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Original Article

Risk factors for additional postoperative adjuvant therapy in patients with locally advanced cervical cancer and construction of a risk model

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Abstract: Objective: To investigate the influencing factors of postoperative adjuvant therapy for stage IB1-IIA2 cervical cancer, and establish a nomogram model to predict the risk of postoperative adjuvant therapy for locally advanced cervical cancer (LACC). Methods: A retrospective analysis was conducted on 144 patients with stage IB1-IIA2 cervical squamous cell carcinoma treated in Wuhan No.1 Hospital from June 2015 to January 2017, and their clinical data were analyzed. The clinical application value of the nomogram risk model was evaluated by receiver operating characteristic curve (ROC). Results: Through logistic regression analysis, we found that squamous cell carcinoma antigen (SCC-Ag), International Federation of Gynecology and Obstetrics (FIGO) stage ≥ IIA1, and laparoscopic surgery were independent influencing factors for additional adjuvant therapy after laparoscopic surgery. The nomogram model for predicting the risk of postoperative adjuvant therapy for cervical cancer constructed according to the selected variables had good predictive performance (with C-index of 0.798) and conformity. The area under the curve of established model in predicting 1-, 3- and 5-year survival time was 0.730, 0.810 and 0.830, respectively, indicating that the model has good performance. Conclusion: History of diabetes, tumor size, FIGO stage ≥ IIA1, and SCC-Ag >1.5 are independent influencing factors for additional adjuvant therapy after laparoscopic surgery of LACC patients. In addition, the constructed risk model is effective in predicting the postoperative risk of additional adjuvant therapy, which is expected to provide a reference for clinical treatment selection.

Keywords: Nomogram, locally advanced cervical cancer, postoperative adjuvant therapy, influencing factors, risk model

Introduction

The incidence of cervical cancer remains high worldwide, with confirmed annual cases of about 600,000 and a mortality rate of approximately 34%. About 90% of the patients are in developing countries with underdeveloped medical and health standards [1]. The disease has been included in the early screening, and HPV vaccination is recommended for people of appropriate age; however, its incidence still remains high due to multiple reasons, such as bad living habits and frequent sex, as well as the limited coverage and awareness of cervical cancer screening [2-4]. The International Federation of Obstetrics and Gynecology (FIGO 2009 criteria) defined stage IB2 and IIA2 cervical cancer, that is, cervical cancer with a mass greater than 4 cm, as locally advanced cervical cancer (LACC) [5]. Due to its large mass, high lymph node metastasis rate, rapid progression, and easy recurrence, patients usually have poor quality of life and short survival time [6].

At present, the clinical treatment of LACC, especially for patients with lesions greater than 4 cm, has been controversial [7]. In the National Comprehensive Cancer Network (NCCN) guidelines, concurrent chemoradiotherapy is recommended for patients with LACC. For underdeveloped countries, due to regional and economic constraints, neoadjuvant chemotherapy followed by surgery is mainly applied, and adjuvant radiotherapy is supplemented after surgery according to whether there are risk factors [8, 9]. For young patients with demands of pre-

serving ovarian function, it is better to adopt neoadjuvant therapy followed by radical surgery [10]. However, there are still a considerable number of patients who have additional adjuvant radiotherapy or radiochemotherapy due to postoperative risk factors, which exacerbates complications of patients and burdens them psychologically and economically. Therefore, choosing concurrent radiotherapy and chemotherapy at the beginning of treatment would be a better choice [11]. At present, there is no unified treatment standard for such patients in China and abroad.

In this study, our innovation is to build a risk model of predicting additional adjuvant therapy after laparoscopic surgery for IB1-IIA2 cervical cancer through nomography, which provides a tool for predicting and evaluating the treatment effect of patients.

Methods and materials

Clinical information

A retrospective analysis was conducted on 144 patients with stage IB1-IIA2 cervical squamous cell carcinoma treated in Wuhan No.1 Hospital from June 2015 to January 2017, and their clinical data were analyzed. According to the postoperative adjuvant therapy, the patients were divided into postoperative adjuvant therapy group (ATG) (n=54) and unassisted treatment group (UTG) (n=90). In addition, 67 patients with stage IB1-IIA2 cervical squamous cell carcinoma who were treated in Wuhan No.1 Hospital from January 2018 to January 2019 were collected for verification. This study was approved by the Medical Ethics Committee of Wuhan No.1 Hospital.

