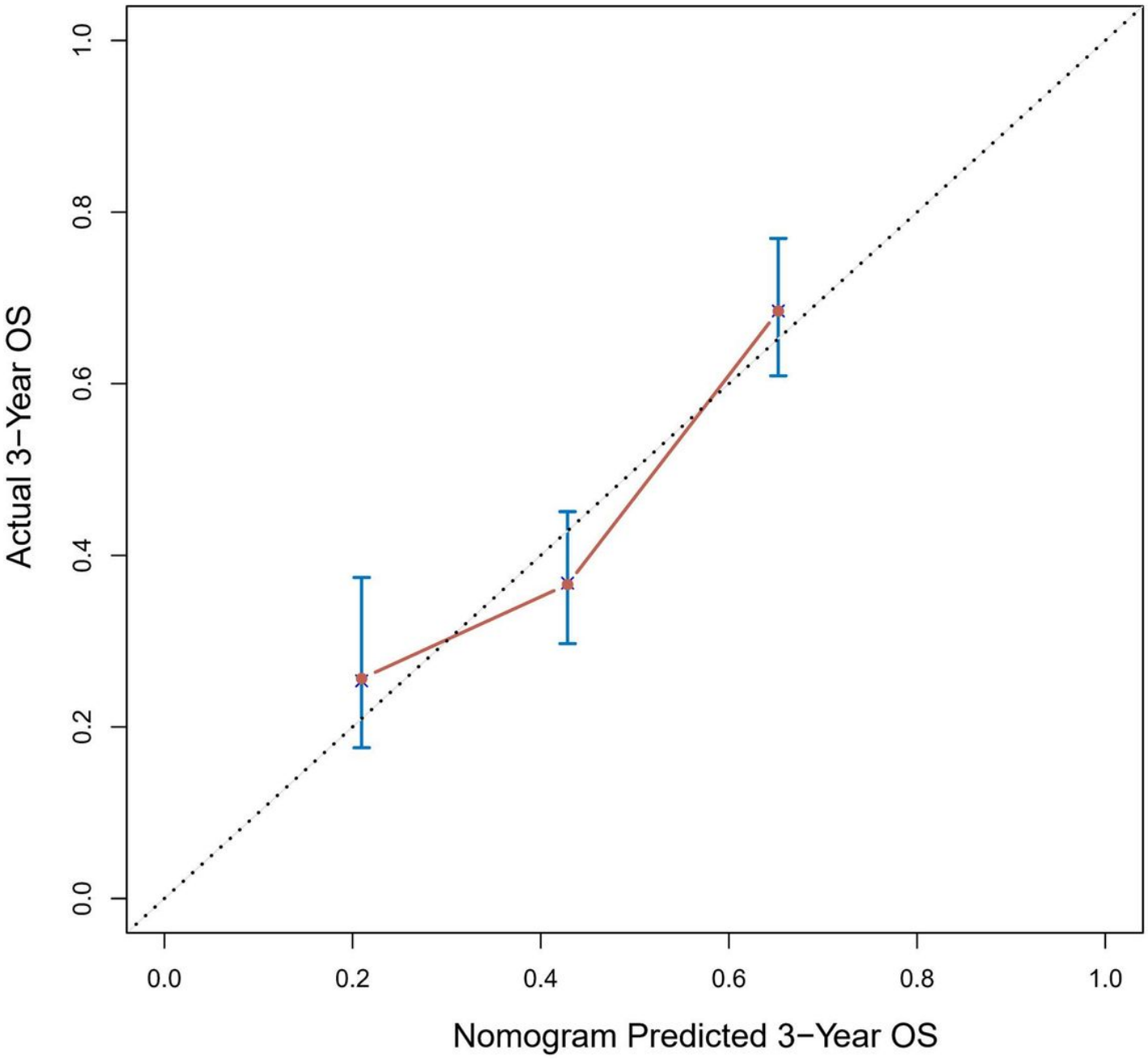

Figure 4

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

