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A nomogram model to predict recurrence-free survival in appendiceal pseudomyxoma peritonei following complete or near complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Abstract

Purpose

Appendiceal pseudomyxoma peritonei (PMP) is a rare malignancy. Although favorable outcomes can be achieved following complete or near complete cytoreductive surgery(CRS) and hyperthermic intraperitoneal chemotherapy(HIPEC), recurrence remains a significant clinical concern. This study aimed to identify independent predictors of recurrence and to develop a nomogram for individualized recurrence risk stratification, thereby informing postoperative surveillance strategies.

Methods

We retrospectively analyzed 148 who underwent complete or near complete CRS+HIPEC treated at Aerospace Center Hospital between January 2016 and December 2023. Univariate and multivariate Cox regression analyses were performed to identify independent predictors of recurrence-free survival (RFS), and a nomogram was constructed based on the selected risk factors.

Results

Among the 148 patients analyzed, 77 (52%) experienced disease recurrence. The median RFS was 41 months(95%CI:19 ~ 63months), and the median follow up time was 54 months (95%CI:43 ~ 65months). Multivariate Cox analysis identified Ki-67 ≤ 1%, pathological subtype, intraoperative PCI ≤ 24, and elevated ascites CA19-9 as independent predictors of RFS. Based on the selected results, A nomogram was plotted and underwent internal validation. The C-index was 0.728, and the corrected C-index was 0.716. The AUC of the ROC curve was 0.858 (95% CI, 0.796–0.919). Calibration curves and DCA indicated robust predictive performance.

Conclusion

The nomogram developed in this study demonstrates good discriminatory ability in predicting individualized recurrence risk following CRS+HIPEC for appendiceal PMP, providing a reliable quantitative tool to support postoperative surveillance and clinical decision-making.

Introduction

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignancy characterized by progressive accumulation of mucinous ascites within the abdominal cavity, with an estimated annual incidence of 2–3 cases per million population[1].The primary tumor most commonly originates from the appendix[2]. According to the 2020 clinical guidelines developed by PSOGI/EURACAN, PMP is classified into four histological subtypes: acellular mucin, low grade mucinous carcinoma peritonei, high grade mucinous

carcinoma peritonei, high grade mucinous carcinoma peritonei with signet ring cells[3] .The advent of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has transformed PMP from a universally fatal condition into a potentially curable disease, with high-volume centers reporting 10-year disease-free survival rates of 61%[4]. However, even after complete cytoreductive surgery, disease recurrence remains a persistent clinical concern: 25–40% of patients experience recurrence at a median interval of 19–21 months postoperatively[5–6].

The postoperative management of appendiceal PMP following complete CRS+HIPEC is complicated by the heterogeneous natural history of the disease and the absence of validated tools for individualized recurrence risk stratification. Critical determinants of recurrence include peritoneal cancer index (PCI) scores, elevated preoperative tumor markers, high-grade histology, and radiological features such as hepatic scalloping, which confers a hazard ratio of approximately 4.3 for shortened disease-free survival[7]. Despite recognition of these risk factors, clinicians lack a unified, externally validated prediction model to quantify individualized recurrence probability. Nomogram, which translate complex multivariable regression models into visually intuitive scoring systems, have demonstrated good predictive accuracy and clinical utility across multiple tumor types [8–9]. Accordingly, we developed a comprehensive nomogram to predict individualized recurrence risk following complete or near complete CRS-HIPEC for appendiceal PMP, expecting to provide clinical doctors with a quantitative and visual decision support tool.

Materials and methods

Ethical Approval

Formal ethical approval was not required for this retrospective observational study, as it used fully de-identified pre-existing clinical data without additional interventions or patient contact. All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was waived given the retrospective nature of the study.

Patients

We retrospectively identified patients who underwent complete or near complete CRS at the Aerospace Center Hospital, Beijing, China, from January 2016 to December 2023. The pathological subtype was confirmed by at least two experienced pathologists. Prior to CRS surgery, all patients underwent routine abdominal and pelvic enhanced CT, along with measurement of serum tumor markers, including CA-125, CEA, and CA-199. Postoperative follow-up was performed every 3–6 months, with a final follow-up date of December 2024. The study flowchart is presented in ***Fig1***.

