Original article

Predictive Nomogram for Recurrence Following Surgery for Non-Metastatic Renal Cell Cancer with Tumor Thrombus

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Abstract

Background

Following surgery for non-metastatic renal cell carcinoma (RCC) with tumor thrombus, the risk of recurrence is significant but variable among individual patients. The purpose of this study is to develop and validate a predictive nomogram for individual estimation of recurrence risk following surgery for RCC with venous tumor thrombus.

Methods

Comprehensive data was collected for non-metastatic RCC patients with thrombus treated at 5 institutions from 2000-2013. Independent predictors of RCC recurrence from a competing risks analysis were developed into a nomogram. Predictive accuracy was compared between development/ validation cohorts and between the nomogram, the UCLA Integrated Staging System (UISS), SSIGN and Sorbellini models.

Results

A total of 636 patients were analyzed (development cohort n=465, validation cohort n=171). Independent predictors (tumor diameter, BMI, Preoperative hemoglobin < lower limit of normal, thrombus level, perinephric fat invasion, and non-clear cell histology) were developed into a nomogram. Estimated 5-year recurrence free survival (RFS) was 49% overall. The 5 year RFS for patients with 0, 1, 2, >2 risk factors was

77%, 53%, 47%, and 20% respectively. Predictive accuracy was similar in development and validation cohorts (AUC 0.726 and 0.724).

Predictive accuracy for the thrombus nomogram was higher than the UISS (AUC 0.726 vs. 0.595, p=0.001), SSIGN (AUC 0.713 vs. 0.612, p =0.04) or the Sorbellini models (AUC 0.709 vs. 0.638, p=0.02).

Conclusions

A predictive nomogram for postoperative recurrence in non-metastatic RCC patients with venous thrombus is presented. Improving individual post-operative risk assessment may allow better design and analysis of future adjuvant clinical trials.

Introduction

Following surgery for non-metastatic renal cell carcinoma (RCC) with tumor thrombus approximately 50% of patients have disease recurrence, making these patients ideal to study in adjuvant clinical trials.[1] Although the overall recurrence risk varies significantly, individual risk can be estimated using clinical and pathologic variables. Since non-metastatic RCC patients with thrombus represent a relatively unique population, risk assessment following surgery may not be similar to other RCC patients. In a prior study, risk factors were identified and used to separate patients into favorable, intermediate and high risk groups with 22%, 55%, and 79% 5-year recurrence free survival following surgery for RCC with thrombus.[2] However, a nomogram for individual risk assessment has not been previously described for this unique population of RCC patients, who are at high risk for recurrence following surgery.

Clinical trials of adjuvant therapy following surgery for RCC have been disappointing with the exception of the recent S-TRAC trial.[3] One persistent criticism of adjuvant clinical trial design is that there is significant heterogeneity of recurrence risk among patients enrolled. [4] Assigning accurate baseline risk is critical in when trying to evaluate whether patients actually have risk reduction from adjuvant therapies. In the recently published ASSURE and the S-TRAC clinical trials, patients were stratified into intermediate or high risk for recurrence based on the well-known and validated UCLA Integrated Staging System (UISS). [5] However, this system and others [6, 7] were developed to stratify risk among a general population of RCC patients, and it is unclear

how well this system performs to further stratify a population of high risk patients, such as non-metastatic RCC patients with tumor thrombus. Therefore, the purpose of our study was to develop a nomogram to predict individual 5- year recurrence risk following surgery in non-metastatic RCC patients with tumor thrombus, to evaluate the predictive accuracy in independent populations and to compare the predictive ability of this nomogram with the UISS, SSIGN, and Sorbellini models.

Materials and Methods

Following IRB approval, comprehensive clinical and pathologic data were reviewed for consecutive non-metastatic RCC patients with tumor thrombus from 2000-2013 at 5 institutions. The development cohort included patients from: the University of Wisconsin (UW), the University of Texas Southwestern Medical Center (UTSW), and the MD Anderson Cancer Center (MDA), while the validation cohort included patients from: Emory University, Indiana University (IU). Preoperative assessment for metastatic disease was similar for each institution and included preoperative laboratory evaluation in addition to computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. All patients with radiographic or pathologic evidence of distant metastatic or nodal metastases at presentation were excluded from analysis. No patients had pre-surgical systemic therapy. Follow up after surgery generally consisted of CT of chest, abdomen, and pelvis every 3-6 months for the first 5 years and yearly thereafter.

Clinical and laboratory factors assessed for each patient included the following: age, gender, BMI, tumor width and height, albumin levels, neutrophil count, lymphocyte count, neutrophil/ lymphocyte ratio, hemoglobin, creatinine, and tumor diameter. Surgical and pathologic factors assessed for each patient included: year of surgery, grade, stage, thrombus level according to Neves system,[8] sarcomatoid features, tumor histology, local and systemic symptoms, estimated blood loss, perinephric fat invasion, and perioperative blood transfusion. All pathologic specimens were examined by an institutional genitourinary pathologist. Histological subtypes were categorized according to the 2004 World Health Organization classification.

Statistical Analysis

To evaluate the effect of death from other causes, competing risks analysis was integrated with univariate and multivariate Cox proportional hazard models for putative risk factors for RCC recurrence.[9] Significant variables following multivariate competing risks analysis were used to construct a predictive nomogram. The predictive accuracy of the nomogram was evaluated using receiver operating characteristics (ROC) curves for the development and validation cohorts and further evaluated for clinical applicability according to decision curve analysis.[10] Estimated recurrence-free survival (RFS) rates were calculated using the Kaplan-Meier method. A p-value < 0.05 was considered statistically significant and SAS 9.4 (SAS Institute, Cary, NC, USA) or R 3.3.1 was used for all analyses.

Results

A total of 636 non-metastatic RCC patients treated with radical nephrectomy and tumor thrombectomy were available for analysis. Table 1 shows patient clinical and pathologic characteristics. Median follow up for the study period was 24.8 months (IQR 9.2-50.3). Tumor thrombus level included 342 (53.8%) renal vein, 92 (14.5%) level 1, 100 (15.7%) level 2, 45 (7.1%) level 3, and 57 (9.0%) level 4. Recurrent renal cell carcinoma was identified in 239 (37.5%) patients during follow-up. Competing risk analysis identified variables associated with disease recurrence in the 465 patients for the development cohort (table 2). Independently predictive variables associated with RCC recurrence included: tumor diameter in cm (HR 1.05, 95% CI 1.004-1.09; p=0.03), BMI (HR 0.97, 95% CI 0.95-0.997; p=0.03), Preoperative hemoglobin < lower limit of normal (HR 1.59, 95% CI 1.11-2.27; p=0.01), thrombus level (HR 2.4, 95% CI 1.3-4.3; p=0.005), perinephric fat invasion (HR 1.5, 95% CI 1.05-2.02; p=0.03), and non-clear cell histology (HR 1.8, 95% CI 1.06-3.0; p=0.03). Estimated 5-year RFS was 49% overall. When independent predictors were considered unweighted, the 5 year RFS for patients with 0, 1, 2, >2 risk factors was 77%, 53%, 47%, and 20% respectively. (Figure 1 supplemental)