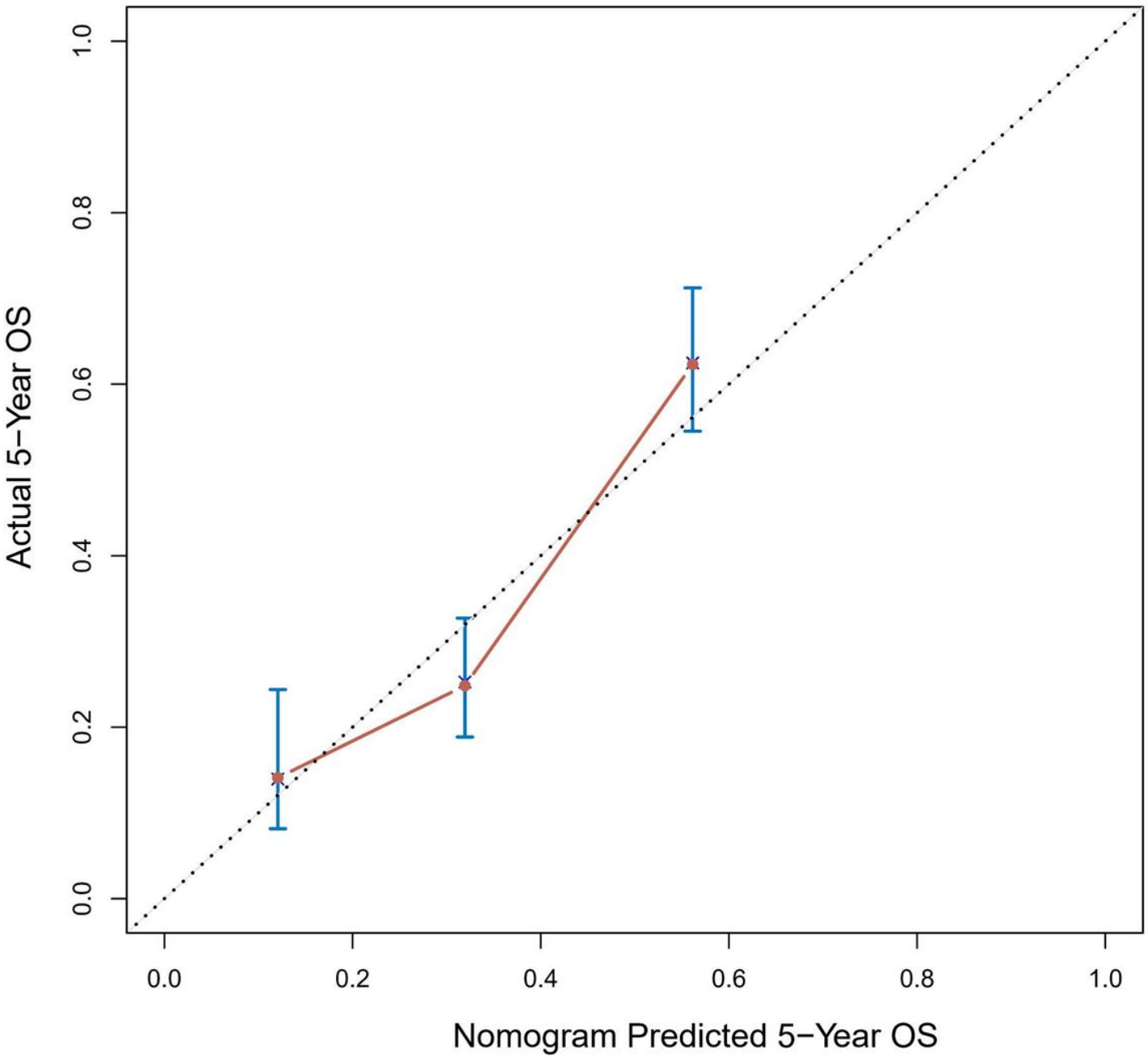

Figure 5

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

