

Nomogram to Predict the Risk of Postoperative Anxiety and Depression in Colorectal Cancer Patients

Zhiqiao Hu

the Second Affiliated Hospital of Harbin Medical University

Hao Zhang

the Second Affiliated Hospital of Harbin Medical University

Jiaqi Wang

the Second Affiliated Hospital of Harbin Medical University

Huan Xiong

the Second Affiliated Hospital of Harbin Medical University

Yunxiao Liu

the Second Affiliated Hospital of Harbin Medical University

Yihao Zhu

the Second Affiliated Hospital of Harbin Medical University

Zewen Chang

the Second Affiliated Hospital of Harbin Medical University

Hanqing Hu

the Second Affiliated Hospital of Harbin Medical University

Qingchao Tang (✉ 13945052628@qq.com)

the Second Affiliated Hospital of Harbin Medical University

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Abstract

To develop and validate the risk nomogram to predict the likelihood of postoperative anxiety and depression in colorectal cancer (CRC) patients. A total of 602 CRC patients from the Second Affiliated Hospital of Harbin Medical University were included in the study and divided into development set and validation set with the 2: 1 ratio randomly. Logistic regression model was used to determine independent factors contributing to postoperative anxiety and depression, which were subsequently applied to build the nomogram for predicting postoperative anxiety and depression. The performance of the risk nomogram was appraised by the area under the receiver operating curve (AUC), calibration curves and decision curve analyses (DCA). Gender, marital status, income, TNM stage and ECOG score were significant indicators for postoperative anxiety and depression. The AUCs of the development and validation sets were 0.696 and 0.677 for postoperative anxiety nomogram, and 0.710 and 0.699 for postoperative depression nomogram. Additionally, calibration curves and decision curve analyses also determined the reliable clinical importance of the proposed nomogram. The current study constructed the risk nomogram for postoperative anxiety and depression, and could help clinicians perform targeted psychological intervention for high-risk patients.

Introduction

Globally, colorectal cancer (CRC) poses a major public health challenge because of its high incidence and mortality rate¹. With the consistent modifies and advances of therapeutic modality, the prognosis of CRC patients has notably improved during the past decade²⁻⁴. However, mental distress secondary to the treatment seems to be an emerging challenge for us^{5,6}.

According to previous studies, the prevalence of anxiety and depression among CRC patients ranged from 1.0% - 47.2% and 1.6-57.0%⁷, respectively. Postoperative psychological disorder in the form of depression and anxiety is a relatively common phenomenon in current clinical practice, which might reduce patient compliance with subsequent treatment, decrease the quality of life and result in a poor immune status. What's more, patients suffering from psychological problems are even associated with unfavorable long-term survival⁸. The prevalence of postoperative psychological disorder in CRC patients has generally been influenced by clinical and demographic factors such as gender, marital status, income, tumor stage and physical performance⁹⁻¹². Given that heterogeneous characteristics of different patients, how likely a patient could suffer from postoperative anxiety and depression is a crucial question for the regular monitoring and screening of postoperative anxiety and depression in CRC patients, which is of eminent significance for clinicians to perform prompt intervention.

Recently, nomogram is widely applied as a new method which could quantify the risk of an outcome event by illustrating and incorporating important factors precisely^{13,14}. However, targeted nomogram for postoperative psychological disorder is still lacking. Therefore, the aim of this study was to develop and validate a nomogram to predict the likelihood of postoperative anxiety and depression in CRC patients and subsequently help clinicians perform targeted psychological intervention for high-risk patients.

Results

Patient characteristics

A total of 602 CRC patients were included in the study. After random division, 401 patients (anxiety rate = 36.2, depression rate = 35.7%) were in the development set and 201 patients (anxiety rate = 41.3%, depression rate = 36.8%) were in the validation set. No significant difference could be found in age ($P = 0.604$), gender ($P = 0.403$), marital status ($P = 0.662$), income ($P = 0.467$), education ($P = 0.534$), TNM stage ($P = 0.294$) and ECOG score ($P = 0.922$) between the two sets (Table 1).

