A practical nomogram for predicting cancer-specific survival in patients with clear-cell renal cell carcinoma

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Abstract

Background: It has limitations in predicting patient survival to use of the traditional American Joint Committee on Cancer (AJCC) staging system alone.

Objectives: We aimed to establish and evaluate a comprehensive prognostic nomogram and compare its prognostic value with the AJCC staging system in adults diagnosed with ccRCC.

Patients and Methods: We used the SEER database to identify 24477 cases of ccRCC between 2010 and 2015. The patients were randomly divided into two groups. In the development cohort, we used multivariate Cox proportional-hazards analyses to select significant variables, and used R software to establish a nomogram for predicting the 3-year and 5-year survival rates of ccRCC patients. In the development and validation cohorts, we compared our survival model with the AJCC prognosis model to evaluate the performance of the nomogram by calculating the concordance index (C-index), area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI), and performing calibration plotting and decision curve analyses (DCAs).

Results: Eleven identified independent prognostic factors were used to establish the nomogram. Age at diagnosis, being unmarried, higher grades, larger tumor size, higher AJCC stage, lymph node metastases, bone metastases, liver metastases, lung metastases, radiotherapy, and no surgery were risk factors for the survival of ccRCC. The C-index, AUC, NRI, IDI, and calibration plots demonstrated the good performance of the nomogram compared to the AJCC staging system. Moreover, the 3-year and 5-year DCA curves showed that the nomogram yielded net benefits that were greater than the traditional AJCC staging system.

Conclusion: This study is the first to indicate that married status is an important prognostic parameter in ccRCC. Our results also demonstrate that the developed nomogram can predict survival more accurately than the AJCC staging system alone. The prognostic factors were easily obtained.

Introduction

Renal carcinoma accounts for around 3% of all adult malignancies[1], and represents the tenth most common cancer in females and the sixth most common in males[2]. It caused an estimated 175,098 deaths (1.8% of the total cancer deaths) ever year [3]. Most (80–85%) renal carcinomas are renal cell carcinoma (RCC), and they constitute the third most commonly diagnosed urogenital malignancy[4]. Clear-cell renal cell carcinoma (ccRCC) patients constitute 80–90% of all RCC patients[5]. ccRCC is a potentially aggressive neoplasm reported to have an overall 5-year progression-free survival rate of 70% and a cancer-specific mortality rate of 24%[6]. Establishing an effective prediction model can help clinicians to make clinical decisions.

The American Joint Committee on Cancer (AJCC) staging system[7] is a classification system for describing the extent of disease progression in cancer patients. It is based on the TNM stage that is generally believed the most powerful prognostic indicator for RCC, and it remains the most-used tool to classify RCC patients in clinical practice. However, research has shown that multivariate Cox proportional-hazards regression analyses including pathological and multiple clinical covariates were more accurate than the TNM stage in predicting patient survival[8]. Several pathology-based systems for predicting clinical outcomes, including those measuring gene expression, have been established to predict the prognosis of patients with RCC, such as the UISS (University of California Los Angeles integrated staging system), Mayo Clinic SSIGN (stage, size, grade, and necrosis) score, TNM stage, and TCGA (The Cancer Genome Atlas)[8]. However, these prediction models are based on difficult-to-obtain genetic data, have a low prediction accuracy, or lack systematic evaluations of the models on which they are based. Moreover, these are used to predict prognosis of patients with RCC rather than ccRCC.

We therefore aimed to establish a comprehensive prognostic nomogram and assumed it has better performance than the AJCC classification in patients diagnosed with ccRCC.

Methods

Patients

Information about all of the included patients was retrieved from the latest version of the Surveillance, Epidemiology, and End Results (SEER) database. This study was approved by the Ethics Committee of the Ninth Hospital of Xi'an. The inclusion criteria were as follows:

1. Renal carcinoma patients with an ICD-O-3/WHO 2008 histological type code of 8312/3 (ccRCC).
2. Positive diagnostic confirmation in histology.
3. Categorized as either alive or with thyroid carcinoma as the cause of death.
4. Age at diagnosis of between 19 and 85 years.