Operation

All surgeries were performed by the same team with extensive experience in the diagnosis and treatment of peritoneal cancer. PCI scoring was performed before and after tumor reduction, as

described by Sugarbaker[10], which ranges from 0 to 39. A CCR score was recorded after CRS, and the standard is as follows : CCR0: no visible residue; residual tumor: CCR1: <2.5 mm. Intraoperative measurement of ascites and delivery of ascites tumor markers. If there is no ascites, lavage and delivery of tumor markers were performed.

HIPEC: HIPEC was performed after CRS and before gastrointestinal reconstruction using a closed-circuit technique. Two inflow and two outflow catheters were placed intraperitoneally and connected to a thermotherapy-chemotherapy perfusion machine (product of Jilin Minda Company, RHL-2000B) . Perfusion was maintained for 60 minutes at an inflow temperature of 43.5°C and a circulation rate of 800–1,000 mL/min, with an outflow temperature of 41°C. Cisplatin (60–80 mg) dissolved in 3,500–4,000 mL of normal saline was used as the perfusate. HIPEC was administered to all patients achieving CCR0 or CCR1.

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, NY, USA) and R 4.1.2 (http://www.r-project.org) were used for statistical analysis. The continuous variables were expressed as (interquartile ranges, IQR). The categorical variables were presented as frequency with percentage [n (%)]. Optimal cutoff values for intraoperative PCI, age, and Ki-67 were determined using the "maxstat" package in R. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify independent predictors of RFS, and results were visualized using forest plots. A nomogram was constructed based on the multivariate Cox regression results, and the C-index was calculated to assess discriminatory ability. ROC curves were used to evaluate predictive sensitivity and specificity, with AUC reported. Model calibration was assessed using calibration curves with 1,000 bootstrap resamples, and clinical utility was evaluated using DCA. Additional R packages used included "survival," "forestplot," "rms," and "rmda". The significance level for all statistical tests was set at 0.05.

Results

Patient characteristics

A total of 175 patients who achieved CCR0/1 were initially identified. Of these, 27 patients were pathologically diagnosed with acellular mucus; this subtype was excluded from the primary analysis because no recurrence was observed and all patients survived throughout follow-up. The remaining 148 patients, constituted the study cohort, comprising 27 males (18.2%) and 121 females (81.8%). The median age was 55 years (IQR: 48–62 years). Among these, 33 patients (22.3%) achieved CCR0 and 115 (77.7%) achieved CCR1. During follow-up, 37 patients (25.0%) died, yielding a 5-year overall survival rate of 68.2%. By histological subtype, 93 patients (62.8%) had low-grade, 42 (28.4%) had high-grade, and 13 (8.8%) had high-grade with signet ring cells. The overall recurrence rate was 52.0% (77/148); subtype-specific recurrence rates were 36.6% (34/93), 76.2% (32/42), and 84.6% (11/13), respectively. Detailed patient characteristics are presented in ***Table 1***.

Univariate and multivariate Cox regression analysis for risk factors of RFS

Univariate Cox regression results are presented in Forest plot 1. Ki-67 ≤1%, pathological subtype, intraoperative PCI ≤24, elevated serum CA-125, elevated serum CA19-9, elevated ascites CEA, and elevated ascites CA19-9 were each significantly associated with RFS. All significant variables were subsequently entered into multivariate Cox regression analysis. After multivariate adjustment, Ki-67 ≤1%, pathological subtype, intraoperative PCI ≤24, and elevated ascites CA19-9 were identified as independent predictors of RFS (Forest plot 2).

Construction of the nomogram and Validation

A nomogram was constructed based on the four independent predictors identified by multivariate Cox regression (Figure 2). Among the four predictors, pathological subtype exerted the greatest influence on RFS, followed by Ki-67. Each variable was assigned a point score proportional to its regression coefficient; the sum of individual scores yielded a total score from which the probability of recurrence at specified time points could be directly read. The C-index was 0.728, and the corrected c-index was 0.716. The AUC of the ROC curve was 0.858 (95 % confidence interval, 0.796 to 0.919, Figure 3). Calibration curves based on 1000 bootstrap resamples demonstrated close agreement between predicted and observed recurrence probabilities (Figure 4).