Risk factors for recurrence were developed into a predictive nomogram for recurrence of RCC following nephrectomy and tumor thrombectomy (figure 1). ROC curves were constructed to evaluate the predictive accuracy of the model. The area under the curve (AUC) for the nomogram in the development cohort (n=465; UW, UTSW, MDA) and validation cohort (n=171; Emory, IU) were 0.726 and 0.724 respectively (Figure 2). Decision curve analysis was performed to determine the

potential clinical benefit of the nomogram to predict RCC recurrence for differing thresholds. Decision curves for net benefit are displayed in Figure 2 supplemental. The decision curve analysis demonstrates predictive ability for the nomogram for risk thresholds between 20-80%. Sites of recurrence are shown in supplemental figure 3.

Patients were classified according to UISS system as previously described,[5] and figure 3a shows Kaplan Meier estimated survival according to UISS intermediate or high risk groups (p=0.001). Using only patients from the UISS high risk cohort, risk factors from the thrombus nomogram were able to further predict recurrence risk, with 5 year RFS for 0, 1, 2, >2 risk factors of 84%, 48%, 44%, and 17% respectively (figure 3b). Similarly, for intermediate risk UISS patients, the number of risk factors from the thrombus nomogram were able to significantly predict recurrence risk, with 5 year RFS for 0, 1, 2, >2 risk factors of 75%, 57%, 53%, and 30% respectively (figure 3c). ROC curves were constructed to evaluate the predictive accuracy of the thrombus model vs. the UISS model (figure 4a), the SSIGN model (figure 4b), and the Sorbellini model (figure 4c). Predictive accuracy for the thrombus nomogram was higher than the UISS model (AUC 0.726 vs. 0.595, p=0.001), SSIGN model (AUC 0.713 vs. 0.612, p =0.04) or the Sorbellini model (AUC 0.709 vs. 0.638, p=0.02).

Discussion

Non-metastatic RCC patients with venous tumor thrombus are ideal candidates for studying in adjuvant clinical trials because approximately 50% of patients are non-metastatic at presentation and approximately 50% of patients recur following surgery. However, there is significant variability with respect to individual recurrence risk. Herein, we present a predictive nomogram for risk of 5-year recurrence that was developed and validated using contemporary independent populations of patients treated at five centers. Importantly, the predictive accuracy of the nomogram was greater than the UISS model, which is used to stratify RCC patients in recently reported adjuvant therapy clinical trials.[3, 11] The low predictive accuracy of the original UISS model was not surprising as it included only 13.9% high risk patients.[5] Similarly, the SSIGN and Sorbellini models were developed with general RCC patients and these models have low predictive accuracy when compared to the nomogram. Importantly, the thrombus nomogram also demonstrated the ability to further stratify patients who were already identified as high risk by the UISS model. Improved ability to identify individual recurrence risk in non-metastatic RCC patients with thrombus may allow for better postoperative patient counseling and facilitates ideal patient selection and analysis for future adjuvant therapy clinical trials.

When developing risk assessment tools that will be applied widely, multicenter data have advantages because it minimizes potential institutional biases. The use of

contemporary data is also helpful to avoid inaccuracies associated with comparing patients treated over different decades during which imaging techniques, pathologic definitions, and surveillance regimens evolved significantly.[12-14] However, because RCC with thrombus is relatively rare, many prior studies include patients treated at a single center of excellence over several decades, include both metastatic and non-metastatic patients, and use survival endpoints to stratify individual risk.[15] However, recurrence following surgery is a more stable and clinically useful endpoint since survival for metastatic RCC (mRCC) has changed significantly during the last decade.[11, 16] Furthermore, risks for non-metastatic patients should be evaluated separately from mRCC patients since the presence of metastatic disease itself, is the critical determinant of survival in these patients. In the current series, data from non-metastatic consecutive patients treated surgically at 5 independent centers since 2000 were used to create a risk prediction model with a similar predictive accuracy in the development and validation cohorts, which outperform the current risk models for general RCC. In 2016, the S-TRAC clinical trial showed improvement in disease free survival for patients receiving sunitinib vs. placebo.[3] If future studies demonstrate improved survival, many non-metastatic RCC patients with thrombus would be excellent candidates to begin adjuvant therapy following surgery.

It is estimated that 10% of all RCC tumors will have thrombus extension into the venous system, [17, 18] and these patients are ideal for clinical trials of adjuvant therapy because of their high risk for recurrence. Improving the ability to identify the highest risk RCC patients will facilitate better clinical trial design and more accurate analysis when

investigating future adjuvant therapies. Decreasing heterogeneity within the trial population while targeting the highest risk patients may also allow for easier identification of potential benefits using fewer patients. To date, adjuvant clinical trials have used risk stratification tools that were developed for the general RCC population, which is more appropriate to separate and exclude low risk patients since these models were developed largely (86%) from low and intermediate risk patients,[5] reflecting the risk for a balanced population of RCC patients overall.[19] However, since adjuvant clinical trials primarily seek to enroll high risk patients, it is critical to use predictive models that are developed from high-risk cohorts of patients which enable stratification among a primarily high risk population. Non-metastatic RCC patients with thrombus have high but variable risk of recurrence and may benefit improved baseline risk assessment when considering enrollment in future adjuvant therapy clinical trials.

Limitations to this study include the retrospective approach and subsequent potential for biases. There were likely subtle differences in diagnostic and treatment approaches at different centers that could bias results. However, this multi-institutional approach may also allow findings to be more applicable at other centers. To evaluate associations with recurrence risk and putative risk factors while adjusting for risk in patients who died of other causes following surgery, a competing risks analysis was used. The independent predictors in this study are similar to prior study which did not use a competing risk model and also included tumor grade as a risk factor.[2] Tumor grade was not included in the final nomogram, as there was no increase in predictive accuracy when grade was considered (AUC=0.724 vs. 0.726, data not shown). Data

from 3 independent centers were included in the development cohort, and data from 2 additional centers were used for validation. The variables that have been evaluated in this study are commonly measured and should be able to be applied widely to measure risk. Common pathology traits were reviewed but there was no centralized pathology review. However, this approach more closely represents current practice. Finally, the predictive accuracy of the nomogram measured by ROC curves was fair, similar in the development and test cohort, and superior to the UISS, SSIGN and Sorbellini models.