The exclusion criteria were as follows:

1. Unknown age, race, sex, marital status, insurance recode, tumor grade, tumor size, tumor site, AJCC stage, Mayo Clinic stage, surgery status, radiation status, chemotherapy status, lymph node metastases, bone metastases, brain metastases, liver metastases, or lung metastases, or incomplete SEER cause-specific death classification.
2. Unknown survival time for a patient who was still alive.
3. Diagnosis made by a death certificate or only an autopsy.

We collected the following data for each patient: age, race, sex, marital status, insurance recode, tumor grade, tumor size, tumor site, AJCC stage, Mayo Clinic stage, surgery status, radiation status, chemotherapy status, lymph node metastases, bone metastases, brain metastases, liver metastases, lung

metastases, and survival time (in months). The SEER cause-specific death classification was the endpoint event. The application of the inclusion and exclusion criteria resulted in the identification of 24477 patients in the SEER database between 2010 and 2015.

Statistical analysis

All variables are presented as median (25th–75th percentile) values because continuous variables such as age and survival time did not conform to a normal distribution. The cox regression model analysis determined the hazard ratios (HRs) and 95% confidence intervals (CIs).

Patients were randomly divided into a validation cohort (30% of patients) and a development cohort (70% of patients). The log-rank test was used to verify any differences between these two cohorts. In the development cohort, significant variables selected by multivariate Cox regression analysis were used as predictors for the nomogram, which was established using R software. Interactions between variables were assessed. The nomogram was internally and externally validated in the development and validation cohorts, respectively.

To compare the discrimination performance of our nomogram with AJCC modeling, we calculated the concordance index (C-index) as described by McKeigue et al. [13] and used the areas under the two receiver operating characteristic (ROC) curves (AUCs) as described by DeLong et al. [14]. We also evaluated the improvement in the predictive discrimination of our nomogram by calculating the relative integrated discrimination improvement (IDI) and the net reclassification improvement (NRI), as described by Pencina et al.[15]. Calibration plots were generated to evaluate the predictive accuracy by comparing the nomogram-predicted and actually observed 3-year and 5-year survival probabilities, as described by Vuk et al. and Cohen et al.[16,17]. We also estimated the clinical usefulness and net benefit of our nomogram using decision curve analysis (DCA), as described by Vickers et al.[18].

All *P* values were two-sided, with $P \leq 0.05$ considered statistically significant. The data were obtained using SEER* Stat version 8.3.5, and the statistical analyses were performed using SPSS version 21.0 and R software.

Results

Clinicopathological characteristics

The 24477 patients were divided into 17133 in the development cohort and 7344 in the validation cohort. The median age was 60 years in both cohorts. Most of the patients in the development and validation cohorts were white (85.6% and 85.6%, respectively), male (62.2% and 61.2%), and married (66.0% and 66.3%). Most of the patients had insurance, a tumor size of ≤70 mm, a tumor of grade Ⅱ, AJCC stage I, and localized Mayo Clinic stage, a tumor that had not metastasized to the lymph nodes, bone, brain, liver, or lung, and had received surgery but not radiation or chemotherapy. The survival time was 27 months in

the development cohort and 28 months in the validation cohort, respectively. The demographics and tumor characteristics of patients are summarized in Table 1.