Table 1
 Characteristics of patients in the development and validation sets

Variable	Development set	Validation set	P
Gender			
Male	212 (52.9)	99 (49.3)	0.403
Female	189 (47.1)	102 (50.7)	
Age (years)			
< 65	260 (64.8)	126 (62.7)	0.604
≥ 65	141 (35.2)	75 (37.3)	
Marital status			
Married	331 (82.5)	163 (81.1)	0.662
Single	70 (17.5)	38 (18.9)	
Income			
Satisfied	233 (58.1)	123 (61.2)	0.467
Unsatisfied	168 (41.9)	78 (38.8)	
Education			
Middle school or less	291 (72.6)	141 (70.1)	0.534
Higher than middle school	110 (27.4)	60 (29.9)	
TNM stage			
I/II	256 (63.8)	137 (68.2)	0.294
III	145 (36.2)	64 (31.8)	
ECOG score			
0–1	255 (63.6)	127 (63.2)	0.922
2–4	146 (36.4)	74 (36.8)	
Anxiety rate	36.2	41.3	0.221
Depression rate	35.7	36.8	0.781
HADS			
Anxiety ^a	6.71 ± 4.38	6.67 ± 4.26	0.917

^a Mean ± SD

Variable	Development set	Validation set	P
Depression ^a	6.03 ± 4.23	6.14 ± 4.17	0.748
^a Mean ± SD			

Risk factors related to postoperative anxiety in the development set

Univariate analysis revealed the association between each factor and postoperative anxiety, including age (P = 0.516), gender (P = 0.027), marital status (P = 0.000), income (P = 0.024), education (P = 0.857), TNM stage (P = 0.000) and ECOG score (P = 0.004). Multivariate analysis indicated that gender (OR = 2.176, 95%CI = 1.367–3.463 for female, P = 0.001; using male as the reference), marital status (OR = 3.302, 95%CI = 1.854–5.880 for single, P = 0.000, using married as the reference), income (OR = 1.782, 95%CI = 1.116–2.844 for single, P = 0.016 for unsatisfied, using satisfied as the reference), TNM stage (OR = 2.131, 95%CI = 1.351–3.362 for stage III, P = 0.001, using stage I/II as the reference) and ECOG score (OR = 2.493, 95%CI = 1.548–4.013 for 2–4 points, P = 0.000, using 0–1 point as the reference) were the statistically significant predictors related to postoperative anxiety (Table 2).

Table 2
Logistic regression analysis for postoperative anxiety in the development set

Variable	Univariate analyses		Multivariate analyses	
	HR [95%CI]	P	HR [95%CI]	P
Gender				
Male	1		1	
Female	1.589 [1.054–2.394]	0.027	2.176 [1.367–3.463]	0.001
Age (years)				
< 65	1			
≥ 65	0.867 [0.564–1.333]	0.516		
Marital status				
Married	1		1	
Single	2.870 [1.694–4.861]	0.000	3.302 [1.854–5.880]	0.000
Income				
Satisfied	1		1	
Unsatisfied	1.625 [1.066–2.476]	0.024	1.782 [1.116–2.844]	0.016
Education				
Middle school or less	1			
Higher than middle school	0.959 [0.607–1.515]	0.857		
TNM stage				
I/II	1		1	
III	2.150 [1.410–3.279]	0.000	2.131 [1.351–3.362]	0.001
ECOG score				
0–1	1		1	
2–4	1.872 [1.229–2.851]	0.004	2.493 [1.548–4.013]	0.000

Risk factors related to postoperative depression in the development set

Similarly, univariate analysis revealed the association between each factor and postoperative depression, including age ($P = 0.350$), gender ($P = 0.002$), marital status ($P = 0.000$), income ($P = 0.037$), education ($P = 0.857$), TNM stage ($P = 0.004$) and ECOG score ($P = 0.002$). Multivariate analysis indicated that gender

(OR = 2.667, 95%CI = 1.665–4.273 for female, P = 0.000; using male as the reference), marital status (OR = 3.40, 95%CI = 1.900-6.085 for single, P = 0.000, using married as the reference), income (OR = 1.671, 95%CI = 1.045–2.672 for single, P = 0.032 for unsatisfied, using satisfied as the reference), TNM stage (OR = 1.854, 95%CI = 1.171–2.935 for stage III, P = 0.008, using stage I/II as the reference) and ECOG score (OR = 2.702, 95%CI = 1.671–4.369 for 2–4 points, P = 0.000, using 0–1 point as the reference) were independent indicators for postoperative depression (Table 3).