. DCA indicated that the nomogram provided superior net clinical benefit compared with both the treat-all and treat-none default strategies across most clinically relevant decision thresholds (Figure 5).

Discussion

This study establishes a parsimonious, clinically deployable nomogram integrating four independent predictors-Ki-67≤1%, pathological subtype, intra-operative PCI≤ 24, and elevated ascites CA19-9, that stratifies post-CRS+HIPEC recurrence risk in appendiceal pseudomyxoma peritonei (PMP) . This addresses a critical gap in personalized surveillance strategies for PMP, a rare malignancy where recurrence patterns remain heterogeneous despite complete or near complete CRS+HIPEC.

By quantifying individual recurrence probability, the nomogram enables risk-adapted surveillance intensity, trial stratification, and informed shared decision-making regarding adjuvant strategies in a disease where 5-year recurrence rates approach 30–40% even after optimal treatment[6,11] Unlike existing prognostic schemas that rely predominantly on histologic grade or PCI thresholds alone, our nomogram captures the multidimensional biology of PMP recurrence. The inclusion of ascites CA19-9, a parameter infrequently reported in prior PMP cohorts, represents a novel contribution that warrants mechanistic and validation scrutiny.

The prognostic relevance of ki-67 levels is closely related to the prognosis of PMP[12-14].Our finding that Ki-67 ≤1% independently predicts lower recurrence risk aligns with and extends the seminal work of Arjona-Sánchez et al. [13]. However, our study diverges in threshold selection whereas Arjona-Sánchez et

al. stratified high-grade disease using 15% as a discriminant, we identify ≤1% as prognostically favorable, effectively isolating a subset with minimal proliferative activity. This difference likely reflects distinct cohort compositions — our cohort may include a higher proportion of low-grade cases where Ki-67 approaches zero, whereas the Arjona-Sánchez cohort enriched for high-grade disease.

The independent prognostic significance of pathological subtypes has been widely confirmed[5,6,15-16]. The present study adopted the 2020 PSOGI/EURACAN classification, and the 27 acellular mucin cases—none of which recurred—were appropriately excluded from the prognostic model. Among the remaining subtypes, recurrence rates increased substantially with histological grade (low-grade: 36.6%; high-grade: 76.2%; high-grade with signet ring cells: 84.6%), consistent with the established biology of mucinous peritoneal tumors and supporting the dominant weighting of pathological subtype in the nomogram. The prognostic dominance of PCI ≤ 24 in our model aligns with decades of data establishing PCI as the cornerstone predictor of CRS+HIPEC outcomes . Multiple institutional series report PCI as an independent predictor of overall survival and progression-free survival, with threshold effects commonly observed at PCI 20–24[17-18]. Critically, PCI reflects not only tumor burden but also the feasibility of complete cytoreduction (CC-0/1 resection), which itself is the strongest predictor of long-term survival in PMP [11]. Our threshold of ≤24 likely captures cases where complete macroscopic clearance is technically achievable and residual microscopic disease burden is minimized, thereby reducing recurrence substrate.

Serum CA19-9 elevation is widely recognized as a marker of high tumor burden and aggressive biology in PMP [17,19]. However, direct measurement of CA19-9 inperitoneal fluid has been infrequently reported. In the preliminary research of our center, it has been found that ascites tumor markers in ascites are associated with the prognosis of PMP[20-21]. In this study, our identification of elevated ascites CA19-9 as an independent recurrence predictor represents a relatively underexplored dimension in PMP prognostication. Mechanistically, ascites CA19-9 may reflect local tumor cell shedding, mucin-associated glycoprotein secretion, and peritoneal inflammatory signaling that collectively sustain a pro-recurrence microenvironment. This mechanistic hypothesis, while biologically plausible, remains speculative and requires prospective validation. Several important caveats apply: ascites CA19-9 measurement is not standardized across institutions; prognostic cutoff values have not been externally validated; and whether the association is causal or merely reflective of overall tumor burden remains to be determined.

Limitations

This cohort was derived from a single high-volume institution, which may introduce selection bias and limit generalizability. The nomogram has undergone internal validation only; external validation in independent cohorts is required before broad clinical adoption. The model does not incorporate potentially relevant prognostic variables such as prior systemic chemotherapy history or appendiceal pathology features.