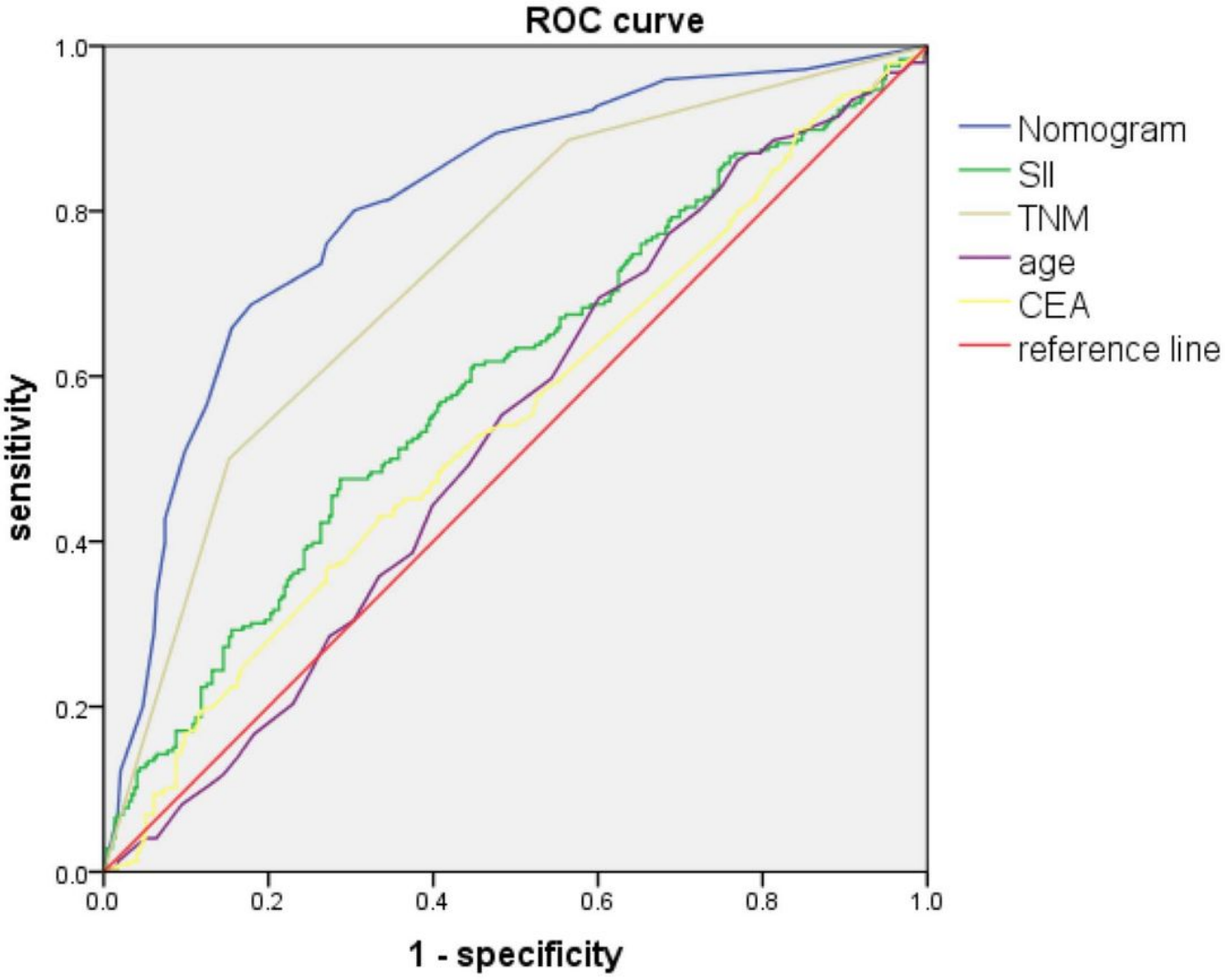

Figure 6

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