Inclusive and exclusive criteria

Inclusion criteria: Patients diagnosed with cervical squamous cell carcinoma of stages IB1 to IIA2 according to the 2018 FIGO staging criteria [12]; Patients with complete clinical data; Patients treated with adjuvant radiotherapy or radiochemotherapy in accordance with the diagnosis and treatment standards for cervical cancer; Patients with extensive total hysterectomy plus pelvic lymph node dissection. All patients had no contraindications to surgery.

Exclusion criteria: Transferred patients; Patients with other malignant tumors; Patients who had received targeted anti-tumor therapy before this treatment; Patients intolerant to treatment drugs; Patients dropped out of the hospital; Patients combined with severe cardiovascular, cerebrovascular, liver and kidney insufficiency and other systemic diseases; Patients in pregnancy.

Treatment regimen

Nine weeks before surgery, 150 mg/m^2 paclitaxel (Jiangsu Jiuxu Pharmaceutical Co., Ltd., GYZZ H20067715) and 50 mg/m^2 cisplatin (Yunnan Bio Pharmaceutical Co., Ltd., GYZZ H20043889) were given by continuous intravenous drip for 3 days at an interval of 3 weeks for a total of 6 weeks as a course of treatment, 10 mg dexamethasone (Yunnan Dianchi Pharmaceutical Co., Ltd., GYZZ H53021373) was orally administered 6 and 12 h before paclitaxel intravenous drip, and 50 mg diphenhydramine (Yichang Humanwell Pharmaceutical Co., Ltd., GYZZ H42021982) was orally administered 30 min before paclitaxel intravenous drip. All preoperative examinations were performed 3 weeks after the end of neoadjuvant chemotherapy, and total hysterectomy plus pelvic lymphadenectomy was performed.

Clinical data collection

Age, body mass index (BMI), weight, menstrual history, reproductive history (pregnancy, parity, mode of delivery), underlying diseases (with hypertension and diabetes), and marital status were collected from each patient.

Pathological data collection

Clinical stage (IB1-IIA2), lymph node metastasis, tumor diameter, hemoglobin (Hb), squamous cell carcinoma antigen (SCC-Ag), degree of tissue differentiation, pathological type, distant metastasis and tumor recurrence, etc. were collected. In addition, preoperative neoadjuvant therapy plan, surgical route, and postoperative additional adjuvant therapy plan, etc. were also collected.

Statistical analysis

The collected data were analyzed using SPSS 20.00 (IBM Corp., Armonk, NY). Kolmogorov-

Table 1. Comparison of clinical data

Factors	Adjuvant treatment group (n=54)	Unassisted treatment group (n=90)	χ^2	P
Age			0.016	0.896
≥ 30 years old	24	41		
<30 years old	30	49		
Age of Menarche			1.159	0.282
≥ 14 years old	25	50		
<14 years old	29	40		
Number of Pregnancies			4.320	0.037
≥ 2 times	24	56		
<2 times	30	34		
Calving Number			0.663	0.188
≥ 2 times	22	40		
<2 times	32	50		
History of Hypertension			0.503	0.447
Yes	18	35		
No	36	55		
History of Diabetes			10.254	0.001
Yes	22	15		
No	32	75		

Smirnov normality test was applied for data distribution assessing. The normally distributed data were expressed as mean ± SD. and compared by Student's t-test. The categorical variables were expressed as percentage and compared by chi-square test. Multivariate logistic regression analysis (LR) was used to determine the risk factors for postoperative additional surgery in cervical cancer. The nomograms were constructed using the rms package in R version 3.6.1 (https://www.r-project.org/) as previously described [13]. Concordance indices and calibration curves were used to evaluate the accuracy of the validation model derived from regression analysis, and Hosmer-Lemeshow test was used to evaluate calibration of the model. P<0.05 (two-sided) was considered as the significance level.

Results

Comparison of clinical data

Subjects were comparable because no significant differences were observed in age, age at menarche, parity and history of hypertension between the two groups (all P>0.05, **Table 1**). However, the number of patients with more than 2 pregnancies and those without history of diabetes in UTG was significantly higher than that in ATG (both P<0.05, **Table 1**).