Conclusion

Using multi-institutional contemporary data, we developed a predictive nomogram with external validation for 5-year recurrence risk following surgery for non-metastatic RCC with thrombus. Improving risk assessment following surgery allows for improved postoperative counselling and better design and analysis of future adjuvant clinical trials in high risk RCC patients.

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Figure legends:

Figure 1. Predictive nomogram for recurrence following surgery in non-metastatic RCC patients with thrombus

Figure 2. ROC curves evaluating predictive accuracy in development cohort (n=465) vs. validation cohort (n=171) for 5-year recurrence following surgery in non-metastatic RCC patients with thrombus

Figure 3a. Kaplan Meier analysis recurrence following nephrectomy with thrombectomy in intermediate or high risk groups according to UISS

Figure 3b. Kaplan Meier analysis recurrence following nephrectomy with thrombectomy using risk factors from thrombus nomogram in UISS high risk group only

Figure 3c. Kaplan Meier analysis recurrence following nephrectomy with thrombectomy using risk factors from thrombus nomogram in UISS intermediate risk group only

Figure 4a. ROC curves evaluating predictive accuracy in UISS model (AUC 0.595) vs. thrombus nomogram (AUC 0.726) for 5-year recurrence following surgery in non-metastatic RCC patients with thrombus p=0.001

Figure 4b. ROC curves evaluating predictive accuracy in SSIGN model (AUC 0.612) vs. thrombus nomogram (AUC 0.713) for 5-year recurrence following surgery in non-metastatic RCC patients with thrombus p =0.04

Figure 4c. ROC curves evaluating predictive accuracy in Sorbellini model (AUC 0.638) vs. thrombus nomogram (AUC 0.709) for 5-year recurrence following surgery in non-metastatic RCC patients with thrombus p=0.02

Figure 1 supplemental. Kaplan Meier analysis according to 6 predictive factors for recurrence following nephrectomy with thrombectomy in 636 non-metastatic RCC patients

Figure 2 supplemental. Decision curve analysis demonstrates that for threshold probability between 20 – 80%, the nomogram has a positive net clinical benefit for predicting RCC recurrence following surgery.

Figure 3 supplemental. Sites of recurrence for non-metastatic RCC patients with thrombus following surgery at 5 institutions

Table 1: Patient and disease characteristics

Characteristic		N=636(%)
Median age in years (IQR)		63.4(55.0-71.4)
Median body mass index (IQR)		29.3(26-34.4)
Gender	Male	423(66.5)
	Female	213(33.5)
Local symptoms	No	292(47.8)
	Yes	319(52.2)
	Missing data	*25*
Systemic symptoms	No	500(79.6)
	Yes	128(20.4)
	Missing data	*8*
ABO blood type	A	206(37.2)
	AB	23(4.2)
	B	63(11.4)
	O	262(47.3)
	Missing data	82
Smoker	No	297(51.2)
	Yes	283(48.8)
	Missing data	*56*
Tumor thrombus	Renal vein only	342(53.8)
	IVC <2cm	92(14.5)
	IVC >2cm	100(15.7)
	IVC below diaphragm	45(7.1)
	IVC above diaphragm	57(9.0)
Surgery year	2000-2007	290(45.6)
	2008-2013	346(54.4)
Median maximum tumor width in cm (IQR)		9(6.5-12)
Perinephric fat invasion	No	301(47.3)
	Yes	335(52.7)
2009 AJCC Pathological T stage	T3a	302(47.5)
	T3b	264(41.5)
	T3c	53(8.3)
	T4	17(2.7)
Nuclear grade	1+2	136(21.4)
	3	351(55.2)
	4	149(23.4)
Histologic subtype	Clear cell RCC	591(92.9)
	Non-clear cell RCC	45(7.1)
Sarcomatoid features present?	No	591(92.9)
	Yes	45(7.1)

Table 2. Univariate and Multivariate Competing Risks Analysis for evaluation of association of RCC recurrence and putative risk factors

	Univariate		*Multivariate*	
Characteristic	**Hazard Ratio [95% CI]**	**p-value**	**Hazard Ratio [95% CI]**	**p-value**
Age	**1.0 [0.99-1.01]**	**0.72**		
Gender				
Male	**ref**			
Female	**1.11 [0.82-1.49]**	**0.49**		
Body Mass Index	**0.97[0.95-0.998]**	**0.03**	**0.97[0.95-0.997]**	**0.03**
Local symptoms				
No	**ref**			
Yes	**0.99[0.74-1.32]**	**0.95**		
Systemic symptoms				
No	**ref**		**ref**	
Yes	**1.78[1.31-2.41]**	**0.0002**	**1.27[0.90-1.79]**	**0.18**
Blood type				
O	**ref**			
A	**1.09[0.79-1.51]**	**0.57**		
AB	**0.48[0.18-1.33]**	**0.16**		
B	**0.88[0.51-1.51]**	**0.63**		
Smoking				
No	**ref**			
Yes	**0.86[0.64-1.14]**	**0.29**		
Thrombus height				
Renal vein only	**ref**		**ref**	
IVC <2cm	**0.94[0.59-1.49]**	**0.81**	**0.83[0.51-1.35]**	**0.45**
IVC >2cm	**1.24[0.84-1.83]**	**0.27**	**0.90[0.58-1.39]**	**0.64**
IVC below diaphragm	**2.96[1.74-5.05]**	**<0.0001**	**2.36[1.29-4.30]**	**0.005**
IVC above diaphragm	**1.91[1.17-3.10]**	**0.009**	**1.18[0.68-2.03]**	**0.55**
Year of surgery				
2000-2007	**ref**			
2008-2013	**1.07[0.79-1.45]**	**0.64**		
Preoperative labs				
Albumin (per g/dl)	**0.91 [0.73-1.15]**	**0.44**		
Hemoglobin <LLN	**2.12[1.57-2.88]**	**<0.0001**	**1.59[1.11-2.27]**	**0.01**
Neutrophil (per unit)	**1.02 [0.99-1.04]**	**0.17**		
Lymphocyte (per unit)	**0.97 [0.87-1.09]**	**0.66**		
Neutrophil: lymphocyte ratio	**1.04 [0.99-1.08]**	**0.08**		
Histologic subtype				
Clear cell	**ref**		**ref**	
Non-clear cell	**2.28[1.44-3.61]**	**0.0004**	**1.78[1.06-2.99]**	**0.03**
Maximum tumor width (per cm)	**1.09 [1.05-1.12]**	**<0.0001**	**1.05[1.004-1.09]**	**0.03**
Pathological stage				
T3a	**ref**			
T3b	**1.27[0.93-1.74]**	**0.12**		
T3c	**2.24[1.36-3.69]**	**0.001**		
T4	**1.75[0.85-3.61]**	**0.12**		
Nuclear grade				
1+2	**ref**		**ref**	
3	**1.53[0.97-2.43]**	**0.07**	**1.04[0.63-1.72]**	**0.87**
4	**2.57[1.58-4.19]**	**0.0001**	**1.56[0.88-2.76]**	**0.13**
Perinephric fat invasion	**1.77[1.33-2.37]**	**<0.0001**	**1.46[1.05-2.02]**	**0.03**
Sarcomatoid features	**1.94 [1.22-3.09]**	**0.01**	**1.09[0.61-1.94]**	**0.77**