Table 3
Logistic regression analysis for postoperative depression in the development set

Variable	Univariate analyses		Multivariate analyses	
	HR [95%CI]	P	HR [95%CI]	P
Gender				
Male	1		1	
Female	1.897 [1.254–2.869]	0.002	2.667 [1.665–4.273]	0.000
Age (years)				
< 65	1			
≥ 65	0.814 [0.528–1.254]	0.350		
Marital status				
Married	1		1	
Single	2.746 [1.623–4.645]	0.000	3.400 [1.900-6.085]	0.000
Income				
Satisfied	1		1	
Unsatisfied	1.568 [1.028–2.391]	0.037	1.671 [1.045–2.672]	0.032
Education				
Middle school or less	1			
Higher than middle school	1.043 [0.661–1.647]	0.857		
TNM stage				
I/II	1		1	
III	1.854 [1.216–2.827]	0.004	1.854 [1.171–2.935]	0.008
ECOG score				
0–1	1		1	
2–4	1.942 [1.273–2.962]	0.002	2.702 [1.671–4.369]	0.000

Nomogram for postoperative anxiety and depression

Subsequently, gender, marital status, income, TNM stage and ECOG score were used to construct the risk nomogram for postoperative anxiety (Fig. 1A) and depression (Fig. 1B).

In terms of nomogram for postoperative anxiety, the AUCs of the development and validation sets were 0.696 (95%CI = 0.640–0.751) and 0.677 (95%CI = 0.598–0.756), respectively (Fig. 2A). The calibration curves also demonstrated good consistencies between predicted and observed anxiety rates in development and validation sets (Fig. 3A). Additionally, DCA also indicated that the proposed nomogram owned excellent net benefits in guiding clinical decision in both sets (Fig. 4A).

Regarding to nomogram for postoperative depression, the AUCs of the development and validation sets were 0.710 (95%CI = 0.655–0.765) and 0.699 (95%CI = 0.621–0.777), respectively (Fig. 2B). Moreover, the same as the nomogram for postoperative anxiety, the calibration curves (Fig. 3B) and DCA (Fig. 4B) also presented satisfy results in both development and validation sets.

Discussion

In the increasing population of CRC patients undergoing radical surgery, postoperative emotional trauma could be a phenomenon desired to be taken attention. As an emerging research area, substantial indicators linked with depression- and anxiety-related disorders and symptoms are still inconsistent and limited in cancer-related studies. To our knowledge, this was the first study to develop and validate risk nomogram to determine the risk of postoperative anxious and depression in CRC patients.

The present study showed that anxiety and depression were associated with gender (female), which was consistent with a large sample study that included 10153 cancer patients and showed that the prevalence of anxiety and depression was higher in female cancer patients in all cancer types⁹. Another study also performed a factor analysis of anxiety, depression and gender and revealed that women were more prone to depression than men ($P = 0.008$) and gender was an independent influence on anxiety ($P < 0.001$)¹⁹. The potential reason accounting for this phenomenon might be that women tend to be less tolerant of malignant events than men and therefore more likely to develop psychological problems after surgical trauma.

Anxiety, depression and marital status (single, divorced and widowed) were also correlated in this paper. Single, divorced or widowed patients with malignancy may lack emotional support because the patients' main emotional confidant is their spouse, and spouseless patients lack emotional support and catharsis, and have insufficient ability to cope with stress, leading to the increased susceptibility to anxiety and depression¹⁰. This study showed that income was also associated with anxiety and depression. Similarly, one previous research conducted a univariate analysis of correlates of depression among colorectal cancer survivors who underwent resection, and income less than \$30,000 was positively associated with depression screening (OR 2.20, 1.57–3.08 95 % CI, $P < 0.001$), and multivariate analysis

showed that low income was an independent influence on depression (OR 1.50, 1.02–2.22 95 % CI, P = 0.04)¹¹. A good economic status is a guarantee to meet the medical needs of patients. Patients with colorectal malignancies require a high cost of treatment, and patients with lower income levels need to bear a lot of financial pressure during the treatment process, which increases the psychological burden of patients, thus leading to anxiety and depression.

Besides, TNM staging was a predictor of anxiety and depression in the research. Simon et al found that patients with advanced pathological staging were more likely to be anxious (P < 0.01) and depressed (P < 0.001), and they also analyzed the relationship between social support and quality of life and staging, and patients with advanced staging had poorer social support (P < 0.01) and quality of life (P < 0.01), which may also contribute to the patients' anxiety and depression¹². The advanced pathological stage indicates a more malignant tumor, which can bring more serious physical symptoms to patients, and these patients also often need follow-up treatment, which increases the financial burden and psychological stress, putting patients at increased risk of postoperative anxiety and depression. The current study also revealed that preoperative performance status is a predictor of anxiety and depression. Patients with poor performance tend to be anxious and depressed, which is consistent with the results of other investigations²⁰.