Independent prognostic factors in the development cohort

The variables of age at diagnosis, marital status, tumor grade, tumor size, AJCC stage, surgery status, radiation status, lymph node metastases, bone metastases, liver metastases, and lung metastases were included in the multivariate Cox regression analyses in the development cohort. These multivariate analyses demonstrated that age at diagnosis (HR=1.0247, $p<0.001$), being unmarried (HR=1.1515 vs married, $p<0.01$), grade II (HR=1.7572 vs grade I, $p<0.01$), grade III (HR=3.3630 vs grade I, $p<0.001$), grade IV (HR=6.6275 vs grade I, $p<0.001$), tumor size >50 mm and <100 mm (HR=1.4638 vs tumor size ≤70 mm, $p<0.001$), tumor size >100 mm (HR=1.8329 vs tumor size ≤70 mm, $p<0.001$), AJCC stage II (HR=2.0843 vs AJCC stage I, $p<0.001$), AJCC stage III (HR=4.3342 vs AJCC stage I, $p<0.001$), AJCC stage IV (HR=10.2613 vs AJCC stage I, $p<0.001$), no surgery (HR=4.9995 vs surgery, $p<0.001$), lymph node metastases (HR=1.7387 vs no lymph node metastases, $p<0.001$), bone metastases (HR=1.7746 vs no bone metastases, $p<0.001$), liver metastases (HR=1.7064 vs no liver metastases, $p<0.001$), and lung metastases (HR=1.6190 vs no lung metastases, $p<0.001$) were risk factors for survival. However, no radiation or any unknown radiation status (HR=0.6534 vs radiation, $p<0.001$) was a protective factor for survival (Table 2).

Prognostic nomogram for 3-year and 5-year survival probabilities

Age at diagnosis, marital status, tumor grade, tumor size, AJCC stage, surgery status, radiation status, lymph node metastases, bone metastases, liver metastases, and lung metastases were significant predictors for ccRCC in the development cohort (Table 2). These variables were used to develop the predictive nomogram (Fig. 1).

Validation of the prognostic nomogram

We used the C-index, AUC, NRI, and IDI to assess the discrimination performance of the nomogram. The C-index was higher for the nomogram than for the AJCC staging system both in the development cohort (0.898 vs 0.856) and in the validation cohort (0.905 vs 0.862). The AUC was better for the nomogram than for the AJCC model in both the development and validation cohorts (Figure 2). Comparing with the AJCC staging system, the 3-year and 5-year NRI values for the nomogram were 0.276 (95% CI=0.214–0.328) and 0.284 (95% CI=0.230–0.352), respectively, in the development cohort, and 0.263 (95% CI=0.161–0.350) and 0.339 (95% CI=0.234–0.408) in the validation cohort. Comparing with the AJCC staging system, the 3-year and 5-year IDI values for the nomogram were 0.060 and 0.052, respectively, in the development cohort, and 0.046 and 0.054 in the validation cohort.

Calibration plots of the nomogram showed that the predicted 3-year and 5-year survival probabilities of the model were almost identical to the actual observations in both the development and validation cohorts (Figure 3). The 3-year and 5-year DCA curves for the nomogram demonstrated net benefits that

were greater than those for the traditional AJCC staging system in both the development set and the validation set, although both models demonstrated net benefits (Figure 4).

Discussion

In addition to histological grade, the tumor size, Mayo Clinic stage at presentation, vascular invasion, and tumor necrosis are prognostic factors that are routinely utilized to predict the ultimate patient survival[19,20]. We found that age at diagnosis, being unmarried, and metastases in the lymph nodes, bone, liver, and lung were risk factors for survival. In particular, this is the first study to include a married status in a survival prediction model of ccRCC. The risk of death increased with Mayo Clinic stage, AJCC stage, and tumor size.

As is well known, surgery remains the most important and probably the only curative approach in ccRCC[21]. Our study found that surgery can improve the prognosis of ccRCC, whereas radiation therapy is a risk factor for survival. This might be due to radiotherapy long being considered a valueless approach for managing primary disease, and so mainly being prescribed to treat distant metastases, especially brain and painful bone metastases, with a palliative intent[2222]. Moreover, patients with radiotherapy were in a more advanced state or had metastases comparing with patients without radiotherapy. Therefore, the prognosis of radiotherapy patients was worse than that of patients who had not received radiotherapy.

Nomograms have been used in most cancer types in recent years[24-31], including for ccRCC [32-34]. However, there has been a lack of overall evaluations of the developed nomograms, or the variables used for prediction have not been readily available. The clinical applicability and ease of use are highly attractive features of the comprehensive prognostic nomogram we constructed in this study, and we have compared its prognostic value with that of the AJCC classification. Our nomogram model contains risk factors that are easy to obtain from historical records.