Figure 1

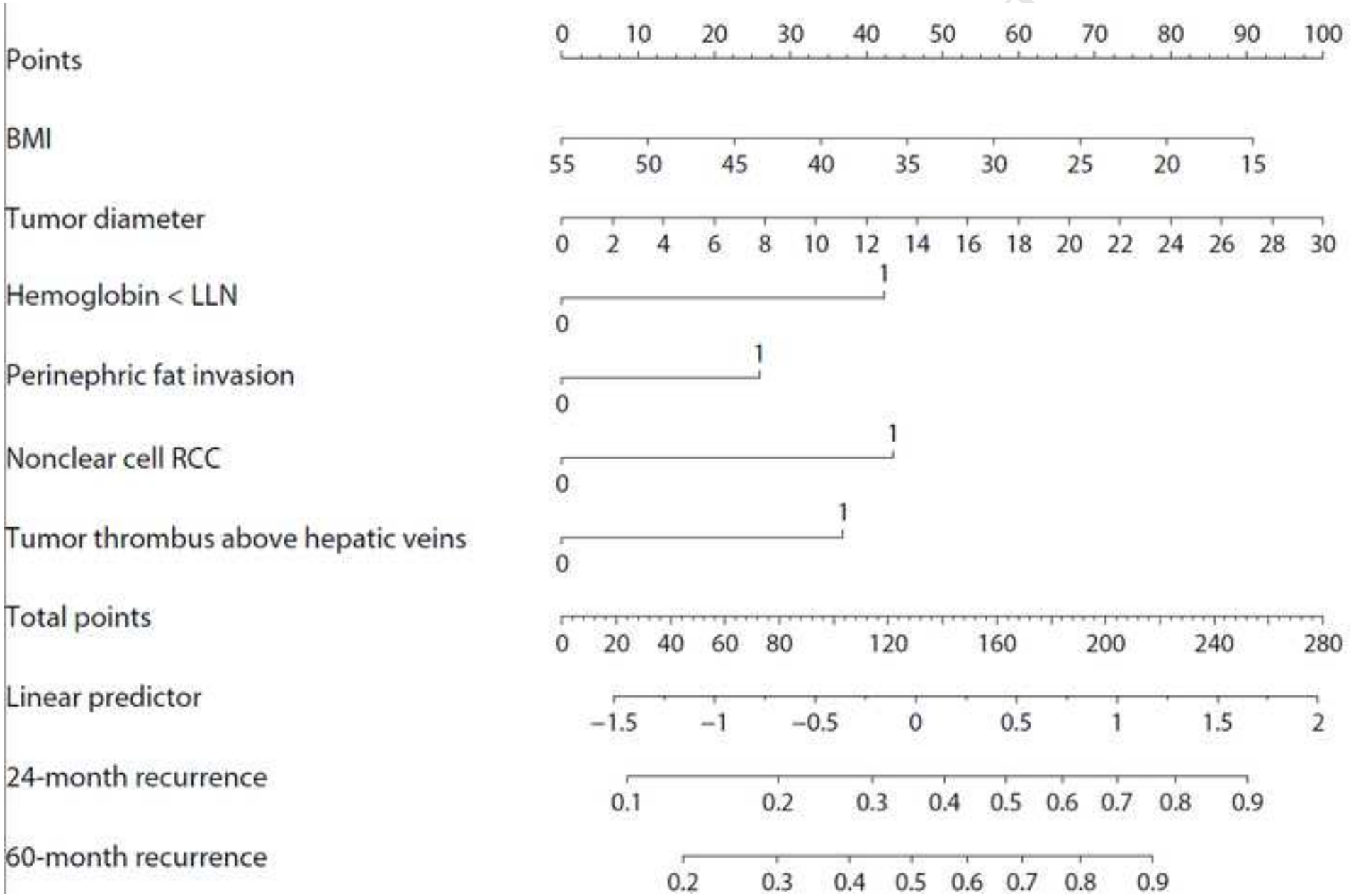

Points
0 10 20 30 40 50 60 70 80 90 100
BMI
55 50 45 40 35 30 25 20 15
Tumor diameter
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Hemoglobin < LLN
1
0
Perinephric fat invasion
1
0
Nonclear cell RCC
1
0
Tumor thrombus above hepatic veins
1
0
Total points
0 20 40 60 80 120 160 200 240 280
Linear predictor
−1.5 −1 −0.5 0 0.5 1 1.5 2
24-month recurrence
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
60-month recurrence
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