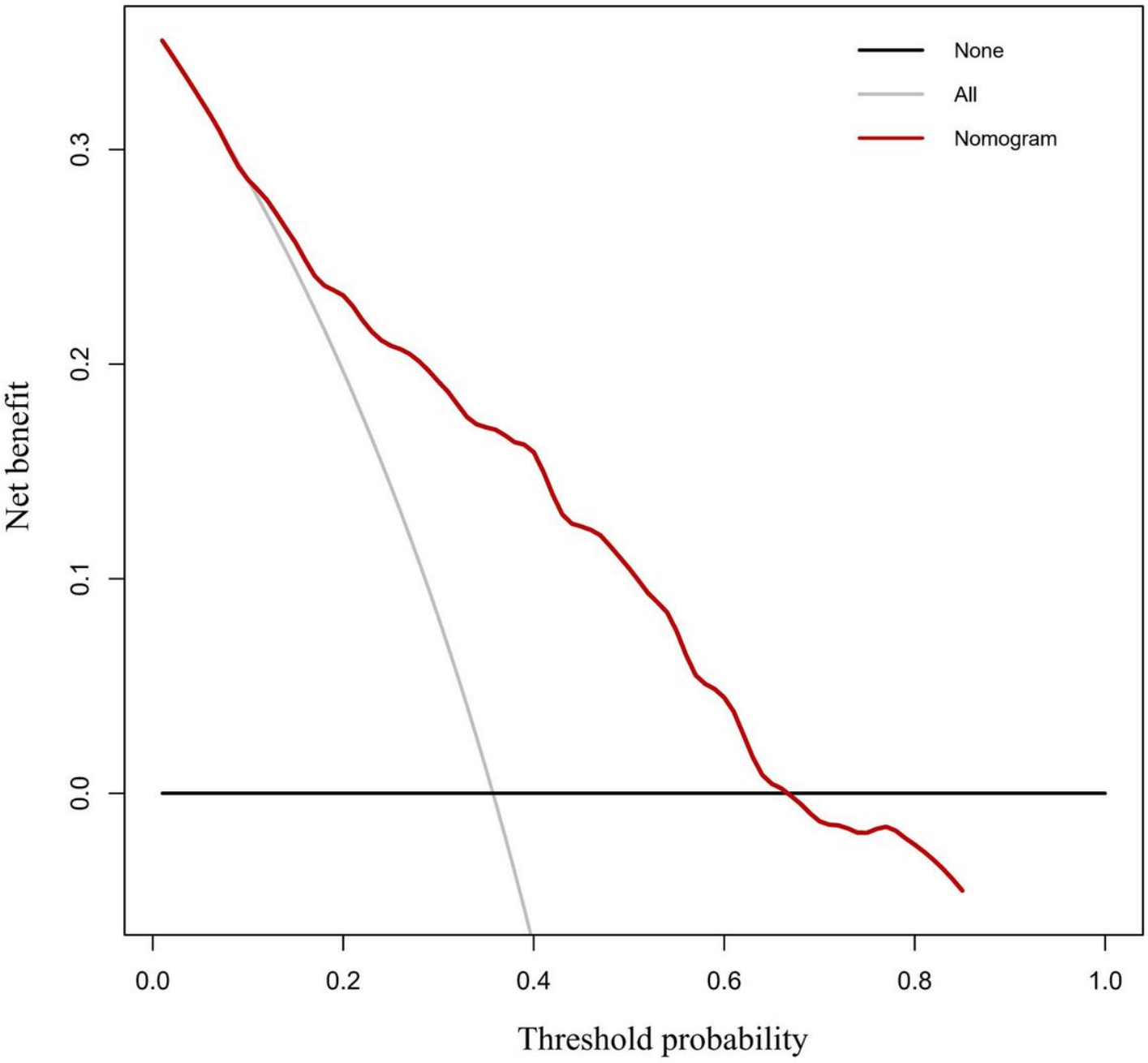

Figure 7

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