To further determine whether the prognostic model performed better than the traditional AJCC staging system, we evaluated the performance of our survival model using several basic features of model validation: C-index, AUC, NRI, IDI, calibration plots, and DCA. The ROC curve or C statistic is typically used to assess the discrimination performance[15]. The IDI and categorical NRI were also used to assess discrimination in terms of the additional diagnostic value of our model compared to the AJCC model. All of these indicators showed that our model has better discrimination performance than the AJCC staging system. The calibration plots resembled a 45-degree line, indicating that the nomogram predictions were well calibrated (Figure 3). DCA is used to evaluate clinical usefulness, and it shows the minimal net benefit of modified scores that incorporate an index. Some studies have demonstrated the benefits of DCA and recommended its use[35,36]. The present results for the 3-year and 5-year DCA curves showed that our model yielded net benefits that were greater than those for the traditional AJCC staging system in both the development and validation cohorts (Figure 4).

The above-described findings indicate that using our new nomogram can ameliorate the gap that exists relative to predictions based on the AJCC staging system alone. This supports that our nomogram is a useful tool for optimizing treatment in the clinical setting of ccRCC.

Limitations

This study was subject to some limitations. The patients were mainly white, and so the results might not be applicable to other racial groups. Our data set and follow-up data came from the SEER database, which is retrospective and so has inevitable inherent bias. There was also selection bias in the selection and exclusion of patients, because we only selected the patients with complete information. In addition, many factors were not included, such as the statuses of VEGF, HIF-1α, HIF-2α, p53, and Ki-67[37,38], which have been shown to influence the prognosis of ccRCC. Another limitation of this study is the relatively small sample, and so more data are needed to provide more accurate performance assessments of the model. Finally, the predicted values calculated from the nomogram are for reference use by clinicians only, and the nomogram should be externally validated in another population in the future.

Conclusions

This study is the first to indicate that married status is an important prognostic parameter in ccRCC. Our results also demonstrate that the developed nomogram can predict survival more accurately than the AJCC staging system alone. The prognostic factors were easily obtained. The nomogram could provide predictions for individual ccRCC patients and help clinicians in decision-making about treatment options and prognosis evaluations.

Declarations

Authors' contributions

(1) Conception and design: Xinwen Wang and Qian Wen. (2) Administrative support: Tao Mei and Xiaoye Wang. (3) Provision of study materials or patients: Tiao Bai. (4) Collection and assembly of data: Qian Wen and Xinwen Wang. (5) Data analysis and interpretation: Qian Wen and Xinwen Wang. (6) Manuscript writing: Qian Wen and Xinwen Wang. (7) Final approval of manuscript: Qian Wen, Xinwen Wang, Xiaoye Wang, Tiao Bai and Tao Mei.

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Competing interests

The author reports have no conflicts of interest in this work

Notes

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ninth Hospital of Xi'an

Consent for publication

All patients came from the SEER database (Surveillance, Epidemiology, and End Result), which is publicly available.

Availability of data and material

The datasets analyzed during current study are available from the corresponding author upon reasonable request.