Conclusion

This study developed and internally validated a four-variable nomogram incorporating Ki-67, pathological subtype, intraoperative PCI, and ascites CA19-9 to predict recurrence-free survival following complete or near-complete CRS+HIPEC for appendiceal PMP. The model demonstrates good discriminatory ability (C-index: 0.728; AUC: 0.858) and robust calibration, offering a reliable quantitative tool to support individualized postoperative surveillance and clinical decision-making. External validation in multicenter cohorts is warranted to confirm the generalizability of these findings.

Declarations

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Data availability statement

The data generated and analyzed during this study can be obtained from the corresponding authors of reasonable request.

Disclosure of conflicts of interest:

There are no ethical/legal conflicts involved in the article.

Author contributions

All authors contributed extensively to the article and approved the submitted version.The author contributions were as follows:

Design of the work: CW,XW, and RM.

Acquisition of data: SY, LA, HZ,ZH, and PZ.

Interpretation of data: CW, XW and PY.

Drafting/Critical revision:CW,PY, and GS.

Final approval: RM, GS.

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Forest plot

Forest plot 1 and 2 are available in the Supplementary Files section.

Figures

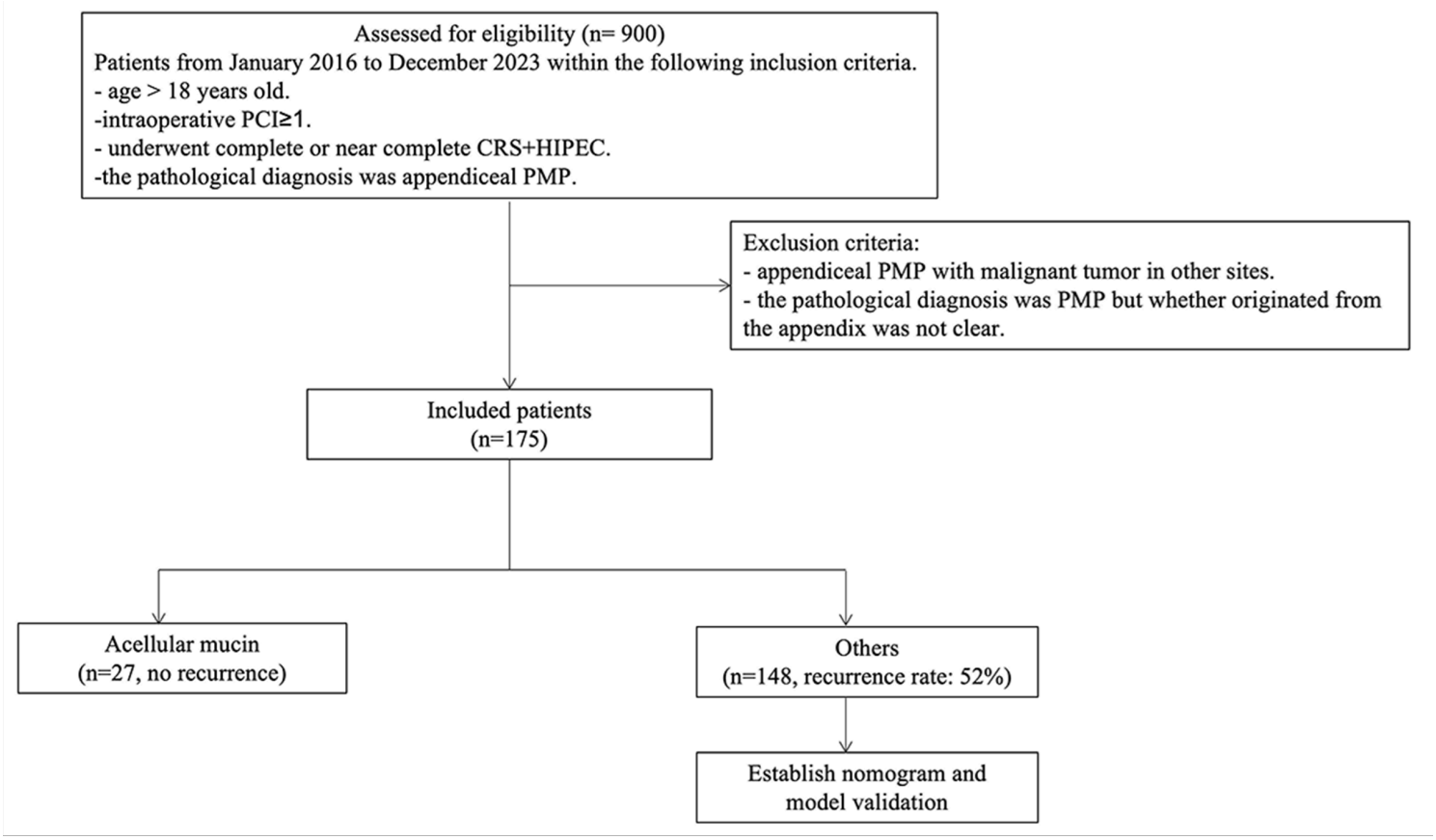


Figure 1

The flowchart of patient screening.

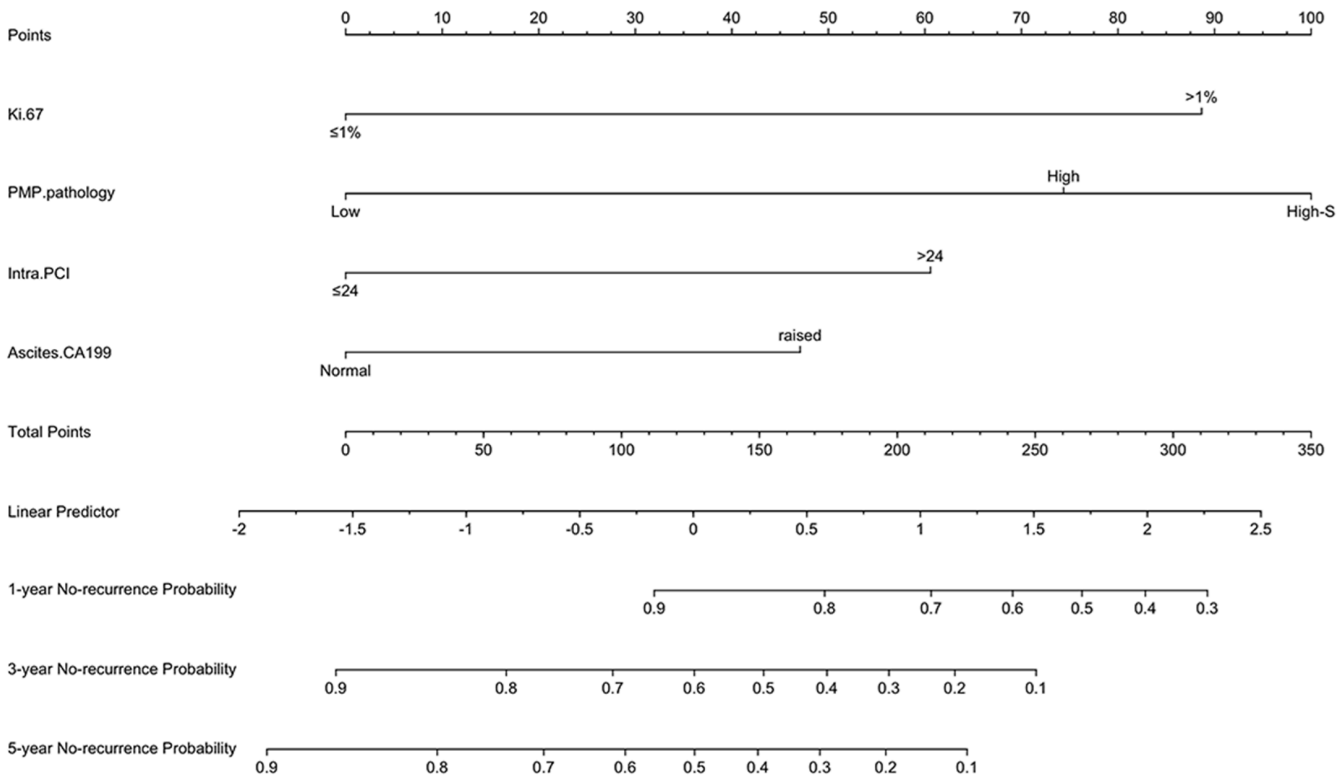


Figure 2

Nomogram to predict RFS rates of appendiceal pseudomyxoma peritonei patients.