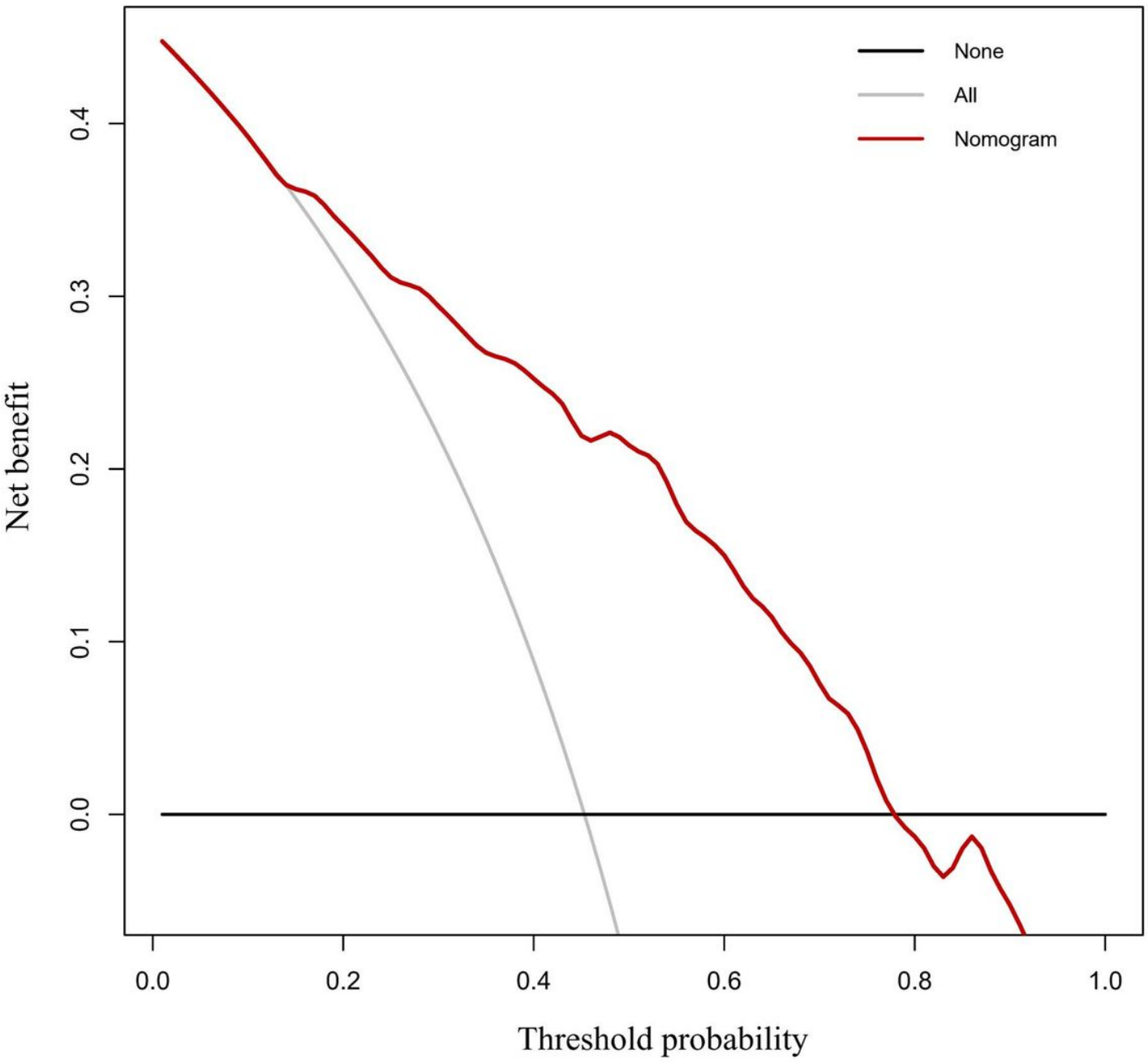

Figure 8

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

