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ORIGINAL RESEARCH

Risk model in stage IB1-IIB cervical cancer with positive node after radical hysterectomy

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Abstract: The purpose of this study was to identify risk factors in patients with surgically treated node-positive IB1-IIB cervical cancer and to establish a risk model for disease-free survival (DFS) and overall survival (OS). A total of 170 patients who underwent radical hysterectomy and bilateral pelvic lymphadenectomy as primary treatment for node-positive International Federation of Gynaecology and Obstetrics (FIGO) stage IB1-IIB cervical cancer from January 2002 to December 2008 were retrospectively analyzed. Five published risk models were evaluated in this population. The variables, including common iliac lymph node metastasis and parametrial invasion, were independent predictors of outcome in a multivariate analysis using a Cox regression model. Three distinct prognostic groups (low, intermediate, and high risk) were defined using these variables. Five-year DFS rates for the low-, intermediate-, and high-risk groups were 73.7%, 60.0%, and 25.0%, respectively ($P<0.001$), and 5-year OS rates were 81.9%, 42.8%, and 25.0%, respectively ($P<0.001$). The risk model derived in this study provides a novel means for assessing prognosis of patients with node-positive stage IB1-IIB cervical cancer. Future study will focus on external validation of the model and refinement of the risk scoring systems by adding new biologic markers.

Keywords: cervical cancer, risk model, lymph node metastasis, disease-free survival, overall survival

Introduction

Cervical carcinoma is one of the most common causes of cancer death in women across the world.[1,2] Experts estimated that there were 527,600 new patients and 265,700 deaths across the world in 2012.[3] In the USA, >12,000 women are diagnosed every year with invasive cervical carcinoma and >220,000 women are living with the disease.[4] Outside of the USA, the prevalence of cervical cancer is more frequent. In some areas of Europe and Asia, also of the People's Republic of China,[5–7] radical surgery is indicated for patients with early cervical cancer. Surgery not only removes the disease but also provides accurate pathologic staging information, and the pathologic staging information facilitates clinicians to target adjuvant therapy.

Although retroperitoneal lymph node status is not included in the International Federation of Gynaecology and Obstetrics (FIGO) staging system, it is an important determinant of treatment, especially to design a radiation treatment plan.[8–11] The positive pelvic node rate in stage IB-IIB is reported to be 15%–31%.[11] Five-year survival rates in patients with lymph node metastasis (LNM) vary greatly and has been declared to range from 30% to 60%. This discrepancy may mainly result from the inclusion of a relative large group of patients with a varying extent of disease spread.[12,13] Currently, patients with LNM receive mainly adjuvant concurrent chemoradiotherapy (CCRT) without evaluation of the risk factors. The recommendations made when pelvic LNM are found remain controversial.

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Models that predict disease-free survival (DFS) in patients with high-risk cervical cancer are useful tools in patient management, while studies involving systemic evaluation of the clinicopathologic variables related to the prognosis for positive pelvic node are scarce. After surgery, an assessment combining the pathological factors with clinical factors makes it possible to predict long-term survival such as recurrence and survival.[12,13] Recently, to improve the predictive accuracy of a single clinicopathologic variable, several risk models have been built, and the risk models integrate the main clinical and pathological variables related to prognosis.[14–20]

This study aimed to 1) identify the prognostic factors in patients with surgically treated node-positive IB1-IIB cervical carcinoma, 2) establish a risk model for DFS rates, and 3) assess the prognostic performance of five published risk models in our patients.

Materials and methods

Patients

The patients were selected from the database from January 2002 to December 2008 (https://clinicaltrials.gov; NCT01267851). This study was approved by the Ethics Committee at Tongji Medical College, HUST, and informed consent was given by each patient. This study included patients who met the following criteria: patient's age was between 20 and 69 years; patients had FIGO IB-IIB cervical cancer diagnosed by at least two clinical gynecologists from 2002 to 2008; patients had only squamous, adenocarcinoma, or adenosquamous histology; and patients who received primary radical surgical treatment consisting of radical hysterectomy, pelvic lymphadenectomy, and oophorectomy and were found to have pelvic LNM. Exclusion criteria included the following: 1) patients with small-cell neuroendocrine carcinoma and cervical sarcoma, 2) patients with other severe comorbidities, 3) patients with psychiatric disease, and 4) patients who received radiotherapy or CCRT before surgery. Therefore, only 170 patients fulfilled all the criteria, and the data employed in this study were from a total of 2,811 patients.