Figure 2

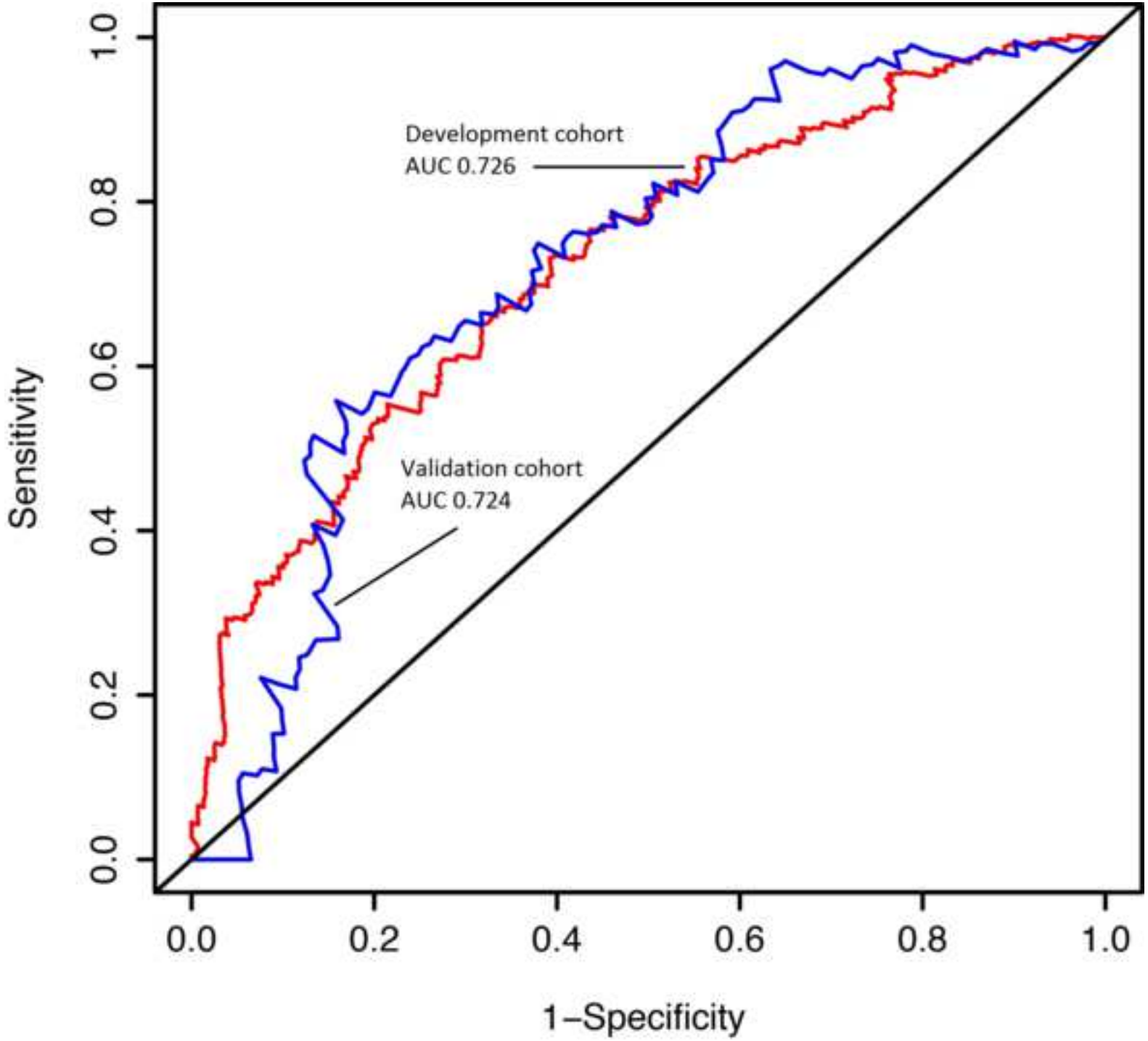

Development cohort
AUC 0.726
Validation cohort
AUC 0.724
Sensitivity
1−Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Figure 3a