Comparison of pathological data of patients

No marked differences were observed in the degree of differentiation, pathological type, courses of neoadjuvant chemotherapy and Hb between the two groups (all P>0.05, **Table 2**). However, in UTG, the proportion of patients with ≥ IIA1, tumor diameter <3 cm, and SCC-Ag <1.5 during laparotomy was evidently higher than that in ATG (all P<0.05, **Table 2**).

Multivariate analysis of risk factors for additional postoperative adjuvant therapy in cervical cancer patients

According to the results of univariate analysis, we assigned values to the variables with statistical significance (**Table 3**). Logistic regression analysis showed that the history of diabetes, FIGO stage, tumor size, surgical route, and SCC-Ag were independent risk factors for patients receiving additional adjuvant therapy after cervical cancer surgery (**Table 4**, all P<0.05).

Relationship between risk prediction scores and clinical data

We established a risk prediction equation logit(p) = -2.154 + (1.535 * diabetes history) + (1.311 * FIGO stage) + (0.911 * tumor size) + (-1.397 * surgical path) + (1.046 * SCC-Ag) and tested the goodness of fit of the regression equation using Hosmer-Lemeshow (P=0.285). The risk score of patients in ATG was found to be evidently higher than that in UTG. ROC analysis found that the area under the curve (AUC) of the risk score for predicting additional adjuvant treatment after surgery was 0.814 (**Figure 1**, 95% CI: 0.7397-0.8898, P<0.001), which was ideal. Furthermore, we found a markedly higher risk score in patients with a history of diabetes, FIGO stage ≥ IIA1, tumor diameter ≥ 3 cm, laparoscopic surgery, and SCC-Ag ≥ 1.5 than that in its counterpart (P<0.05, **Figure 2**).

Table 2. Comparison of pathological data

Items	Adjuvant treatment group (n=54)	Unassisted treatment group (n=90)	χ^2	P
FIGO Staging			12.000	0.001
≥ IIA1	34	30		
< IIA1	20	60		
Tumor Size			4.662	0.031
≥ 3 cm	31	35		
<3 cm	23	55		
Differentiation			0.315	0.574
Moderately differentiated + highly differentiated	28	51		
Poorly differentiated	26	39		
Pathological Type			0.124	0.939
Squamous cell carcinoma	20	35		
Adenocarcinoma	28	44		
Other	6	11		
Number of Cycles of Neoadjuvant Chemotherapy			0.086	0.769
≥ 1 time	8	15		
<1 time	46	75		
Surgical Route			8.533	0.004
Laparotomy	10	38		
Laparoscope	44	52		
SCC-Ag (ng/mL)			4.633	0.031
≥ 1.5	34	40		
<1.5	20	50		
Hb (g/L)			1.912	0.166
≥ 110	35	68		
<110	19	22		

Note: International Federation of Obstetrics and Gynecology (FIGO), squamous cell carcinoma antigen (SCC-Ag), hemoglobin (Hb).

Table 3. Assignment table

Factors	Assignment
Number of Pregnancies	≥ 2 times =1, <2 times =0
History of Diabetes	Presence =1, Absence =0
FIGO Staging	≥ IIA1 =1, < IIA1 =0
Tumor Size	≥ 3 cm =1, <3 cm =0
Surgical Route	Laparotomy =1, Laparoscopic =0
SCC-Ag (ng/mL)	≥ 1.5=1, <1.5=0
Additional Situation	Adjuvant therapy group =1, UTG =0

Note: International Federation of Obstetrics and Gynecology (FIGO), squamous cell carcinoma antigen (SCC-Ag).

Nomogram model construction

According to the variables selected by multivariate logistic regression analysis (diabetes history, FIGO stage, tumor size, surgical route, SCC-Ag), a nomogram risk model for adjuvant therapy after cervical cancer was established. The C-index of the nomogram risk model was 0.798, indicating that this nomogram has high accuracy (**Figure 3**). Bootstrap self-sampling method was used for internal verification, and after repeating the self-sampling 1000 times, the calibration curve was obtained (**Figure 4**). The calibration curve was close to the diagonal line, indicating that the predicted risk was close to the actual risk, and that the model had better predictive ability. Moreover, we found that the area under the curve of the model in predicting 1-, 3-, and 5-year survival was 0.730, 0.810, and 0.830, respectively, which was an ideal model by time-dependent ROC curve analysis (**Figure 5**).