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Figures

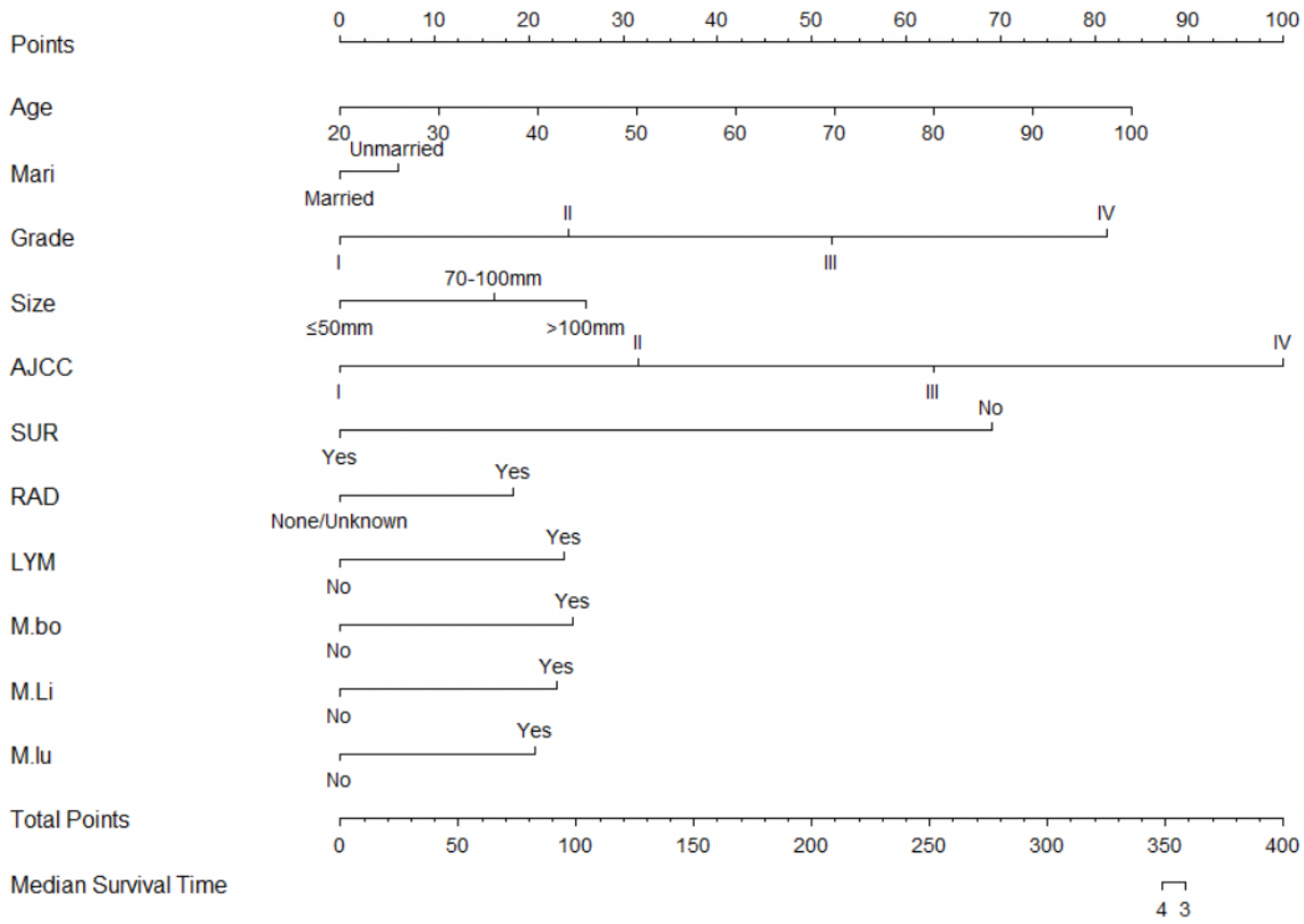

Figure 1

Nomogram predicting 3-year and 5-year survival. Mari: Marital status. Unmarried: Single & Separated & Divorced &Widowed &Unmarried or Domestic Partner. SUR: Surgery. RAD: Radiation. LYM: lymph nodes metastases.M.bo: metastases at bone. M.li: metastases at liver. M.lu: metastases at lung.