Follow-up study

DFS was defined as the time from the first day of assignment until the date of first relapse or death (regardless of cause).[21,22] Monitoring comprised pelvic physical examination and vaginal cytology examination and magnetic resonance imaging (MRI) or computed tomography (CT) scan of the pelvic cavity; abdomen and chest X-ray examinations were carried out every 6 months for the first 2 years and once a year thereafter.

Statistical analysis

DFS is defined as "the time interval from surgery to the first recurrence or death, regardless of any cause".[21,22] Those patients who were alive together with no recurrence were censored at the last medical contact. Log-rank function was used for the overall survival (OS) and DFS comparisons. A Cox model was used for multiple regression analysis to verify whether clinical variables and pathological response variables predict OS and DFS. Before the starting of multiple analysis, variables included in our model were first screened by univariate analysis ($P \leq 0.1$), a method that removes unimportant variables; consequently, the method ensures a more manageable set of variables. These variables can then be analyzed by multivariate regression; they were retained in the multivariate regression if their associated multivariate P-values were <0.05 or they were necessary for the model.[23–25] The statistical analyses were carried out using IBM SPSS 19.0. $P<0.05$ was considered to be statistically significant.

Results

Patient data

Among a total of 2,811 women with FIGO IB1-IIB cervical cancer, 170 women were included in the study. Baseline clinical characteristics of the 170 women are described in Table 1. The table shows that the median value of women's age was 42 years (range: 25–66). The median number of pelvic LNMs was 2.00 (range: 1–15). During our follow-up, 55 cancer recurrences and 42 cancer deaths were identified. The 5-year DFS rates were 65%, and 10-year DFS rates were 52%, whereas the 5-year OS rates were 71% and 10-year OS rates were 55%. Information regarding the location of recurrence is not available in the database and therefore was not analyzed.

Univariate Cox regression for recurrence

Both presenting clinical variables and pathological variables were used to assess the risk factors for patient outcomes after radical hysterectomy. In univariate Cox analysis for recurrence, common iliac LNM ($P<0.001$), FIGO stage ($P=0.02$), parametrial involvement ($P=0.002$), and the number of positive nodes ($P=0.02$) were significantly associated with DFS rate (Table S1).

Table 1 Demographic and clinical characteristics of patients (n=170)

Characteristics	Patients	
	N	%
Age at diagnosis (years)		
<30	7	4.1
30–39	64	37.6
40–49	63	37.1
50–59	29	17.1
60–69	7	4.1
Parity		
<2	76	44.7
≥2	85	50.0
Unknown	9	5.3
Histology		
Squamous	145	85.3
Adenocarcinoma	19	11.2
Adenosquamous	6	3.5
Grade		
1	18	10.6
2	90	52.9
3	62	36.5
Tumor size		
<4 cm	122	71.8
≥4 cm	48	28.2
Number of positive lymph nodes		
1	66	38.8
2	42	24.7
3	29	17.1
4	12	7.1
≥5	21	12.4
Bilaterality of lymph node metastasis		
Unilateral	99	58.2
Bilateral	71	41.8
Common iliac lymph node metastasis		
No	145	85.3
Yes	25	14.7
FIGO stage		
IB1	76	44.7
IB2	29	17.1
IIA	49	28.9
IIB	16	9.4
Lymph-vascular space invasion		
No	124	72.9
Yes	46	27.1
Vaginal margin		
Negative	161	94.7
Positive	9	5.3
Parametrial infiltration		
No	152	89.4
Yes	18	10.6
Corpus invasion		
No	154	90.6
Yes	16	9.4
Deep stromal invasion		
No	72	42.4
Yes	98	57.6

Abbreviation: FIGO, International Federation of Gynaecology and Obstetrics.