Discussion

With the high incidence of cervical cancer worldwide, people's awareness of cervical can-

Table 4. Logistic regression multivariate analysis

Factors	β	Standard deviation	χ^2	P	OR	95% CI	
						Down	Up
Number of Pregnancies	-0.642	0.413	2.411	0.120	0.526	0.234	1.183
History of Diabetes	1.535	0.466	10.877	0.001	4.644	1.864	11.566
FIGO Staging	1.311	0.413	10.072	0.002	3.709	1.651	8.332
Tumor Size	0.911	0.423	4.624	0.032	2.486	1.084	5.701
Surgical Route	-1.397	0.481	8.422	0.004	0.247	0.096	0.635
SCC-Ag (ng/mL)	1.046	0.426	6.02	0.014	2.845	1.234	6.558

Note: International Federation of Obstetrics and Gynecology (FIGO), squamous cell carcinoma antigen (SCC-Ag).

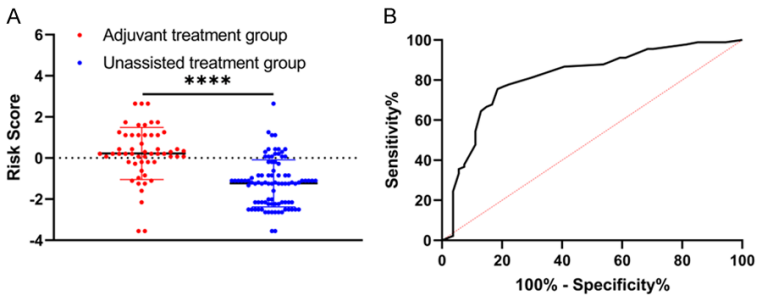

Figure 1. Risk score of the two groups and ROC analysis of the risk score in predicting additional adjuvant therapy after cervical cancer surgery. A. Risk score in patients with and without additional postoperative adjuvant therapy. B. ROC analysis of risk score in predicting additional postoperative adjuvant therapy. Note: **** means P<0.0001.

cer screening and HPV vaccination has gradually increased in recent years [14]. The incidence of cervical cancer in China is high, accounting for about 21% of the global incidence [15]. Early radical surgery is the most effective method for the treatment of cervical cancer, with few side effects and good prognosis [16]. Nonetheless, due to the high rate of vascular invasion, parametrial involvement, and lymph node metastasis, the 5-year survival rate of patients with LACC is only 50% to 70% [17]. Therefore, there is an urgent need for a reference and standard to assist physicians in making treatment decisions of neoadjuvant chemotherapy followed by radical surgery or direct concurrent chemoradiotherapy.

An earlier study [18] found that, for patients with FIGO stage IB2, IIA2, and IIB cervical squamous cell carcinoma, neoadjuvant chemotherapy with bleomycin, vincristine, mitomycin, and cisplatin regimens before radical surgery was not conducive to improving overall survival, but it could reduce the chances of patients receiving additional radiotherapy during the treatment process. Besides, another randomized controlled study [19] revealed that patients with LACC who received neoadjuvant chemotherapy plus radical surgery had higher overall and progression-free survival rates than those treated with radiotherapy alone. Therefore, combined treatment of neoadjuvant chemotherapy and radical surgery appears to have a survival benefit compared with radiotherapy alone in LACC. Surgery, for patients who want to preserve ovarian and vaginal function, seems to be a better option since the toxicity of chemoradiotherapy tends to appear early and persist for a long time [20, 21]. However, supplemental adjuvant radiotherapy or radiochemotherapy, in some cases, was needed after surgery, which inevitably leads to an increase in the time and frequency of treatment [22], as well as the incidence of adverse reactions. Based on calculated risks, concurrent chemoradiotherapy is considered to be the best practice. As a result, we used logistic regression in this study to analyze the risk factors of postoperative adjuvant therapy for patients with LACC and constructed a nomogram risk model to provide a basis for treatment selection.