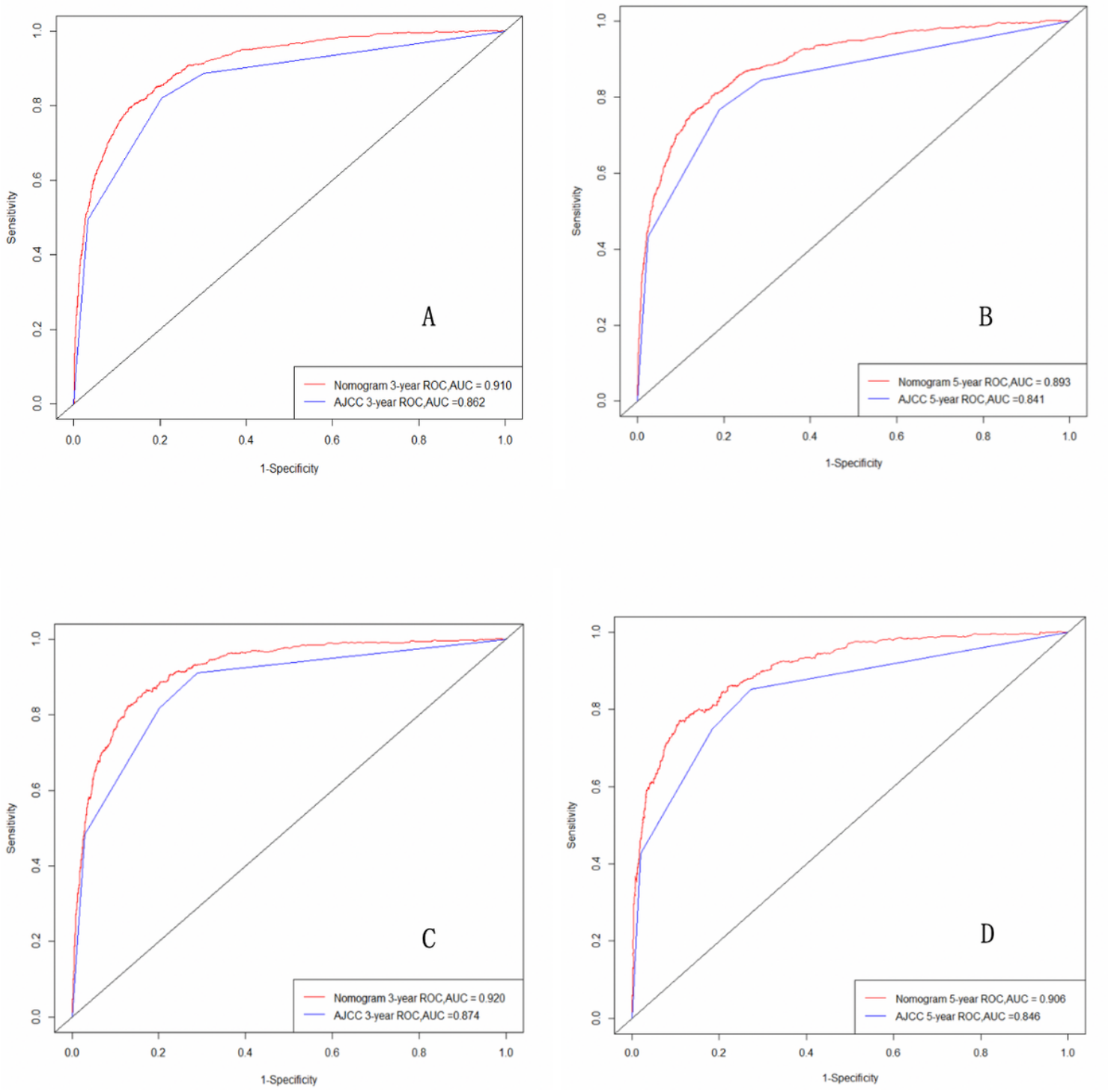

Figure 2

ROC curves. The ability of the model to be measured by the C index. A, B came from the development set, and C, D came from the validation set.