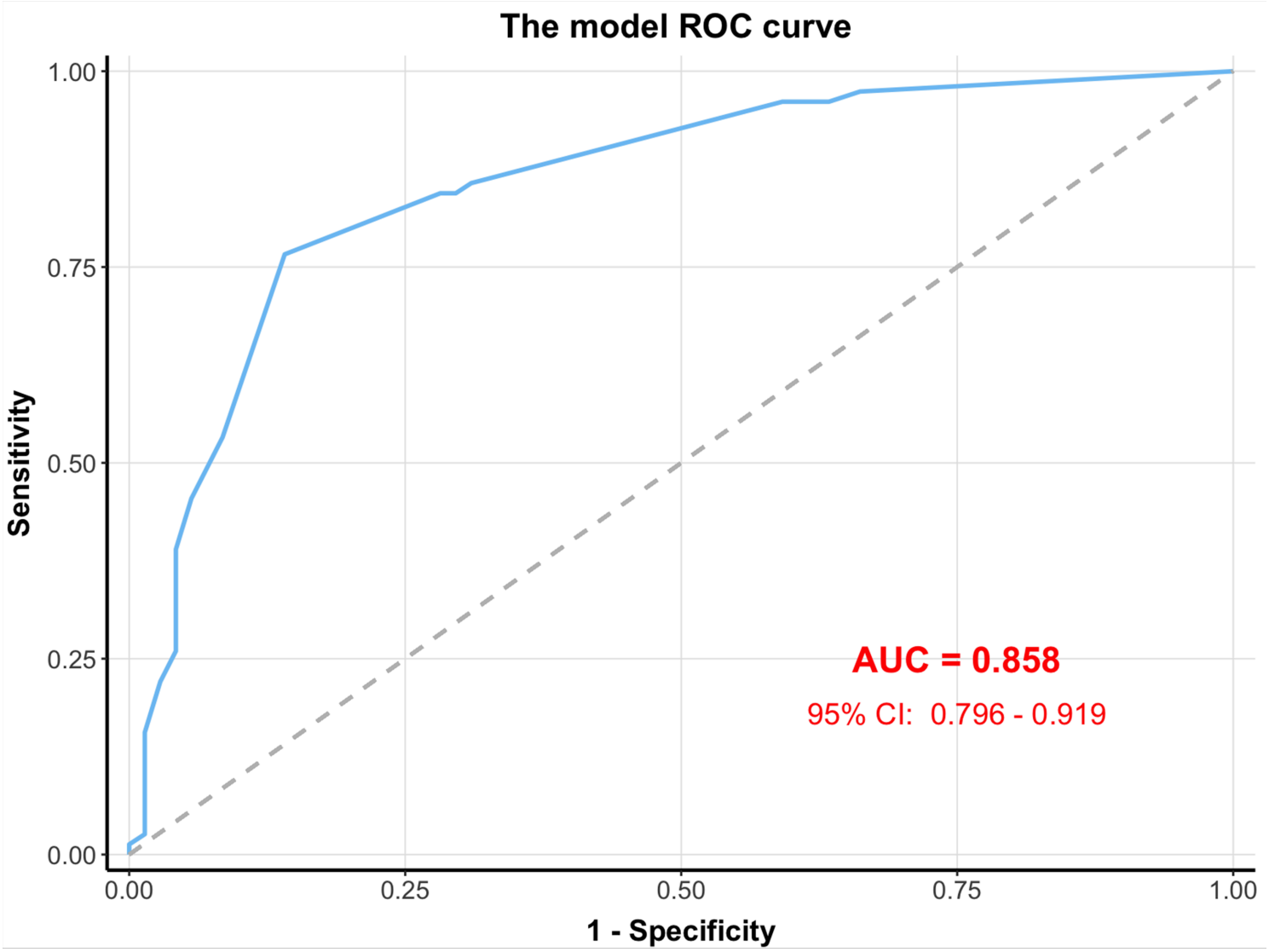


Figure 3

Receiver operating characteristic (ROC) curves of the nomogram. The area under the curve (AUC) of the nomogram was 0.858 (95 % CI, 0.796 - 0.919).