We found that history of diabetes, FIGO stage ≥ IIA1, tumor diameter ≥ 3 cm, laparoscopic approach, and SCC-Ag ≥ 1.5 (ng/mL) were independent risk factors for patients receiving additional adjuvant therapy after surgery. Diabetes is a high-risk factor for cancer, and people diagnosed with diabetes or higher fast-

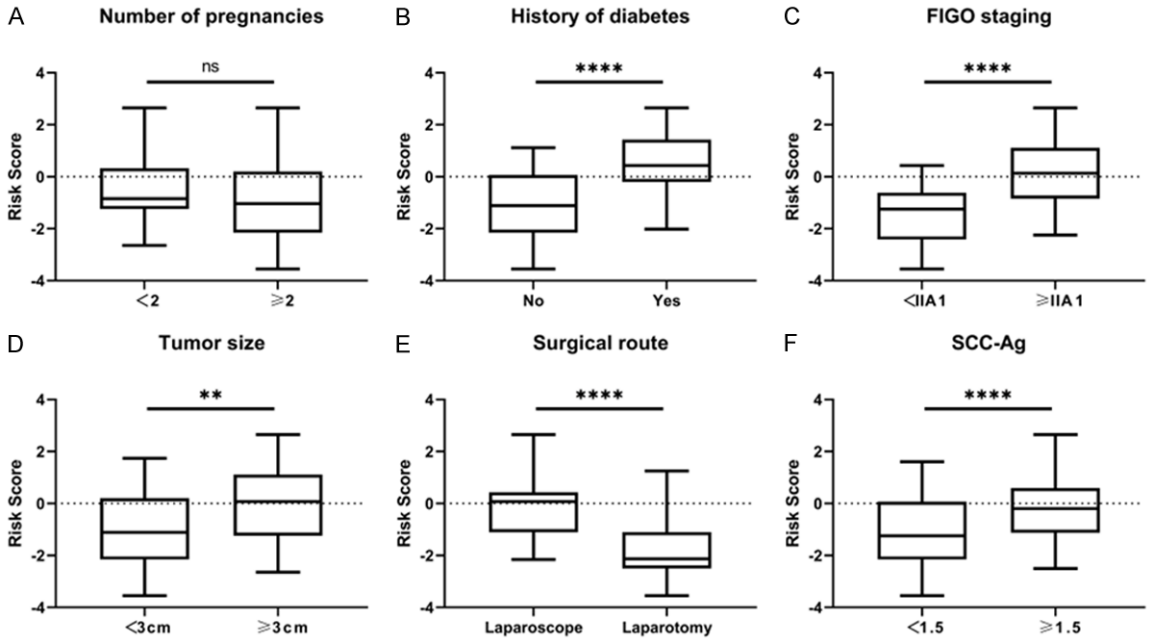

Figure 2. Relationship between the risk score and pathological data of patient. A. Risk scores of patients with different numbers of pregnancies. B. Risk score of patients with or without a history of diabetes. C. Risk score of patients with different FIGO stages. D. Risk score of patients with different tumor diameters. E. Risk score of patients with different surgical approaches. F. Risk score of patients with different SCC-Ag level. Note: ns means P>0.05 for the comparison between the two groups, ** means P<0.01 for the comparison between the two groups, **** means P<0.0001 for the comparison between the two groups. International Federation of Obstetrics and Gynecology (FIGO), squamous cell carcinoma antigen (SCC-Ag).

