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Research Article

Development And Validation Of A Simple-To-Use Nomogram To Predict 3-Year Recurrence Rate Of Ovarian Cancer.

Fanyuan Li[1], Liping Lai[1], Hong Wang[2], Shanrong Shu[1]*.

1. Department of Gynecology and Obstetrics, The First Affiliated Hospital of Jinan University, 510630, Guangzhou, People's Republic of China.

2. Department of Gynecology and Obstetrics, Guangzhou Nansha District maternal and child health hospital, 511466, Guangzhou, People's Republic of China.

Abstract

Objective: To establish a reliable nomogram model to predict the recurrence rate of ovarian cancer after surgery.

Methods: We retrospectively reviewed 216 patients diagnosed with ovarian cancer in our hospital, of which 164 cases were considered valid. Chi-square test and binary logistic regression model were used to analyze the possible predictors. After that, a nomogram model based on those significantly related predictors was established. We used the bootstrap to internally validate the predictive ability of the nomogram model and used the decision curve analysis (DCA) to compare the performance of the FIGO stage with this model.

Results: The nomogram included four significant recurrence predictors: FIGO stage (advanced ovarian cancer), omentum involvement, lymphovascular space invasion (LVSI), CA125. The accuracy of predicting the recurrence was 81.7%. The Maximum Deviation (Emax) and the Average Deviation (Eavg) of bootstrap were 0.035 and 0.007, and the area under the curve (AUC) was 0.863, which demonstrated this model had a good predictive ability. Compared with the FIGO stage, this hybrid model is more superior in predicting recurrence risk in ovarian cancer patients

Conclusions: We developed and validated a non-invasion and user-friendly nomogram model to predict the recurrence risk of patients with ovarian cancer after surgery.

Keywords : Nomogram; recurrence; ovarian cancer.

INTRODUCTION

Ovarian cancer is one of the most common cancers among women. It is highly risky due to poor prognosis and difficult diagnosis by obscure symptoms[1-3]. In China, ovarian cancer is the leading cause of death among gynecologic cancer[4]. Without an effective method to early diagnosis and treatment, it is usually diagnosed when it developed to a terminal stage, which resulted in a recurrence rate as high as 10%~50% and the highest mortality rate of 43.1% among gynecologic malignant tumors [4,5]. The most common therapy is cytoreductive surgery accompanied by chemotherapy or target therapy [6]. Even with effective treatment, most patients will undergo recurrence. How to sieve out the patients at high risk of recurrence is very imperative.

To estimate the risk of recurrence, we must consider many factors such as age, FIGO stage, LVSI, omentum involvement, adjuvant treatment, histological types. Even considering those risk factors, no widely accepted predictive tools exist nowadays.

Nomogram is a kind of graphic score used to predict clinical outcomes, such as long-term survival [7], which is widely used to predict the recurrence or survival of many tumors. However, there are few studies using nomogram models to predict the recurrence of ovarian cancer. The purpose of this study is to establish a nomogram model to predict a 3-years recurrence rate of ovarian cancer after surgery, which can provide effective information for clinicians to individually deal with patients.

***Corresponding Author:** Shanrong Shu , The Department of gynecology and obstetrics, the first affiliated hospital of JiNan university, 613 Huangpu Road West, Guangzhou, People's Republic of China. **Tel.:** +86-(0)20-38688769, **Fax:** +86-(0)20-38688769, **E-mail:** butterfly1705@126.com.

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METHODS

Patients selection

We retrospectively analyzed 216 patients treated in our hospital for ovarian cancer from January 2014 to September 2019. The inclusion criteria were the following: ①patients were diagnosed with ovarian cancer and only experienced one operation for this tumor. ②patients received tissue biopsy during the surgery, which confirmed lymphatic metastasis and omentum involvement. ③patients had no history of other cancers. With these inclusion criteria, only 164 patients were adopted in our study.

Data collection

We collected age as demographic and comorbidity data. Pathology-related data, including histological type, FIGO grade, LVSI, omentum involvement, hepatic invasion, and serum CA125 were taken into consideration as well. This study was undertaken with the ethical approval of the Human Ethics Committee of Jinan University, which was in accord with the Declaration of Helsinki. The enrolled patients have signed the informed consent.

Recurrence

In this study, we referred to recurrence according to radiologic results or tissue biopsy within 3 years after surgery [8].

Statistical analysis

We used SPSS 21.0 and R-Studio (including R language package: rms) to perform statistical analysis. All continuous variables were evaluated by the receiver operating characteristic(ROC) curves. The continuous variables can be divided into two groups based on the cutoff values. The binary logistics regression analysis model was used to assess independent prognostic factors and forecast covariate-synergistic effects on the recurrence of ovarian cancer.