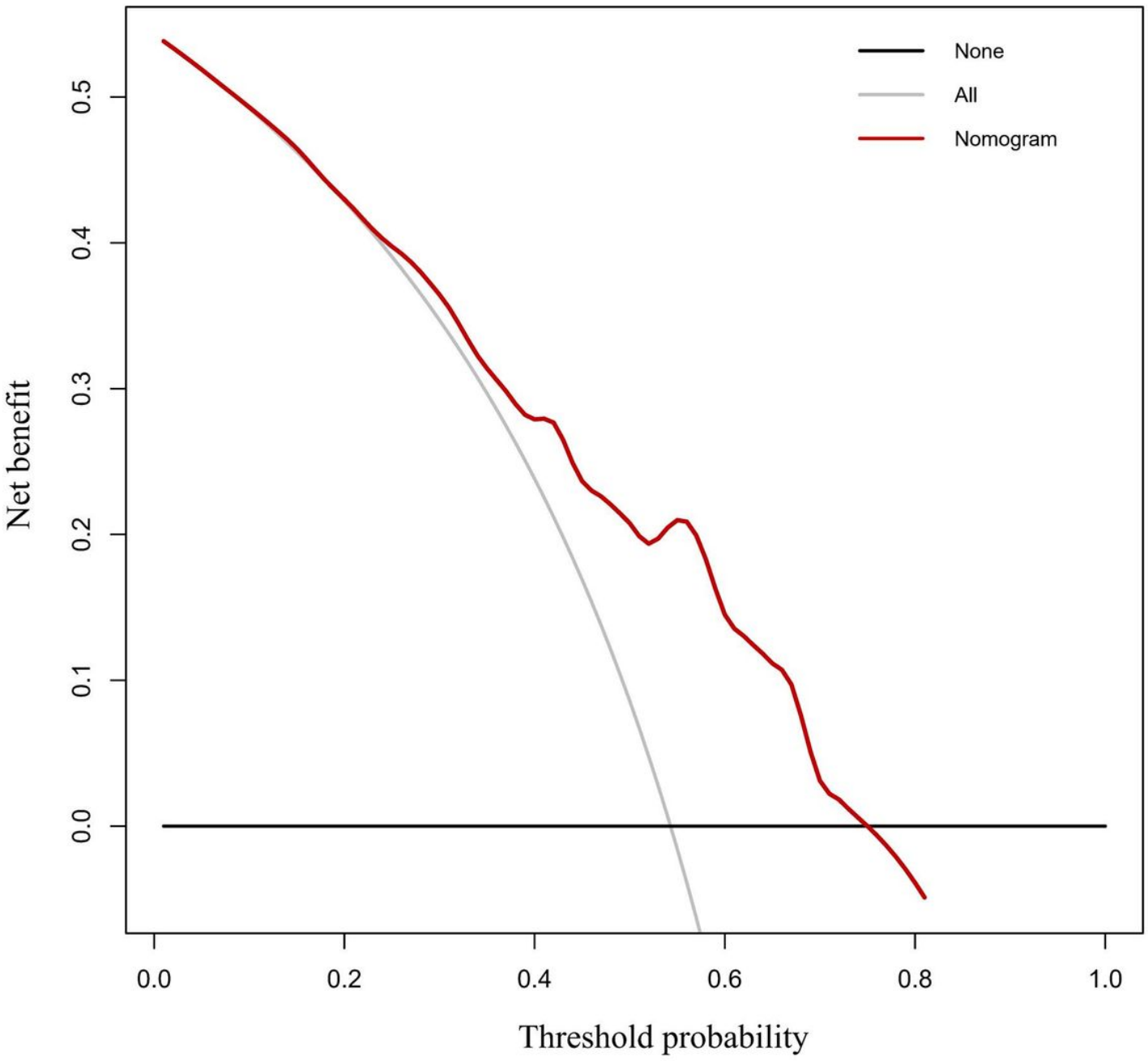

Figure 9

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