Therefore, gender, marital status, income, TNM stage and ECOG score were applied to build the risk nomogram for. The AUCs of the development and validation sets were 0.696 and 0.677 for postoperative anxiety nomogram, and 0.710 and 0.699 for postoperative depression nomogram. What's more, calibration curves and decision curve analyses also determined the reliable clinical significance of the proposed nomogram.

Still, the authors acknowledged several study limitations. Firstly, the results of the current study only reflect the characteristics of our department, but not the whole cohort, meaning that the predictive model needs to be validated by more external works. Secondly, as a retrospective study, it was inevitable to have selective bias and needed to be verified by some prospective clinical studies. Thirdly, we only assess the postoperative anxiety and depression level at the follow-up 2 weeks after discharge, but failed to monitor a dynamic change for these patients.

Conclusion

This paper revealed that gender, marital status, income, TNM stage and ECOG score were significant indicators for postoperative anxiety and depression. Moreover, the risk nomogram based on these five factors could accurately predict the likelihood of anxiety and depression after surgery in CRC patients, which could subsequently help clinicians perform targeted psychological intervention for high-risk patients.

Methods

Study population

Colorectal cancer patients from the the Second Hospital of Harbin Medical University between January 2013 and June 2018 were enrolled in the current research. Inclusion criteria included: (1) radical resection was the first course of treatment; (2) aged ≥ 18 years; (3) patients diagnosed as stage I-III colorectal cancer pathologically; (4) colorectal cancer was the only malignancy and (5) patients realizing the severity of their disease. Exclusion criteria included: (1) patients with unknown data and (2) patients with psychological or mental disease history. All patients are informed upon admission that all of their treatment-related information and the information we prospectively collect will be retained and may be used for scientific research. However, the information we collect will be kept strictly confidential and will not have any impact on the optimal treatment the patient receives. Patients provide informed consent for this. The Ethics Committee of the Second Hospital of Harbin Medical University agreed and approved this study. All procedures in this study conformed to the ethical standards of our institution and were in accordance with the Declaration of Helsinki.

Covariates

According to previous studies, we used a small number of pre-established candidate indicators in order to avoid selection bias and overfitting⁹⁻¹². Additionally, all variables in the model should be readily available in current practice attempting to improve its applicability. Therefore, sociodemographic features (marital status, income and education), health performance status, tumor stage and patient-related factors (gender and age) were reviewed. In this study, all cases were uniformly re-staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system based on the pathological examination of surgical specimens. The Eastern Cooperative Oncology Group Scale (ECOG) was applied to assess the patient pre-treatment performance status¹⁵.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was utilized to evaluate self-reported status of anxiety and depression¹⁶. The HADS includes 14 items (7 items for anxiety symptom and 7 items for depression symptom). The score of each item ranged from 0 to 3 points and the total score ranged from 0 to 21 points for anxiety subscale and depression subscale. The higher points suggested the worse anxiety and depression status. According to previous studies, patients with 8–21 points were considered to be suffering from anxiety and depression¹⁶⁻¹⁸. The postoperative questionnaire was conducted by interview or phone at the follow-up 2 weeks after discharge.

Statistical analysis

All patients were divided into development set and validation set with the 2: 1 ratio randomly. Logistic regression model was used to determine independent indicators contributing to postoperative anxiety and depression. Odds ratio (OR) with 95% confidence interval (CI) were posed as results. Factors with $P < 0.05$ in the multivariate analysis were subsequently chosen to build the risk nomogram. The maximum point of each indicator was set as 100. The performance of nomogram was appraised by calibration curves,

the area under the receiver operating curve (AUC) and decision curve analyses (DCA). $P < 0.05$ (two-sided) was defined as statistically significant. All statistical analyses were performed using R version 3.6.1 software.

Declarations

Acknowledgments

None.

Conflicts of interest

None declared.

Data availability

The data sets used and analyzed during the current study are available

Funding/Support

None

Financial Disclosure

None

Disclaimer

Zhiqiao Hu, Hao Zhang, Jiaqi Wang, Huan Xiong, Yunxiao Liu, Yihao Zhu, Zewen Chang, Hanqing Hu, Qingchao Tang declare that there is no conflicts of interest to disclose.