Development and validation of the risk model based on scoring system

The multivariate Cox model, with both clinical and pathological variables included as potential risk factors, revealed that common iliac LNM (hazard ratio [HR] =3.18; $P<0.001$) and parametrial involvement (HR =2.74; $P=0.001$) were the only two variables significantly correlated with DFS (Table S2). No significant interactions were observed between the two variables retained in the model. The last but not the least, because HRs for the two variables were both of similar magnitude, binary indicators such as 0 or 1 were used to present the status of common iliac LNM and parametrial involvement (Table 2).[26]

Overall risk score was then generated by adding together the points listed in Table 3. For the risk model, three groups of women with scores of 0–2 were identified, and the scores were associated with decreasing DFS rate (Table 3; Figure 1). According to these variables and scores, the patients were classified as following: 1) low-risk group (score =0, n=131), women without any of the two risk factors; 2) intermediate-risk group (score =1, n=35), women with one of the two risk factors; or 3) high-risk group (score =2, n=4), women with two risk factors. In this study, 77.06% of patients were classified as low risk, and 22.94% of the patients were classified as high or intermediate risk. Compared with the low-risk group, the rate of cancer recurrence was much higher in both the high- (HR =7.38; $P=0.001$) and intermediate- (HR =3.21; $P<0.001$) risk groups (Table 2). The 5-year DFS rates in the three groups were 73.7%, 60.0%, and 25.0%, respectively (Figure 1). Kaplan–Meier curves according to risk group and DFS and OS rates are shown in Figure 1. The 5-year OS rates in the three groups were 81.9%, 42.8%, and 25.0%, respectively (Figure 1).

A multivariable Cox analysis was then performed to assess if the risk score system was valid in evaluating the OS rate by using clinical and pathological variables as candidate

Table 2 Factors associated with DFS and OS after multivariate Cox regression after including the risk model as a covariate (n=170)

Variables	No of patients	DFS		OS	
		HR	*P*-value	HR	*P*-value
Our risk model (score)					
0	131	1		1	
1	35	3.21	<0.001	3.04	0.001
2	4	7.38	0.001	14.52	<0.001

Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazards ratio.

Table 3 Prognostic risk models

Factors	DFS model
	Scores
Parametrial involvement	+1
Common iliac lymph node metastasis	+1
Risk groups	Points
Low	0
Medium	1
High	2

Abbreviation: DFS, disease-free survival.

factors. Moreover, compared with the low-risk group, the OS rate was significantly higher in the high- (HR =14.52; $P<0.001$) and intermediate- (HR =3.04; $P=0.001$) risk groups (Table 2).

Validation of published models

In addition, we searched PubMed for reports on risk models of long-term survival in surgically treated, node positive, early patients with cervical cancer since 1989. The search consisted of both MeSH and keyword terms related to the identification of prognostic variables and stratification of risk groups. Only studies published in English language were included. In particular, six risk models for surgically treated node-positive cervical cancer were identified. One model did not categorize the patients into risk groups. The remaining five models were confirmed and included in our study. Table S3 depicts the data used for external validation. The models categorized the patients with cervical cancer into several risk groups. All the studies are described in Table S4.

ROC curves were used to evaluate the discrimination of the models for recurrences and OS. Our new score model (area under the curve [AUC] =0.668 for disease recurrences and 0.667 for OS) has comparative discrimination with Alverez et al,[20] Lai et al,[18] Aoki et al,[15] Samlal et al,[17] and Park et al[14] (AUC =0.609, 0.642, 0.646, 0.564, and 0.575 for disease recurrences; 0.600, 0.630, 0.662, 0.564, and 0.575 for OS, respectively) (Figure S1).

Discussion

The current study analyzed the clinicopathologic data from 170 patients with FIGO IB1-IIB cervical cancer with LNM treated by radical surgery. After multivariate analysis, survival was influenced by common iliac lymph node status and parametrial involvement. Our findings are in accordance with the results showing that the location of LNM and parametrial tumor spread are strongly correlated with poor prognosis of cervical cancer.[27]

The anatomic location of LNM has been considered to be a predictor for DFS. Most of the studies reported that extensive nodal metastasis including metastasis to the nodes in or beyond the region of the common iliac vessels is a poor prognostic nodal characteristic. Several studies have reported poorer survival in patients with para-aortic lymph node involvement.[8,13,28] We found common iliac node involvement