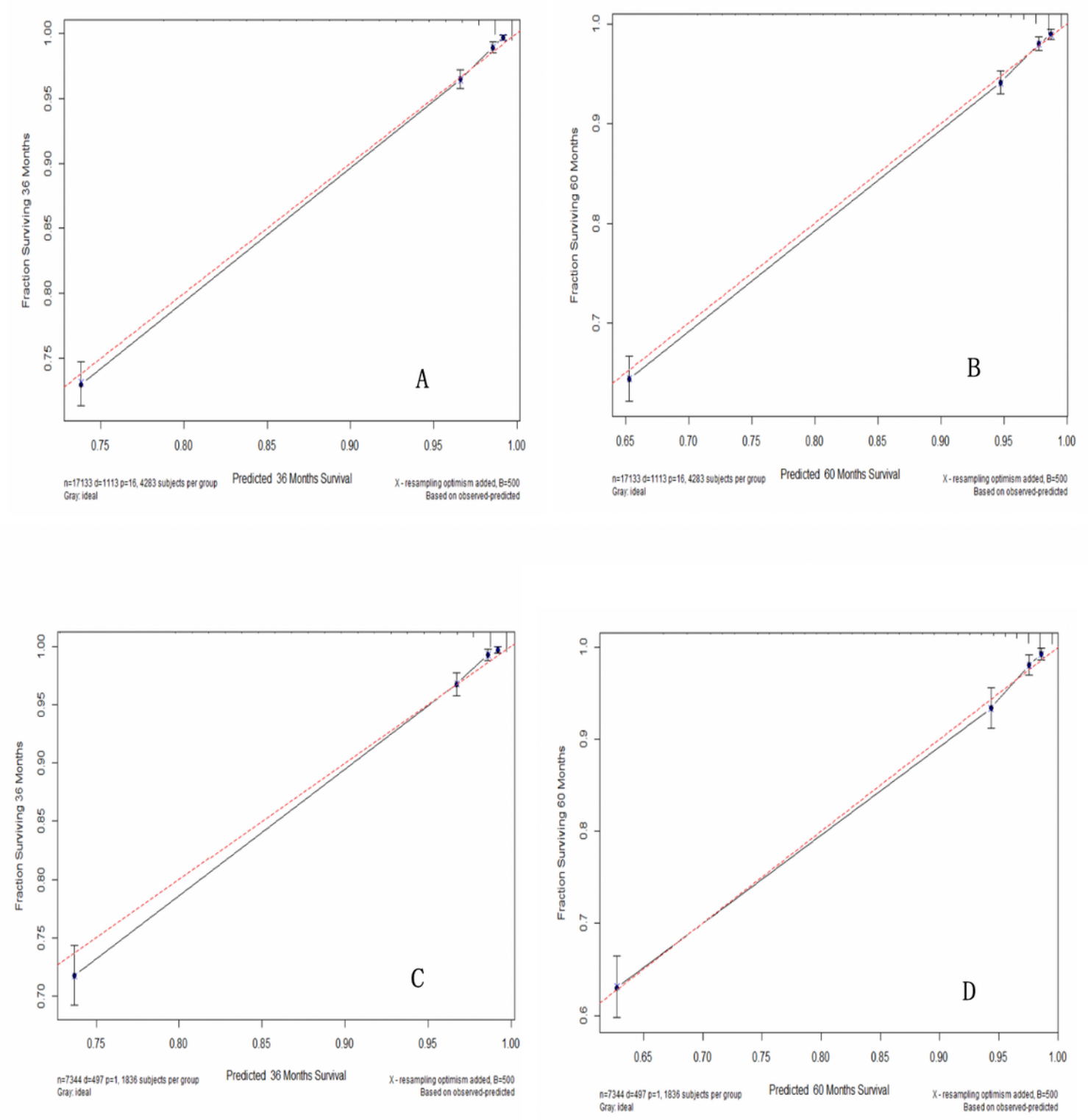

Figure 3

Calibration plots. Show the relationship between the predicted probabilities for 3-and 5-years survival base on the nomogram and actual values in the Validation sets. (A, B in the development set and C, D in the validation set)