Ethical statements

All patients are informed upon admission that all of their treatment-related information and the information we prospectively collect will be retained and may be used for scientific research. However, the information we collect will be kept strictly confidential and will not have any impact on the optimal treatment the patient receives. Patients provide informed consent for this. The Ethics Committee of the Second Hospital of Harbin Medical University agreed and approved this study. All procedures in this study conformed to the ethical standards of our institution and were in accordance with the Declaration of Helsinki.

Author Contributions

Z.H. and H.Z. conceived and designed the study. J.W., H.X., Y.L., Y.Z., Z.C. reviewed medical records and collected data. Z.H. and H.Z. analyzed data and wrote the first draft. Z.H., H.Z., H.H., and Q.T. contributed to

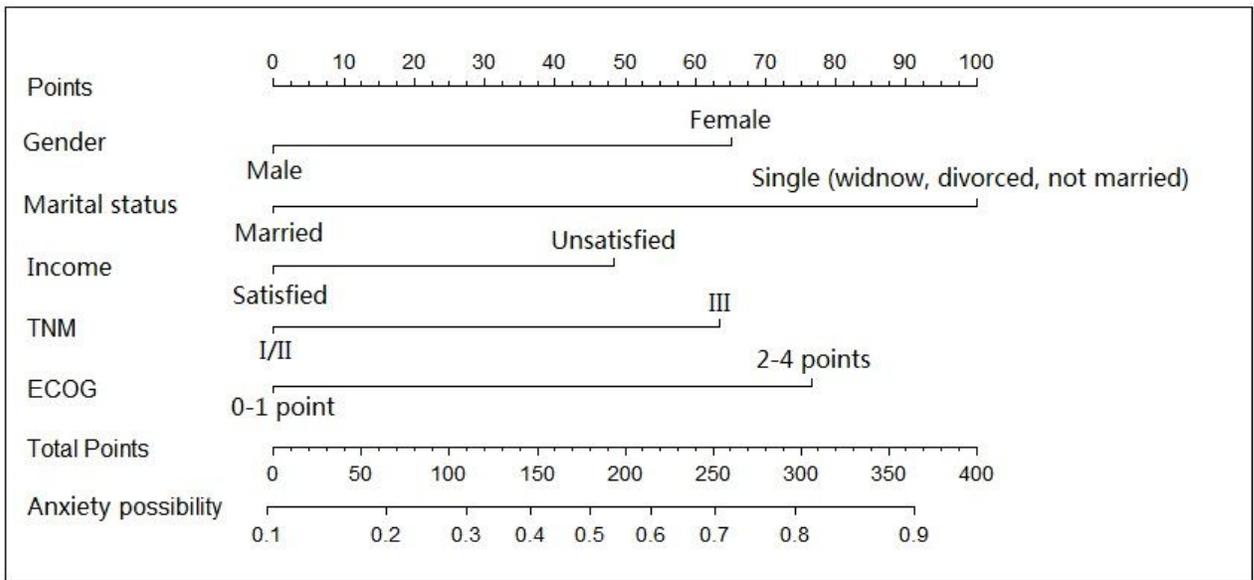
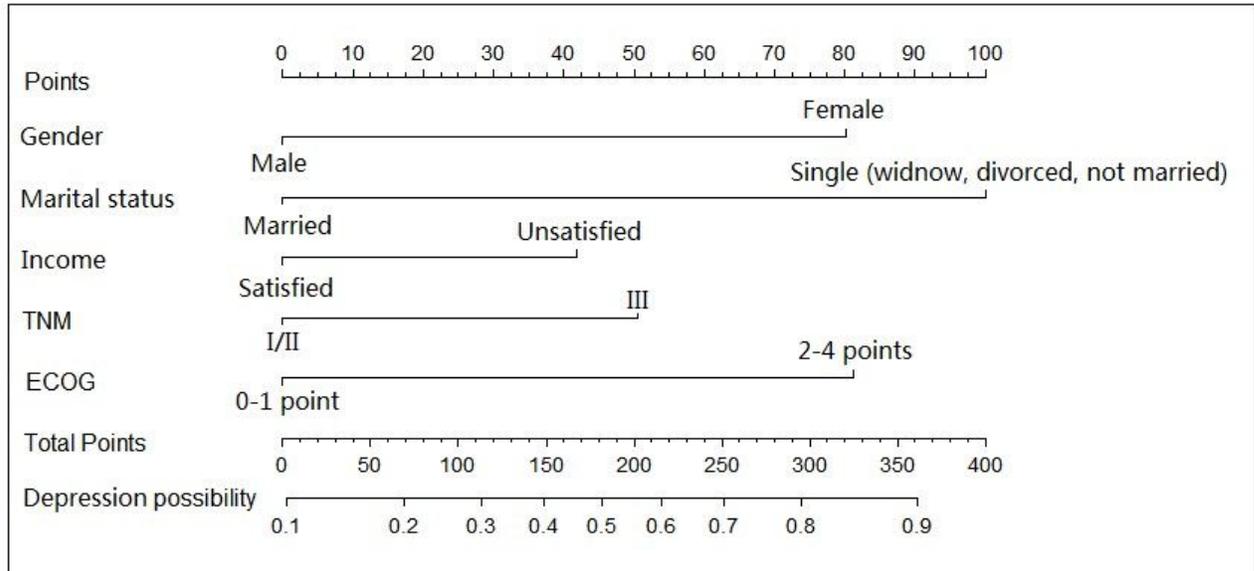
revise the draf. All authors read and approved the fnal version of the manuscript.