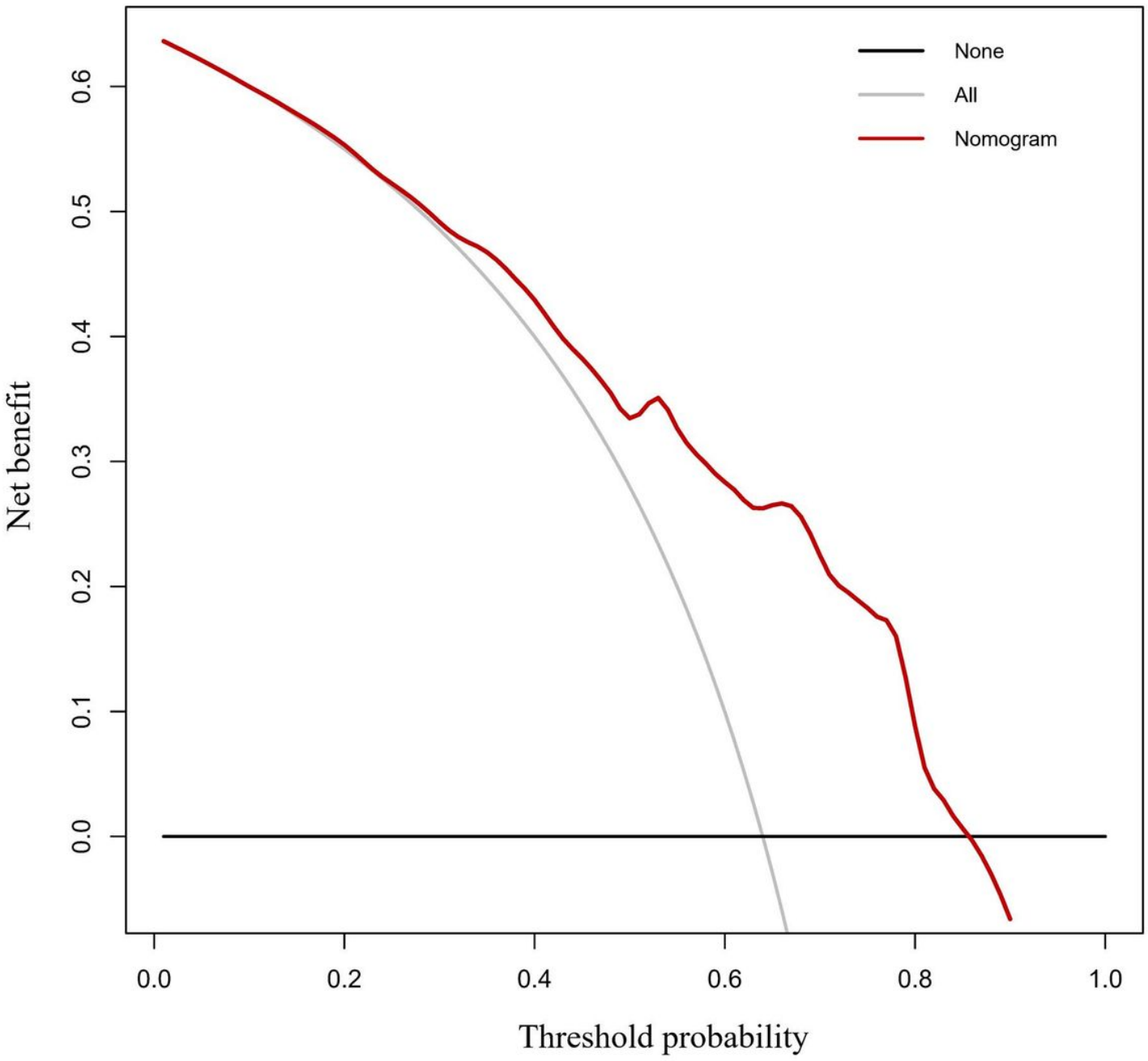

Figure 10

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