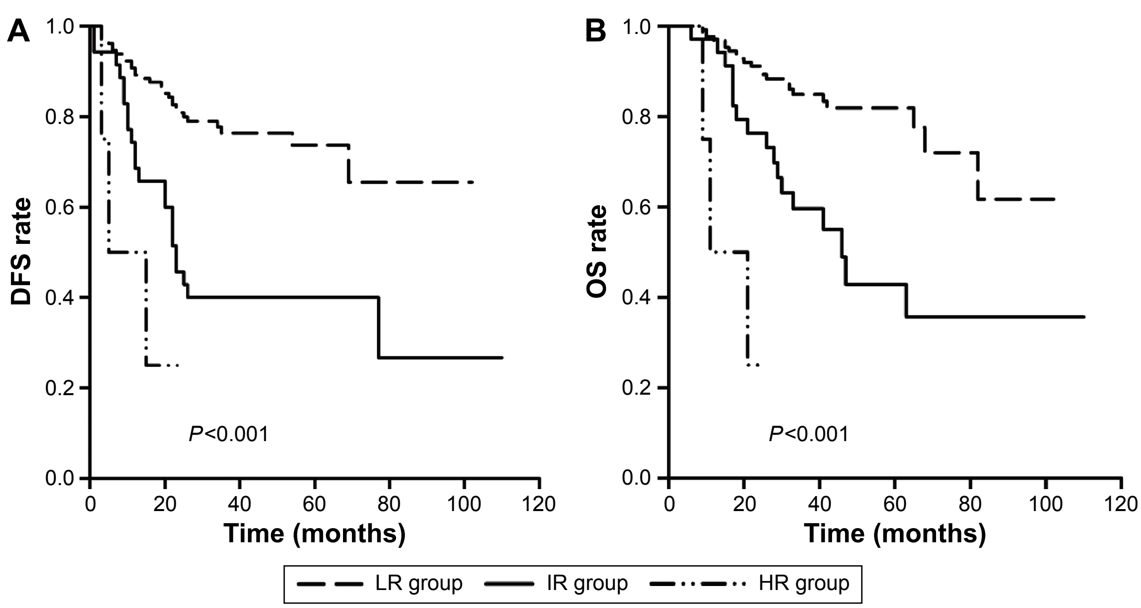

Figure 1 Kaplan-Meier analysis of DFS and OS in the risk groups.

Notes: DFS rates among the risk groups showed statistically significant differences using Log Rank test (**A**). OS rates among the risk groups showed statistically significant differences using Log Rank test (**B**). $P<0.05$ was considered to be significant.

Abbreviations: DFS, disease-free survival; OS, overall survival; LR, low risk; HR, high risk; IR, intermediate risk.

is a risk factor in multivariate Cox model, as para-aortic lymphadenectomy was not performed in all patients.

Data from previous multivariate Cox model also indicate that the involvement of parametria is a prognostic factor,[27] and our results are consistent with the previous finding. The incidence of parametrial involvement has been reported to be from 6% to 31%, and in our study it is 10.6%. Parametrial involvement was also strongly associated with other high-risk factors such as LNM, which was also reported by other scholars.[29] Compared to patients without parametrial involvement, patients with parametrial involvement were approximately seven times more likely to have positive pelvic nodes and ~12 times more likely to have positive para-aortic nodes.[27] Nevertheless, parametrial involvement was revealed to be related with a low survival rate in most of the published risk models.[14,15,17,18] Lymph vascular space invasion is also an important prognostic factor,[30] but it was not entered into multivariate Cox model in our study; this was probably due to the nature of this study, in which only patients with positive nodes were included. For the risk factors such as histology and FIGO stage, similar results were observed in this study.

Furthermore, we tried to determine whether the existing models are still valid in our patients. Table S4 presents a review of these analyses. Only the models of Aoki et al[15] and Lai et al[16] exactly fit our population. The poor performance of a model probably results from the disparity between the patients for which the model was designed and the patients employed for external validation. First, almost each risk model combined a particular set of risk factors. The risk factors selected for building the risk model is an important cause for its poor performance at another population. Second, the guidelines for postsurgery adjuvant therapy differed between the studies.