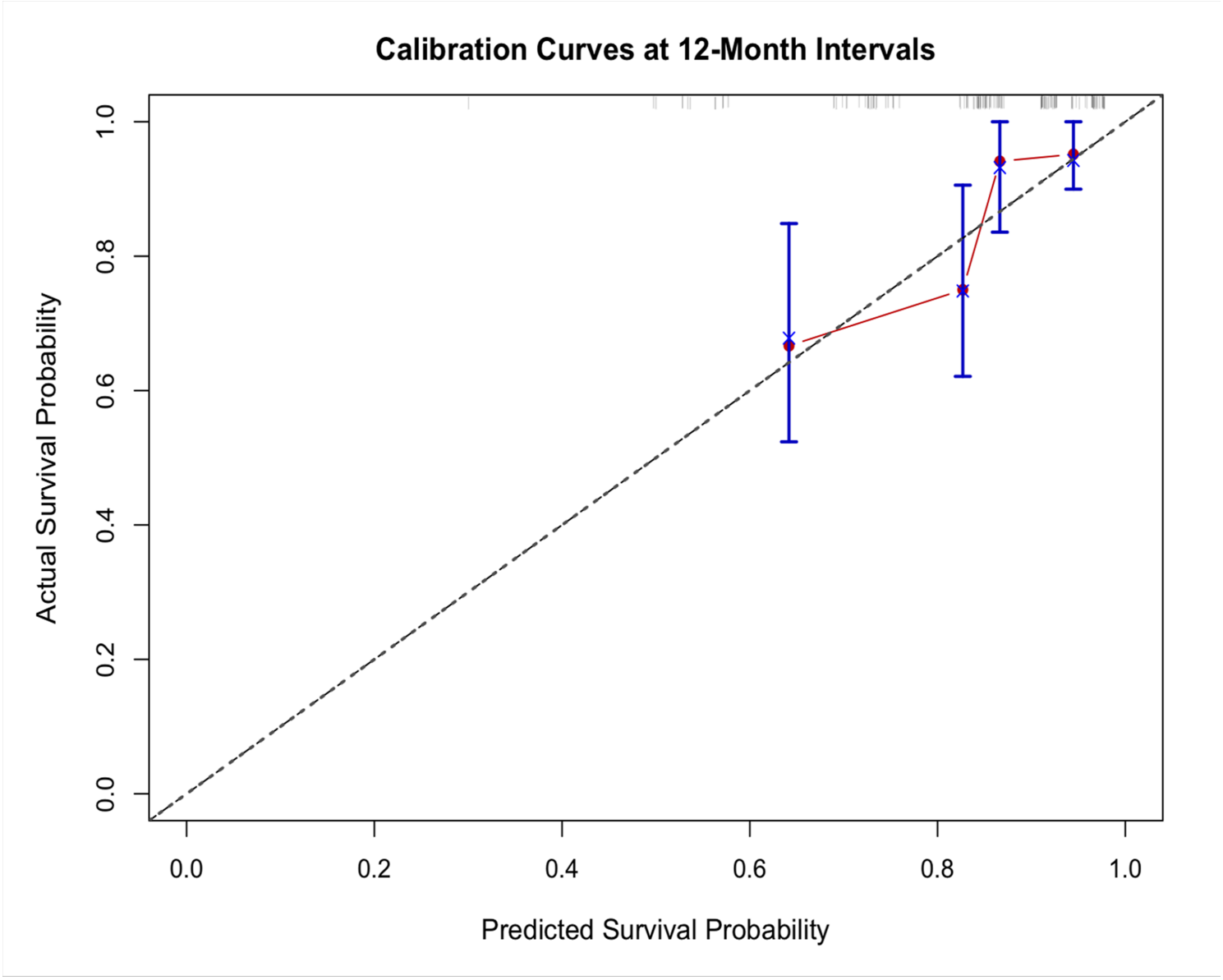


Figure 4

The calibration curve of the nomogram for predicting RFS. The x-axis shows the model's predicted probability, and the y-axis shows the actual probability.