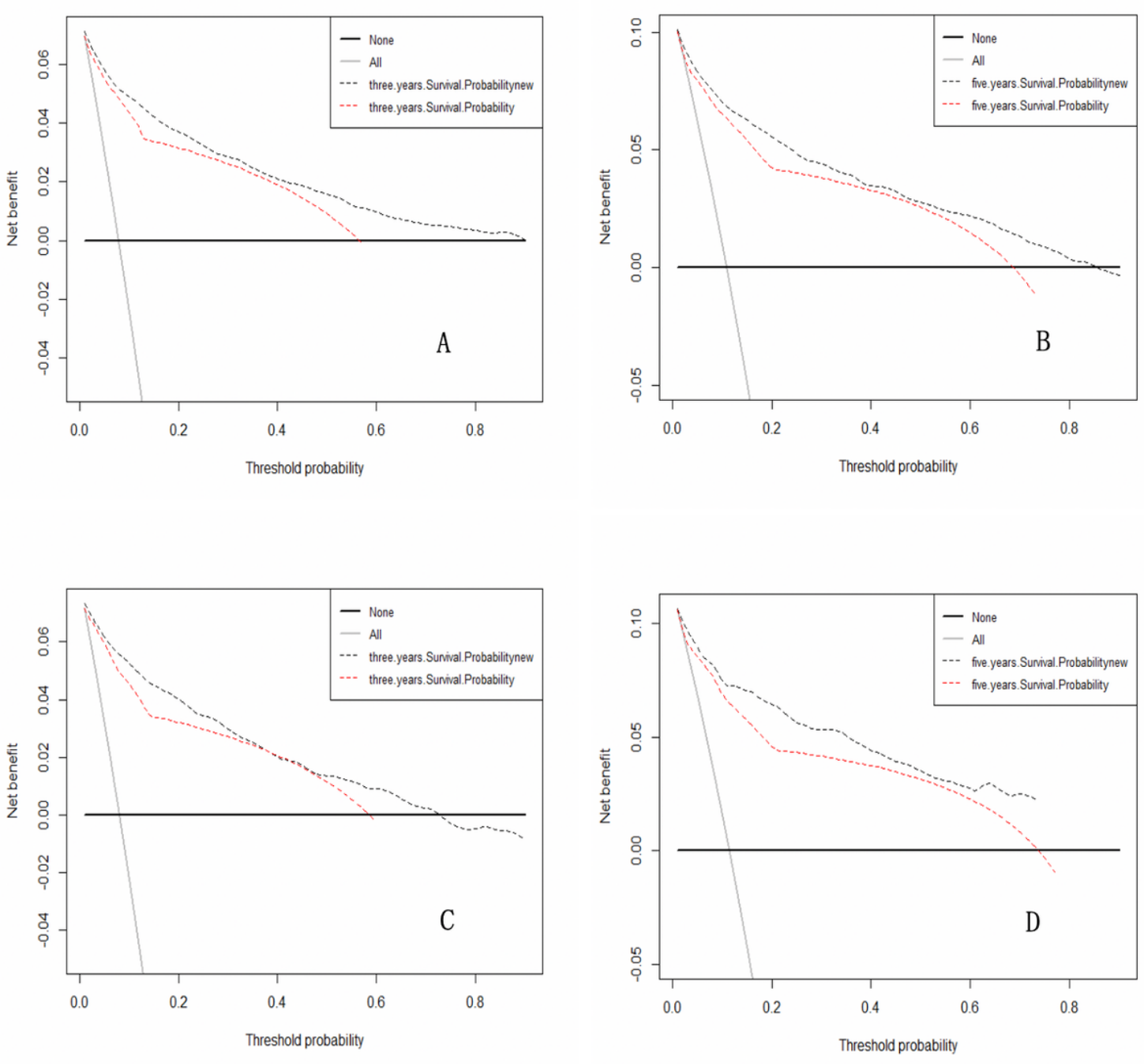

Figure 4

Decision curve analysis in the figure, the abscissa is the threshold probability, the ordinate is the net benefit rate. The horizontal one indicates that all samples are negative and all are not treated, with a net benefit of zero. The oblique one indicates that all samples are positive. The net benefit is a backslash with a negative slope. A, B show prediction for 3- and 5-years survival in the development sets. C, D show prediction for 3- and 5-years survival in the Validation sets. Survival probability new: the nomogram. Survival probability: AJCC.