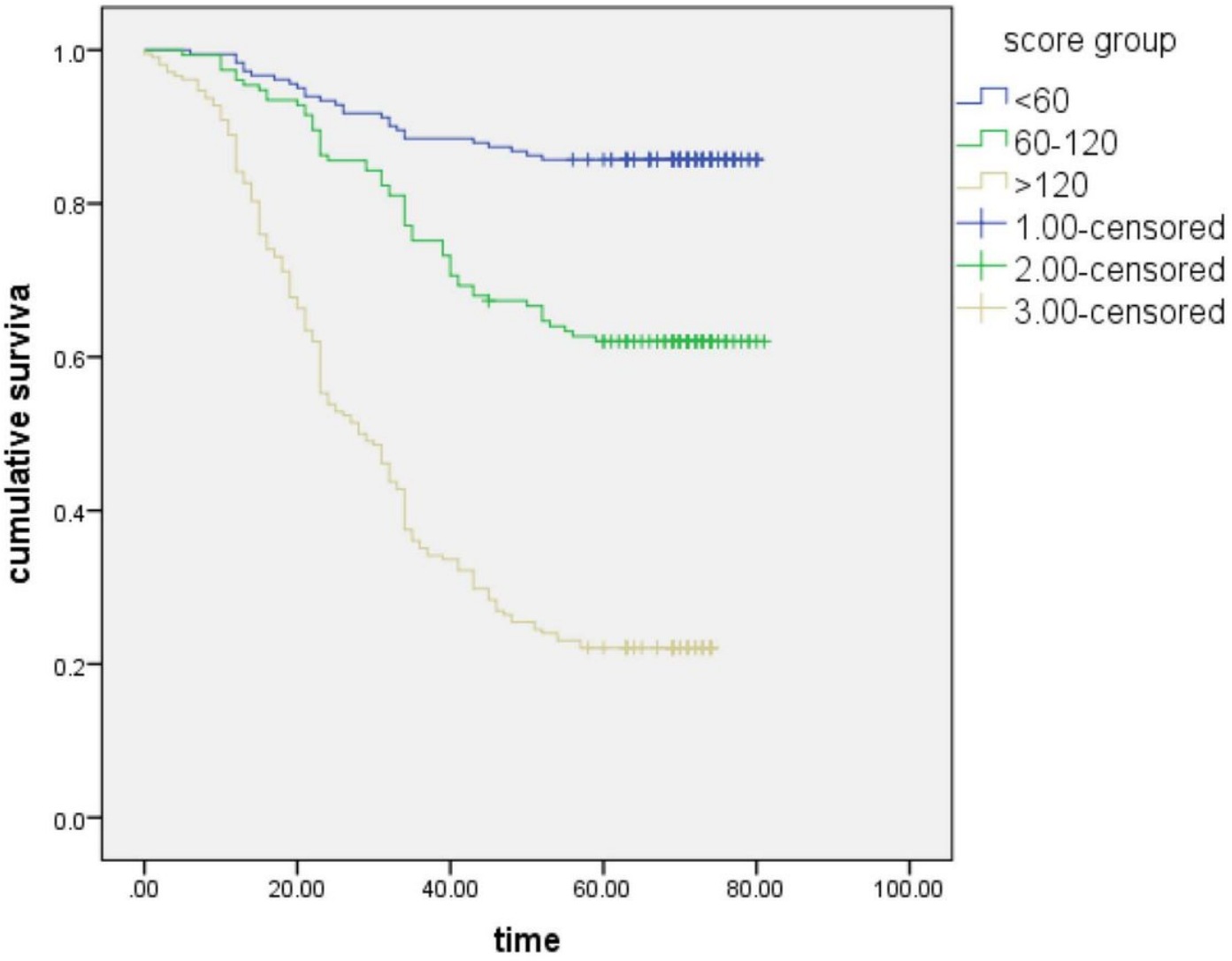

Figure 11

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).