The study included an adequate sample size and had sufficient statistical power for the main outcomes. However, there were quite a few limitations. There may be recall bias due to the retrospective nature of the study. Our model did not integrate biologic makers associated with cancer progression and survival;[31,32] in the future, we will add biomarkers into our new studies. Previous studies also investigated the differences between open radical surgery, laparoscopic radical surgery, and nerve sparing laparoscopic radical surgery,[33–37] but our study did not research on this, as the data were not available at the moment and laparoscopic radical surgery showed survival rate comparable to that of radical surgery.[34,38,39] In addition, new surgery type, such as radical trachelectomy reported by Park et al,[14] should also be carefully investigated in our medical center.

Conclusion

In conclusion, we have built a prognostic risk model by integrating currently available clinicopathologic variables in women with IB1-IIB cervical cancer. Using our point-scoring risk model, patients can be easily classified as low-, intermediate- and high-risk groups for DFS rates by integrating currently available variables; the risk model was also valid in assessing the OS rates. The risk model can be taken into account by doctors when selecting primary treatment strategy for patients with cervical cancer. Meanwhile, prospective randomized controlled trials are needed to validate the risk models and to explore the benefits of postsurgery adjuvant treatment for the intermediate- and high-risk groups.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Factors associated with DFS in univariate analysis (n=170)

Variables	No of patients	DFS		
		Five-year rate (%)	HR	*P*-value
Age at diagnosis (years)				
<35	34	73.4	1	
35–45	82	65.3	1.26	0.57
≥45	54	57.6	2.00	0.09
Parity				
<2	76	68.9	1	
≥2	85	62.3	1.34	0.31
Unknown	9			
Histology				
Squamous	145	64.1	1	
Adenocarcinoma and adenosquamous	25	70.4	0.95	0.89
Grade				
1	18	76.2	1	
2	90	63.7	1.43	0.51
3	62	64.8	1.89	0.24
Tumor size				
<4 cm	122	66.0	1	
≥4 cm	48	62.5	1.31	0.36
Number of positive lymph nodes				
<3	107	73.7	1	
≥3	63	49.6	1.85	0.02
Bilaterality of lymph node metastasis				
Unilateral	99	72.0	1	
Bilateral	71	54.4	1.47	0.16
Common iliac lymph node metastasis				
No	145	70.3	1	
Yes	25	35.6	3.19	<0.001
FIGO stage				
IB1	76	74.4	1	
IB2	29	70.3	1.29	0.55
IIA	49	53.6	2.07	0.02
IIB	16	57.9	1.69	0.24
Lymph vascular space invasion				
No	124	74.4	1	
Yes	46	55.1	1.71	0.055
Vaginal margin				
Negative	161	72.9	1	
Positive	9	27.8	1.90	0.17
Parametrial infiltration				
No	152	73.8	1	
Yes	18	37.0	2.76	0.002
Corpus invasion				
No	156	73.4	1	
Yes	14	55.0	1.39	0.45
Deep stromal invasion				
No	72	70.3	1	
Yes	98	60.4	1.61	0.10

Abbreviations: DFS, disease-free survival; HR, hazards ratio; FIGO, Federation of Gynaecology and Obstetrics.

Table S2 Factors associated with DFS in multivariate Cox regression before including the risk model as a covariate (n=170)

Variables	DFS	
	HR	*P*-value
Common iliac lymph node metastasis		
No	1	
Yes	3.18	<0.001
Parametrial infiltration		
No	1	
Yes	2.74	0.002

Abbreviations: DFS, disease-free survival; HR, hazards ratio.

Table S3 Performance of the population in different models for different risk groups

Risk models	n	Five-year DFS	HR	95% CI	*P*-value	Five-year OS	HR	95% CI	*P*-value
Alvarez et al[1]									
Low	8	100	0				0		0.98
Low–intermediate	87	71.9	1			76.9	1		
High–intermediate	69	52.9	1.63	0.94–2.81	0.08	63.1	1.68		0.10
High	6	50	2.27	0.68–7.55	0.18	53.3	2.28		0.27
Lai et al[2]									
Low	64	78.2	1			82.8	1		
Intermediate	62	62.4	1.70	0.85–3.42	0.14	69.9	2.03	0.90–4.55	0.09
High	44	49.1	2.85	1.42–5.66	0.003	58.3	3.28	1.44–7.43	0.005
Samlal et al[3]									
Low	129	66.9	1			81.5	1		
High	41	58.5	1.54	0.88–2.71	0.13	56.7	1.89	0.99–3.52	0.053
Aoki et al[4]									
Low	63	79.9	1			77.7	1		
Intermediate	92	60.2	2.03	1.05–3.94	0.035	68.9	2.36	1.06–5.23	0.035
High	15	30	4.44	1.91–10.31	<0.001	34.6	6.10	2.35–15.84	<0.001
Park et al[5]									
Low	113	67.3	1			78.2	1		
Intermediate	57	60.1	1.58	0.93–2.69	0.09	60.1	1.78	0.97–3.26	0.06
High	0								
The present study									
Low	131	73.7	1			81.9	1		
Intermediate	35	60.0	3.21	1.85–5.59	<0.001	42.8	3.04	1.61–5.73	0.001
High	4	25.0	7.38	2.23–24.50	0.001	25.0	14.52	4.15–50.88	<0.001