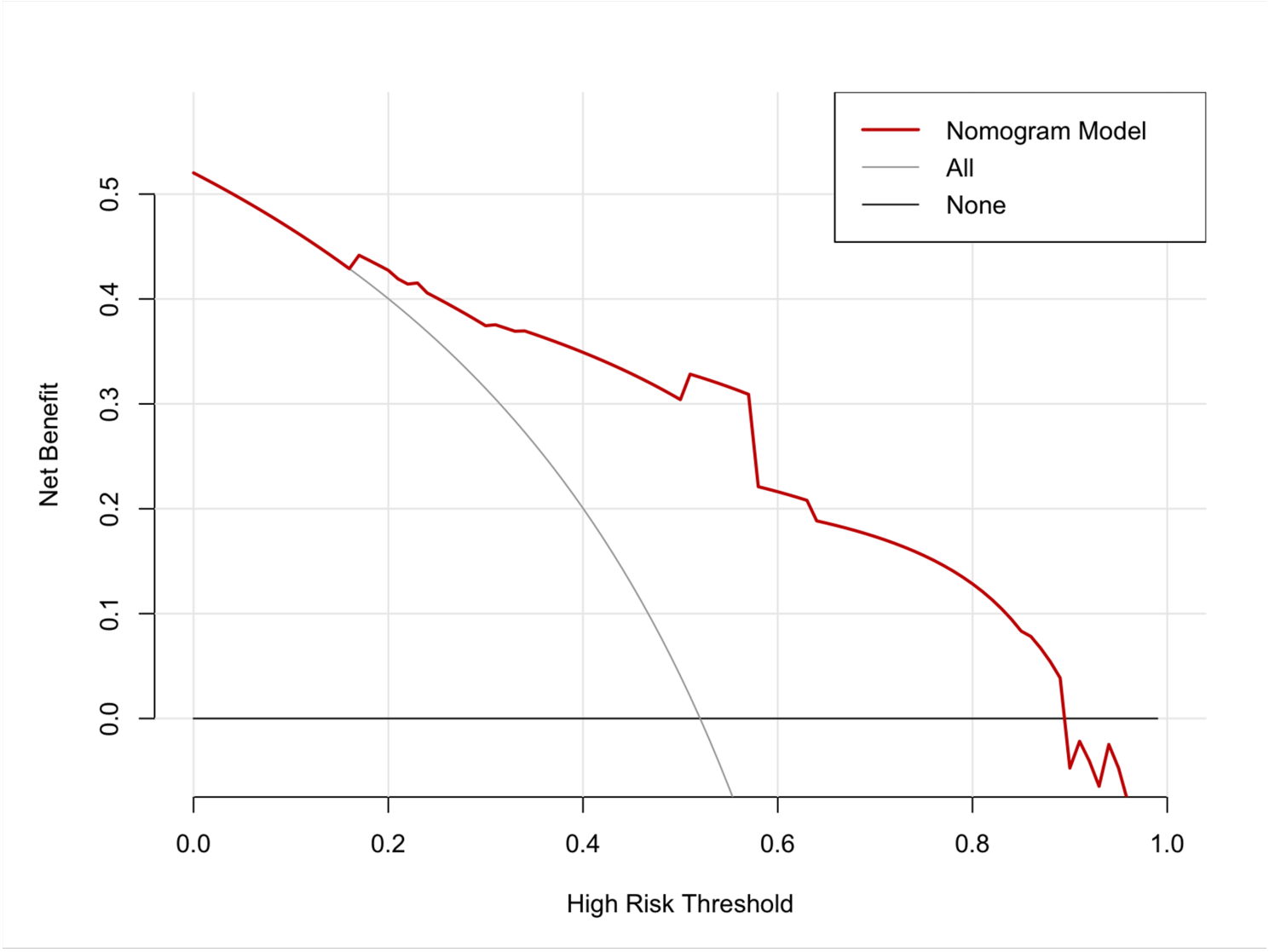


Figure 5

The decision curve analysis of the nomograms for predicting RFS.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Forestplot1.png
- Forestplot2.png