Chi-square test was used in univariate analysis to evaluate the correlation between the predictors and recurrence. Predictors with $p < 0.05$ in univariate analysis were included as candidate variate for binary logistic regression analysis. Only significant variates ($p < 0.05$) in the binary logistic regression were retained in the nomogram model. P values, odds ratio (OR), and 95% confidence intervals (CIs) were used to describe the correlation of all the risk factors with recurrence risk in this study. The most dangerous predictor was assigned to 100 scores, and the other risk factors were calculated respectively as a weighted sum based on the contribution. The bootstrap function is used to validate the predictive ability of the model. AUC, Emax, Eavg ,and S:p were used to describe the predictive ability of the model. Thereafter, we compared the performance of single and combined models using decision curve analysis (DCA).

RESULTS

General information

The total recurrence rate of ovarian cancer was 37.1% (61/164) within 3 years. The specific information of different histological types was shown in **Table 1**, 92% of cases were epithelial ovarian cancer. According to previous studies, we divided our patients into two groups, which were epithelial ovarian cancer and non-epithelial ovarian cancer respectively.

Table 1. Recurrence rate of different histological type

Histological type	Total case	Relapsed case	Recurrent rate(%)
Epithelial ovarian cancer	151	60	39.7%
Germ cell	6	1	16.7%
Sex-cord stromal	7	0	0%

ROC curves for continuous variables

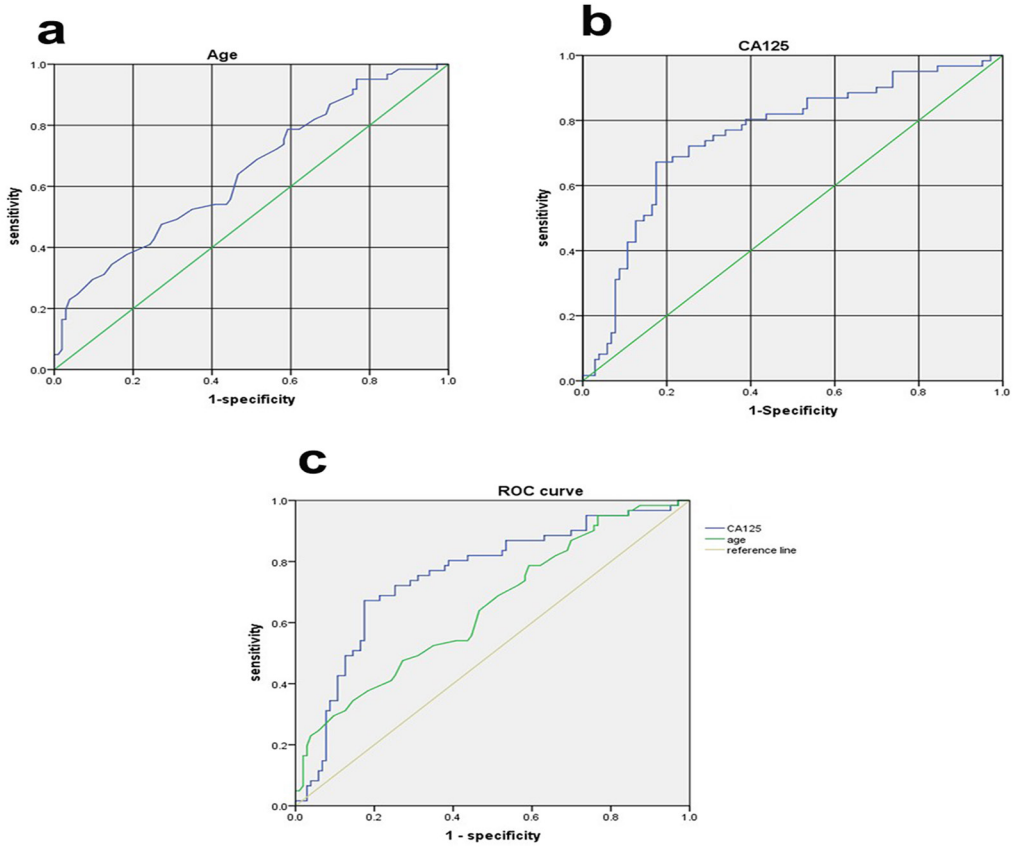
We used the ROC curve to evaluate continuous variables and identify the cutoff value, which was shown in **Fig.1** and **Table 2**. The AUC of the age, CA125 was 0.672 and 0.825 respectively.