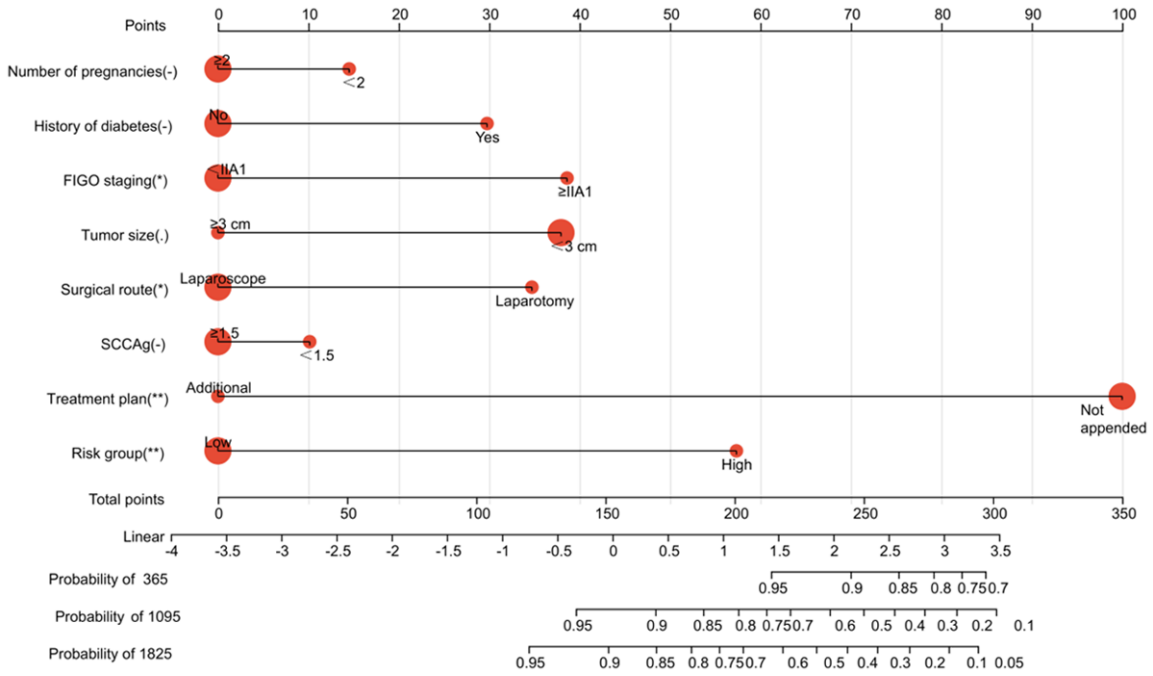

Figure 3. Nomogram model of the risk of adjuvant therapy after cervical cancer surgery. Note: International Federation of Gynecology and Obstetrics (FIGO), squamous cell carcinoma antigen (SCC-Ag).

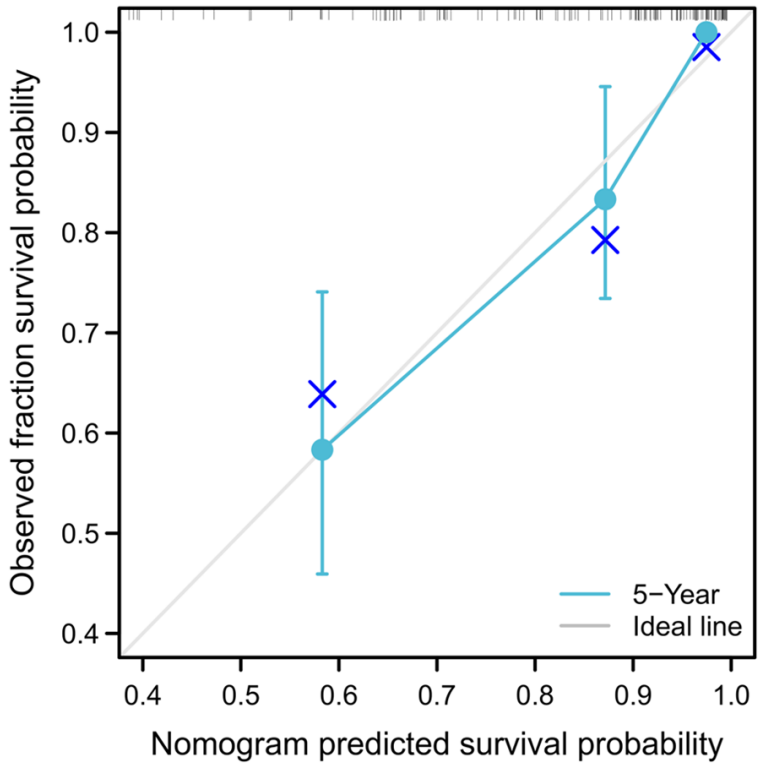

Figure 4. Model calibration curve.