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Figures

A**B****Figure 1**

(A) Nomogram for postoperative anxiety. (B) Nomogram for postoperative depression.

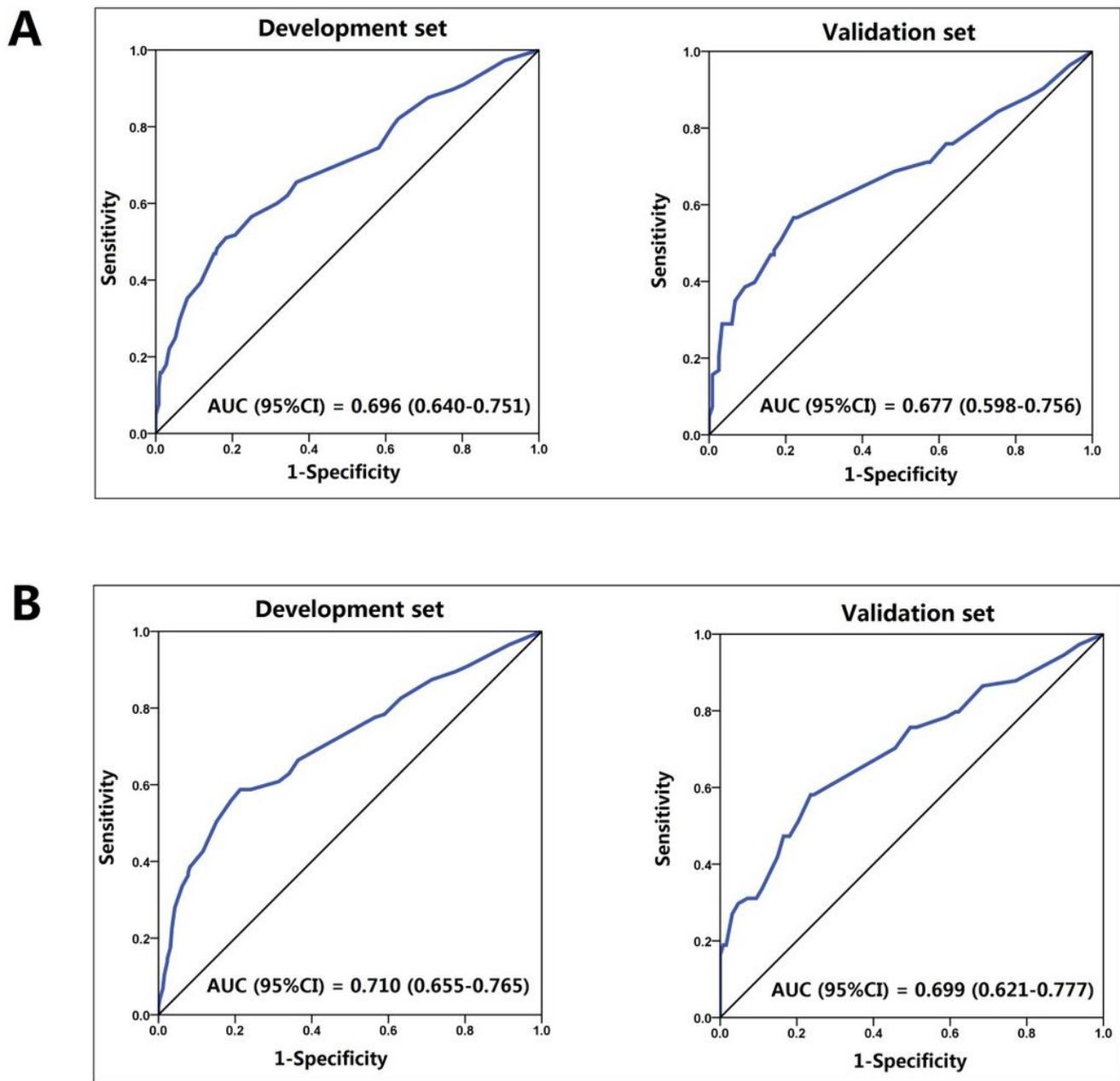


Figure 2

(A) ROC curves of the nomogram for postoperative anxiety in development and validation sets. (B) ROC curves of the