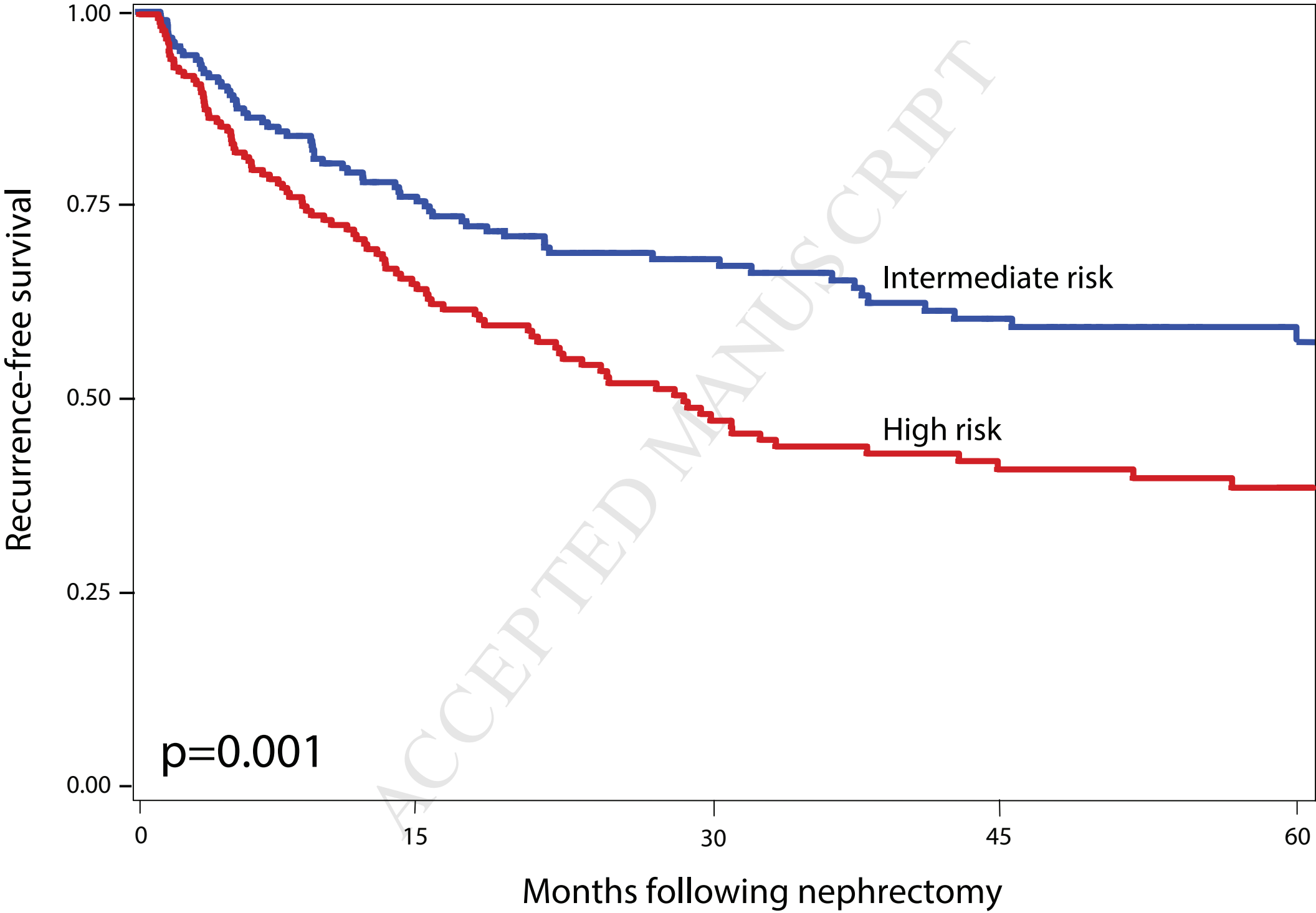


Figure 3b

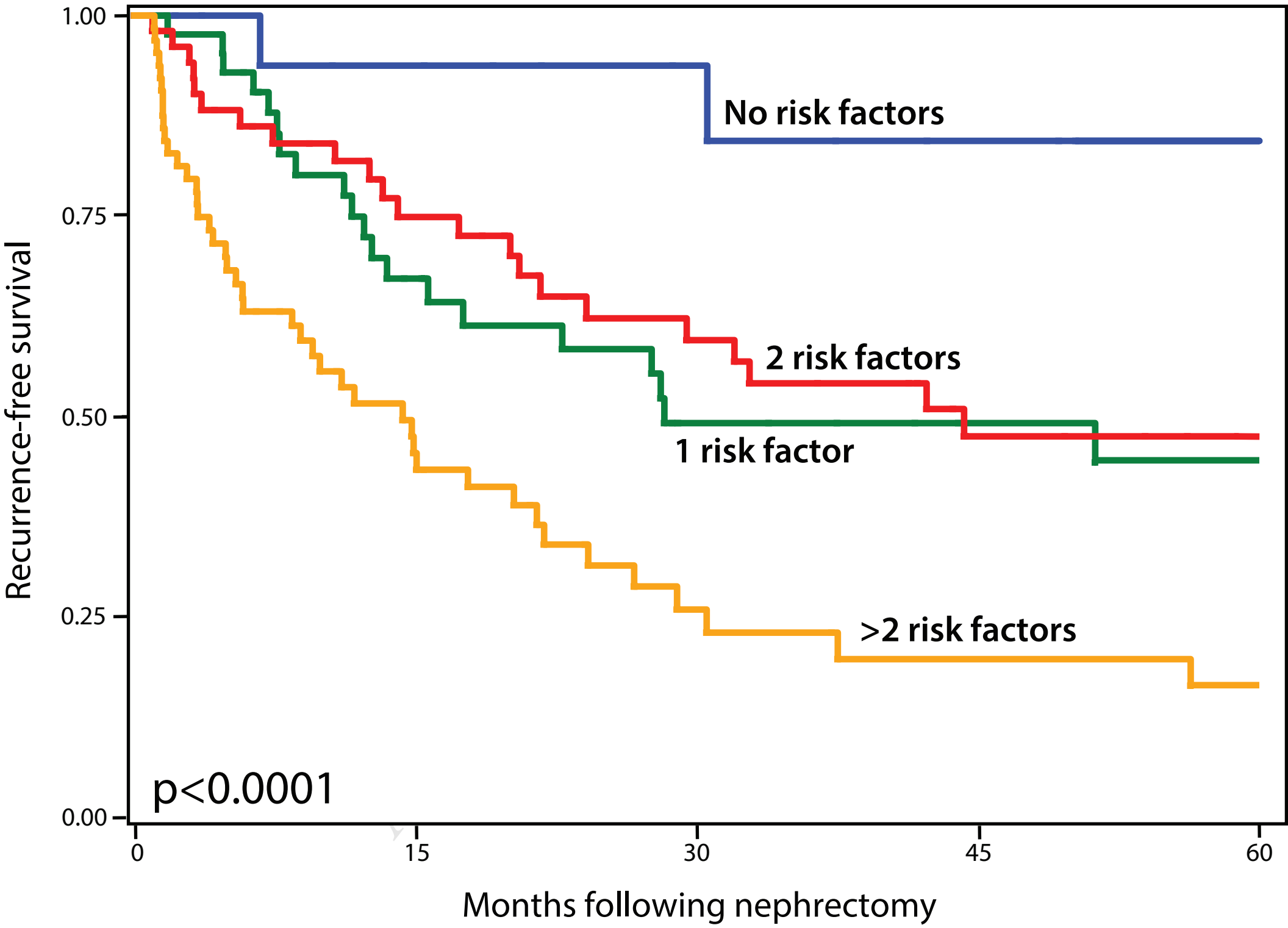

1.00
0.75
0.50
0.25
0.00
Recurrence-free survival
No risk factors
2 risk factors
1 risk factor
>2 risk factors
p<0.0001
0
15
30
45
60
Months following nephrectomy

Figure 3c

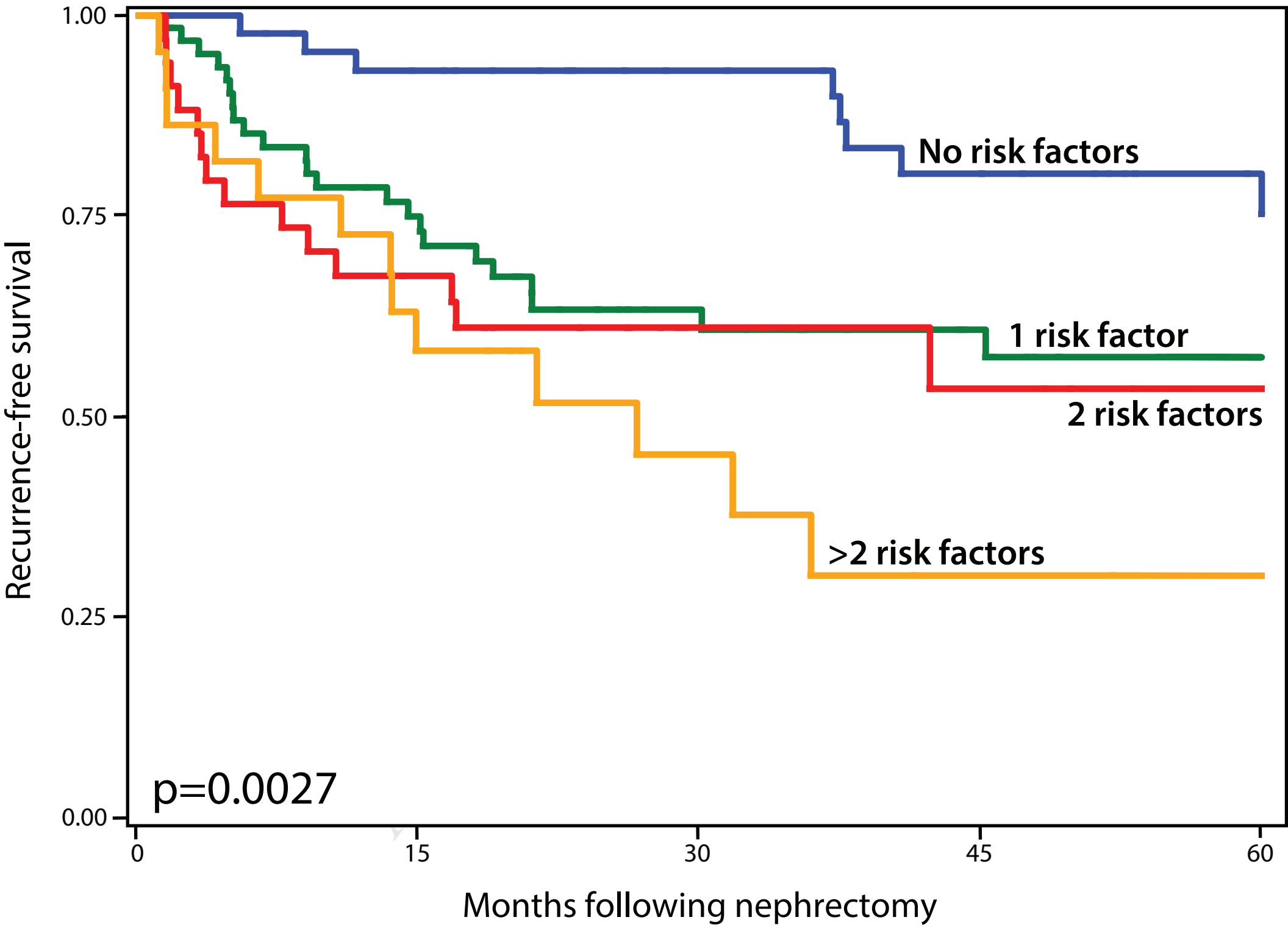

1.00
0.75
0.50
0.25
0.00
Recurrence-free survival
No risk factors
1 risk factor
2 risk factors
>2 risk factors
p=0.0027
0
15
30
45
60
Months following nephrectomy