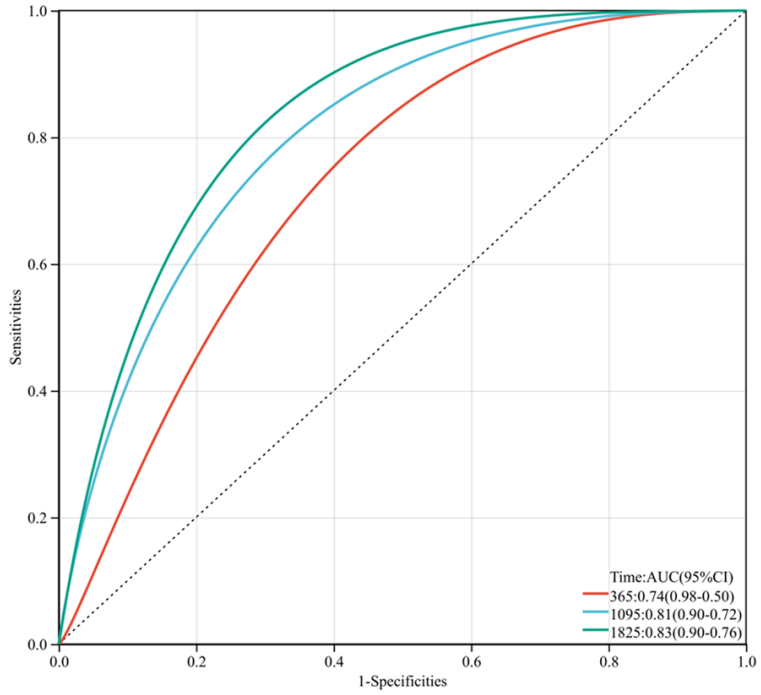

Figure 5. Time dependent ROC curve of nomogram model. Note: Receiver operating curve (ROC).

ing blood glucose typically tend to face increased cancer incidence and mortality [23, 24]. FIGO staging, on the other hand, has important guiding significance for the treatment and prognosis of cervical cancer patients. In the study of Polterauer et al. [25], it was suggested that the higher the FIGO stage, the larger the tumor diameter, the lower the overall survival rate, the worse the prognosis, and the higher the risk of recurrence. More advanced stage indicated greater depth of tumor invasion, higher LVSI positive rate and higher risk of lymph node metastasis, all of which in turn increased the probability of postoperative adjuvant therapy and the risk of recurrence. In the study of Xu et al. [26], no statistically significant difference was observed in the prognosis between patients with stage IB2-IIA2 cervical cancer who underwent laparoscopic non-contact radical hysterectomy and abdominal radical hysterectomy. However, in Ramirez's study [15], patients with early-stage cervical cancer (FIGO staging IA1-IB1) who underwent laparotomy were found to have a higher 4.5-year disease-free survival rate and 3-year overall survival rate. SCC-Ag is a highly specific cervical cancer marker, which has guiding significance for the treatment and follow-up of cervical cancer [27]. Study has shown that the high expression of SCC-Ag was highly related to the poor prognosis of cervical cancer, and patients with low SCC-Ag levels had a higher tumor-free survival rate, a lower local recurrence rate, and were related to lymph node metastasis of cervical cancer [28].

Zou et al. analyzed the risk factors of clinical efficacy in 187 patients with FIGO stage IB2 and IIA2 cervical squamous cell carcinoma by logistic

regression and claimed that pelvic lymph node metastasis was an independent risk factor for patient survival, and that effective NACT treatment was a protective factor [29]. In this study, ROC curve analysis indicated that the area under the curve of our constructed risk model for predicting additional postoperative adjuvant therapy was 0.814. Not only that, we also found that the risk scores of patients with a history of diabetes, FIGO stage ≥ IIA1, tumor diameter ≥ 3 cm, laparoscopic surgery, and SCC-Ag ≥ 1.5 were evidently higher, which indicated that the risk score was related to the clinical data of patients and was expected to provide an objective basis for individualized precise treatment and prognosis prediction of patients with LACC. At the end of the study, we constructed a nomogram risk model based on logistic regression to screen for independent factors influencing whether LACC patients receive postoperative adjuvant therapy. After external verification, the C index is 0.798. The analysis of time related ROC curve shows that the area under the 1-year, 3-year and 5-year survival time curve predicted by the model is 0.730, 0.810 and 0.830 respectively, which is an ideal model. It shows that the accuracy of prediction is good and can effectively evaluate the patients before surgery, which has a certain reference for the selection of clinical treatment for patients with LACC.

However, this study still has certain limitations. First, as a single-center retrospective study, this study is limited by data with insufficient risk factors included, which may directly lead to biases. Second, this study did not use external data for verification, and the generalization of the model is worth further determining. Therefore, it is still necessary to conduct prospective studies with expanded sample size and more influencing factors in the future.

In conclusion, history of diabetes, tumor size, FIGO stage ≥ IIA1, and SCC-Ag >1.5 are independent influencing factors for additional adjuvant therapy after laparoscopic surgery of LACC patients. Moreover, the constructed risk model has good value in predicting the postoperative risk outcome of patients and is expected to provide a reference for clinical treatment selection.

Disclosure of conflict of interest

None.

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