nomogram for postoperative depression in development and validation sets.

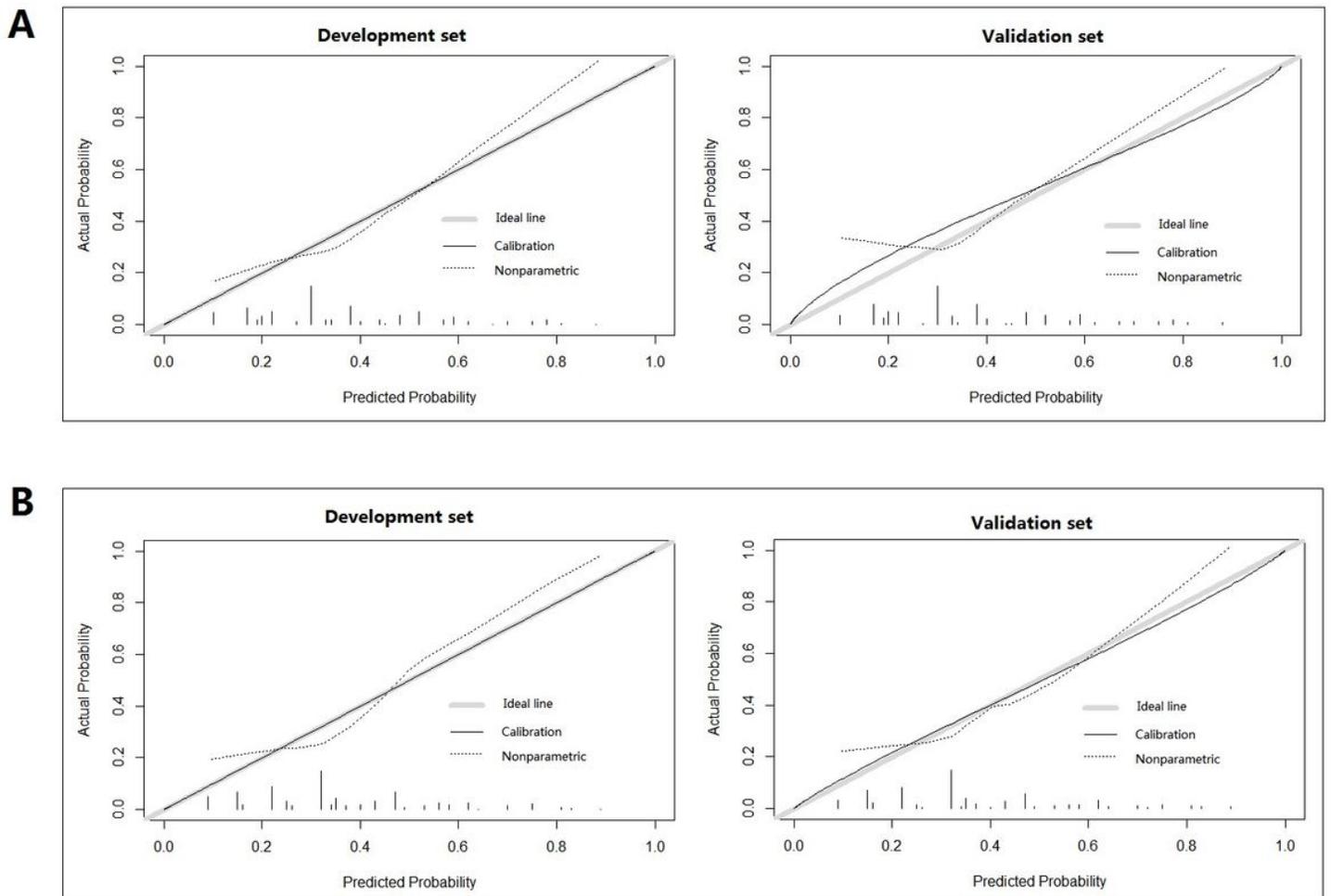


Figure 3

(A) Calibration curves of the nomogram for postoperative anxiety in development and validation sets. (B) Calibration curves of the nomogram for postoperative depression in development and validation sets.