Abbreviations: DFS, disease-free survival; HR, hazards ratio; OS, overall survival; CI, confidence interval.

Table S4 Prognostic models for early-stage cervical cancer treated with radical hysterectomy and pelvic lymph node dissection

References	Characteristics			Prognostic variables employed in the model					
	n	Stage	Histology	TS	LVSI	PMI	Number of LNM	Histology	Others
Alvarez et al[1]	185	IB-IIA	SCC	+			+		
Lai et al[2]	105	IB-IIB	SCC/ASC			+	+		DNA index
Samlal et al[3]	68	IB-IIA	SCC/AC			+		+	
Aoki et al[4]	59	IB-IIB	SCC/AC/ASC			+	+		
Park et al[5]	188	IA2-IIA	SCC/AC/ASC	+		+		+	

Abbreviations: SCC, squamous carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; TS, tumor size; LVSI, lymphatic/vascular space involvement; PMI, parametrial involvement; LNM, lymph node metastasis.

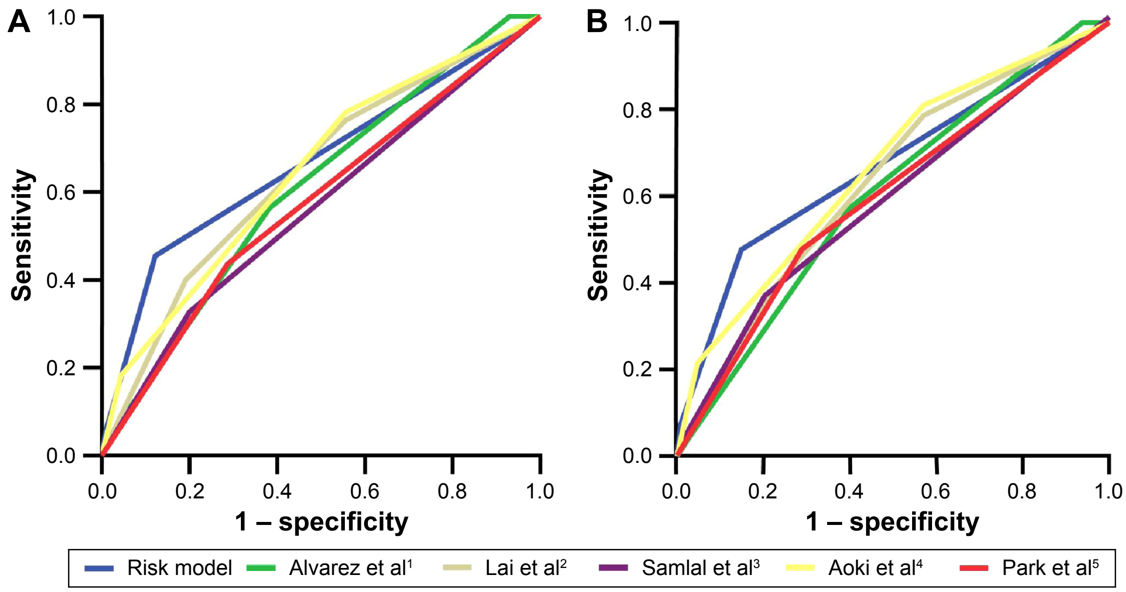

Figure S1 ROC curves for assessing the models.

Notes: The new score model and five published models were compared in evaluating the results of recurrence survival (**A**) and overall survival (**B**). AUCs were calculated to assess the discrimination of the ROC curves.

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

References

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