Figure 4a

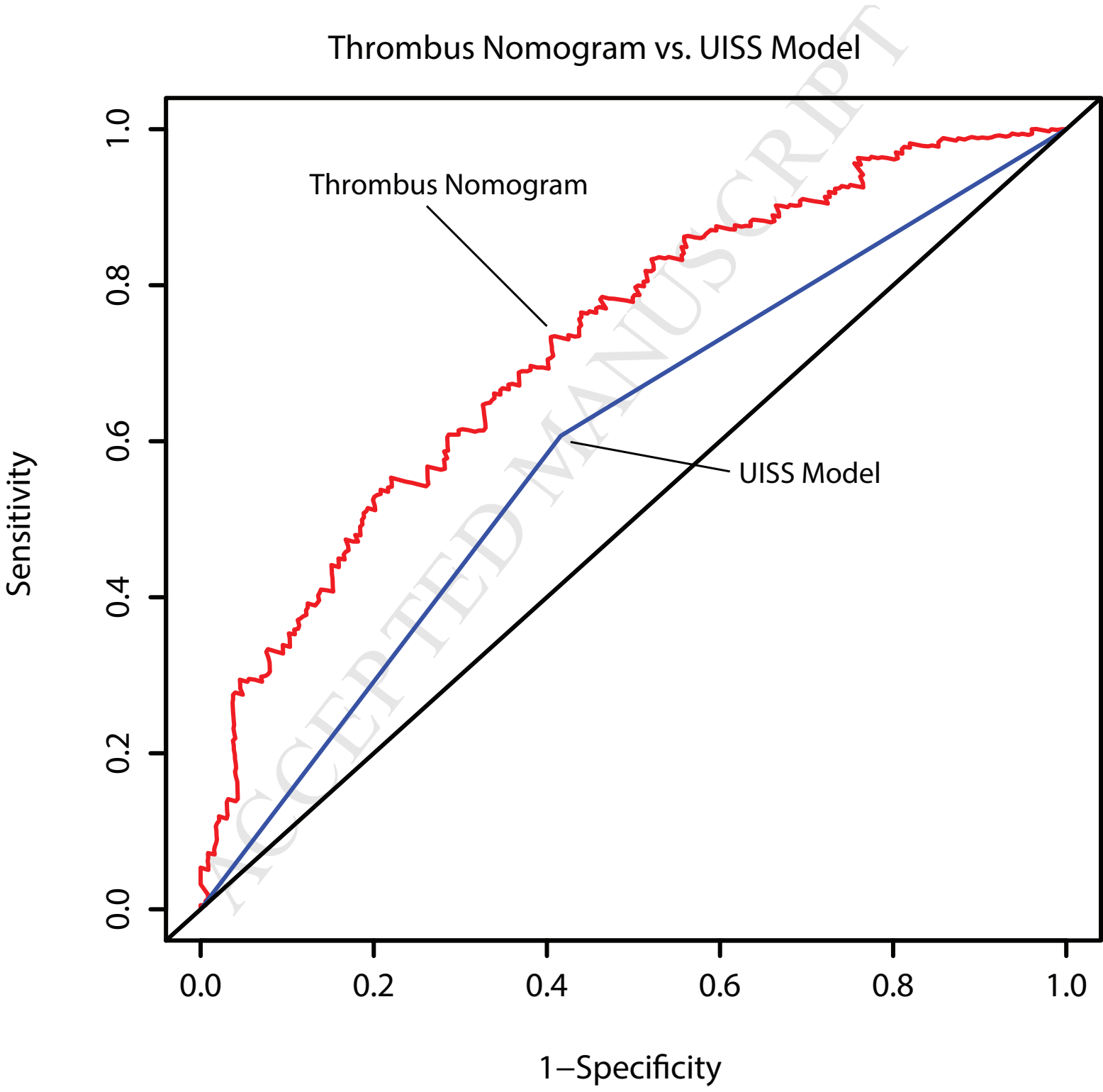


Figure 4b

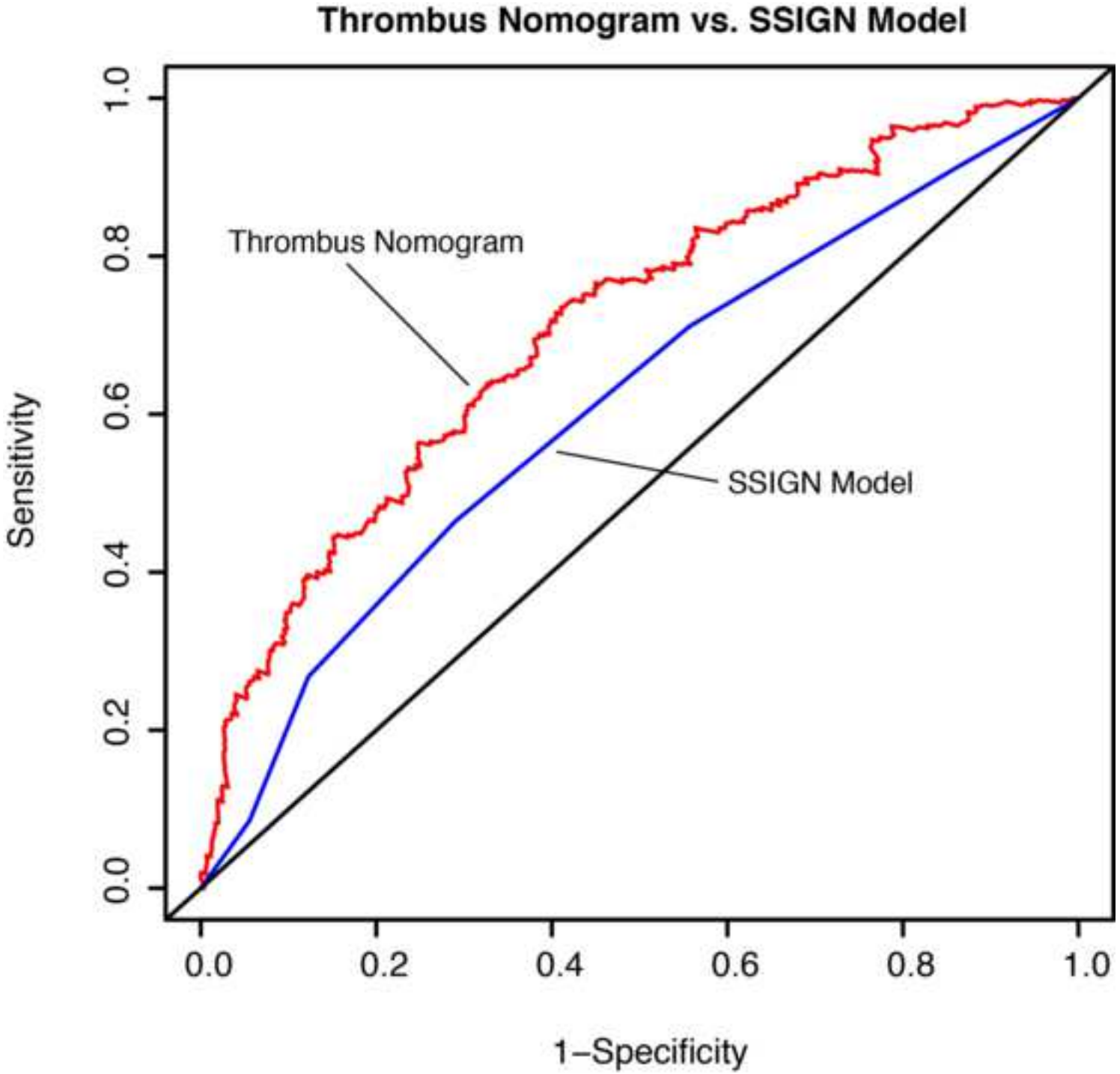
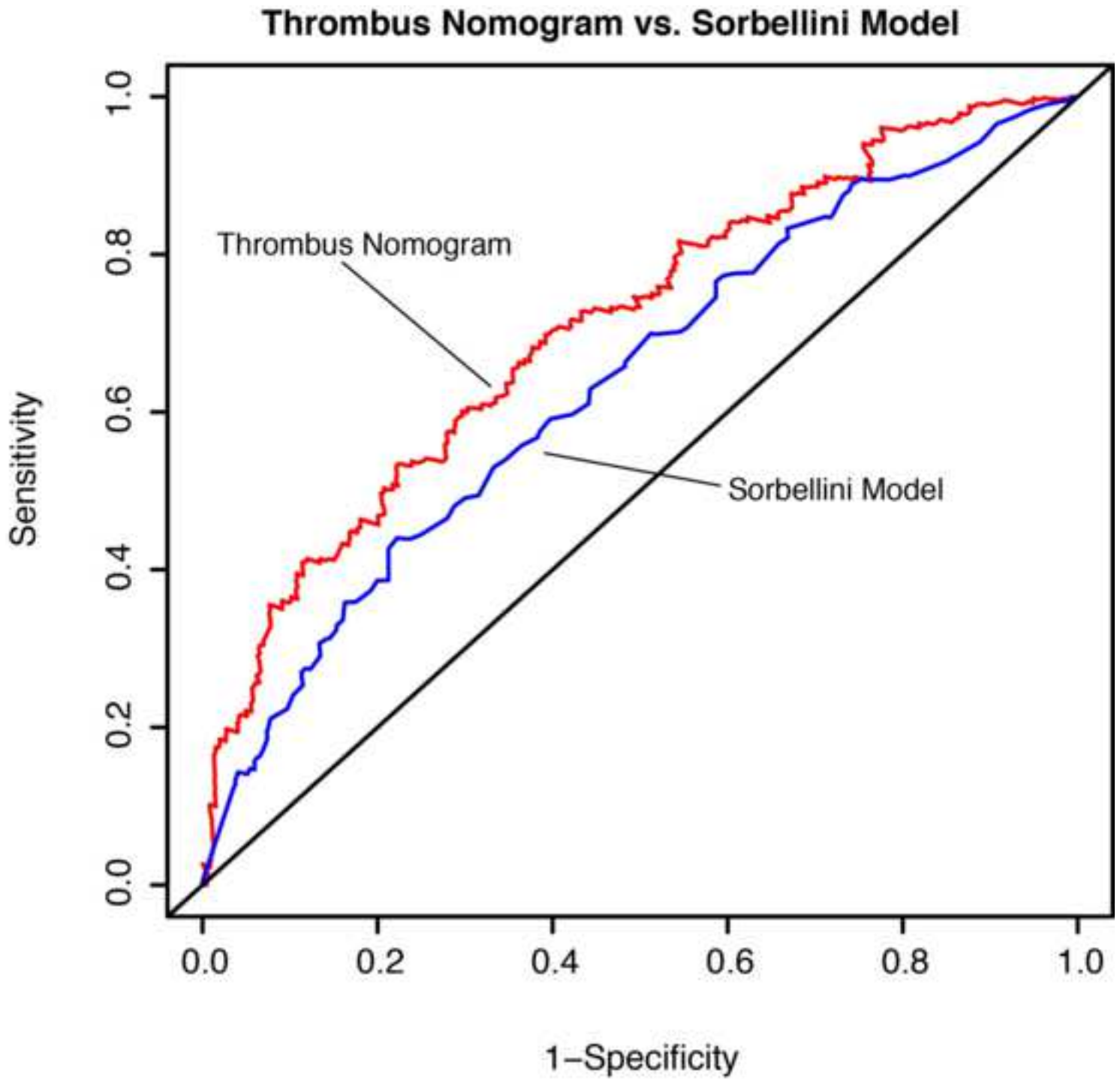

Thrombus Nomogram vs. SSIGN Model
Thrombus Nomogram
SSIGN Model
Sensitivity
1−Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Figure 4c


Thrombus Nomogram vs. Sorbellini Model
Thrombus Nomogram
Sorbellini Model
Sensitivity
1−Specificity
0.0
0.2
0.4
0.6
0.8
1.0

KEY OF ABBREVIATIONS

renal cell carcinoma (RCC), Inferior Vena Cava (IVC), recurrence-free survival (RFS), UCLA Integrated Staging System (UISS), Stage, Size, Grade and Necrosis (SSIGN), body mass index (BMI), inter quartile range (IQR), reference (ref), hazard ratio (HR), confidence interval (CI), year (yr), upper limit of normal (ULN), lower limit of normal (LLN)