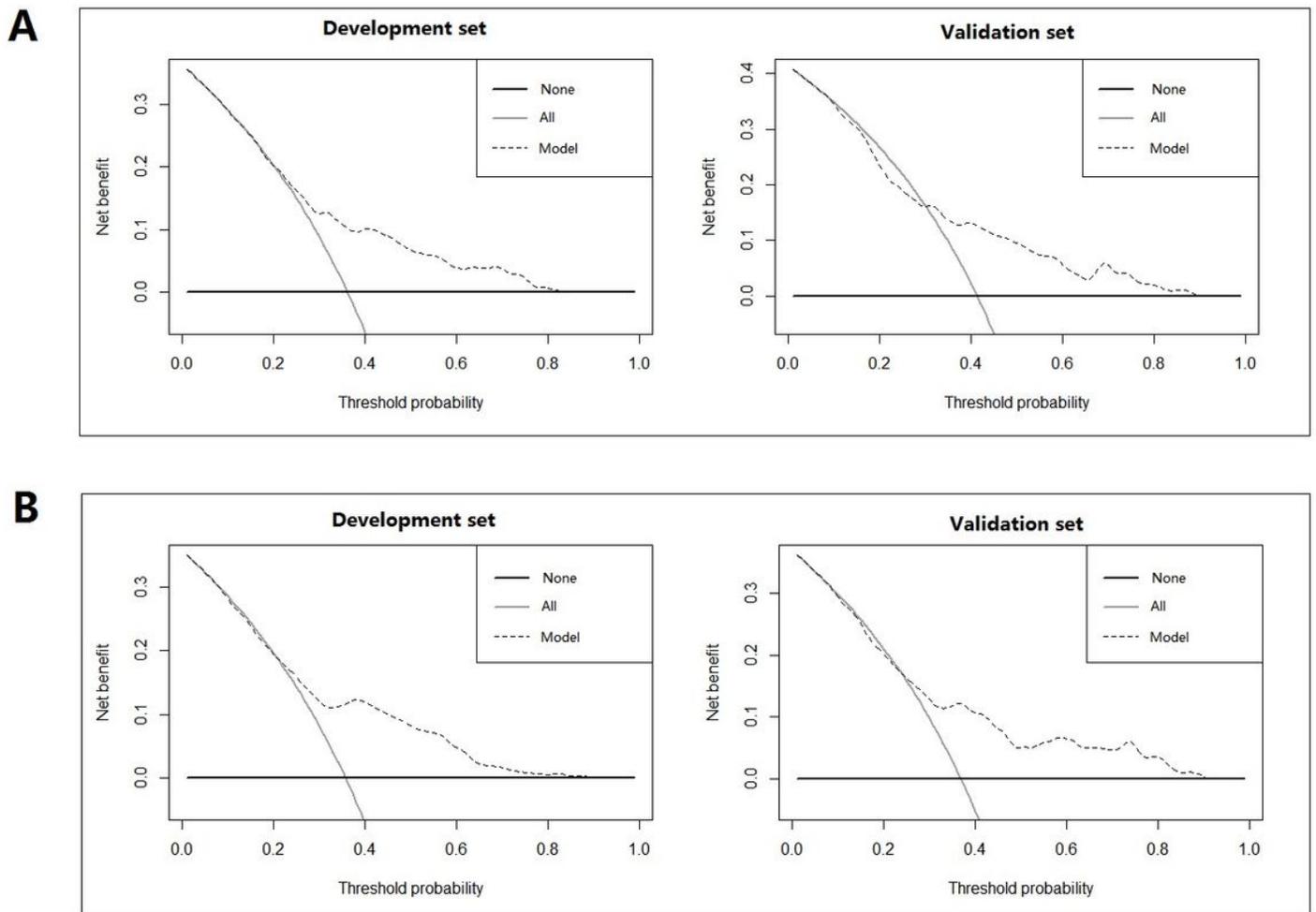


Figure 4

(A) Decision curve analyses the nomogram for postoperative anxiety in development and validation sets.
 (B) Decision curve analyses the nomogram for postoperative depression in development and validation sets.