Table 2. The characteristics of ROC of different continuous variable.

Variable	Cutoff	P value	AUC	Sensitivity(%)	Specificity(%)
Age	50	0	0.672	55.7%	55.3%
CA125	263.37	0	0.825	67.2%	82.5%

AUC: area under curve.

Figure 1. The ROC curve and AUC for each variable. a. Age. b. CA125. c. Age combined with CA125. The AUC of the age and CA125 was 0.672 and 0.825 respectively.



Univariate analysis

We performed a univariate analysis based on Chi-square (**Table 3**). The results showed the following predictors had a significant relation with recurrence, which were histological types, FIGO grade, LVSI, omentum involvement, and CA125. Therefore we used the above-mentioned index to perform further binary logistic regression.

Table 3. Univariate analysis of risk factors in ovarian cancer.

Predictors	Subgroups	Recurrent case	No recurrent case	Recurrent rate	χ2	P value
Age (years)	≤55 >55	32 29	75 28	29.91% 50.89%	7.001	0.008
Histological type	epithelial ovarian cancer	60	91	39.74%	5.261	0.022
	non-epithelial ovarian cancer	1	12	7.69%		
FIGO grade	I II-VI	26 36	87 16	23.01% 69.23%	35.605	0
LVSI	Yes No	38 23	13 90	74.51% 20.35%	44.118	0
Omentum involvement	Yes No	47 14	21 82	69.12% 14.58%	50.675	0
CA125	Yes No	41 20	18 85	69.49% 19.05%	41.147	0

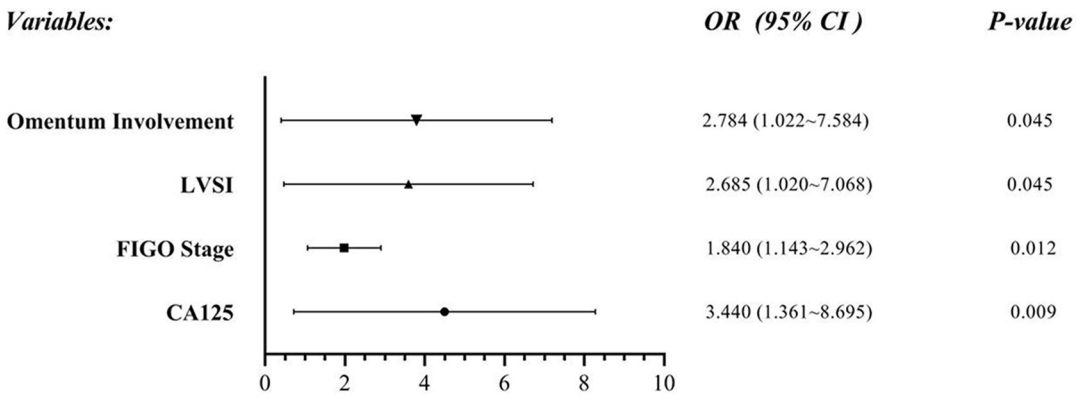
Binary logistic regression analysis

Five predictors entered into the binary logistic regression model, but only four predictors were significantly related to recurrence, which was FIGO stage, LVSI, omentum involvement, and CA125 (**Table 4**). Among them, the FIGO stage was testified to have the highest significance. The results of the multivariate analysis of those predictors were shown in the form of a Forest Plot (**Fig. 2**).

Table 4. Binary logistic regression model for prediction.

Predictors	β	Wald χ2	df	P value	OR (95%CI)
age	0.011	0.446	1	0.504	1.011(0.979~1.044)
CA125	1.235	6.815	1	0.009	3.440(1.361~8.695)
Omentum involvement	1.024	4.009	1	0.045	2.784(1.022~7.584)
LVSI	0.988	4.002	1	0.045	2.685(1.020~7.068)
Histological Type	-0.200	0.100	1	0.751	0.818(0.237~2.827)
FIGO stage	0.610	6.293	1	0.12	1.840(1.143~2.962)

Figure 2. Forest plot of different predictors. The left column listed the names of the predictors. The odds ratio for each predictor is represented by a square, and confidence intervals are represented by horizontal lines.



Establishment and Validation of Nomogram

FIGO stages, LVSI, omentum involvement, and CA125 were used to develop a nomogram model (**Fig.3**). According to the result of the nomogram (**Table 5**), FIGO stages have the greatest point (100 points), followed by CA125 (71.5 points) and omentum involvement (60 points). LVSI had the least effect on the recurrence (57 points).

Figure 3. A nomogram was constructed to quantify risk assessment for individual patient.

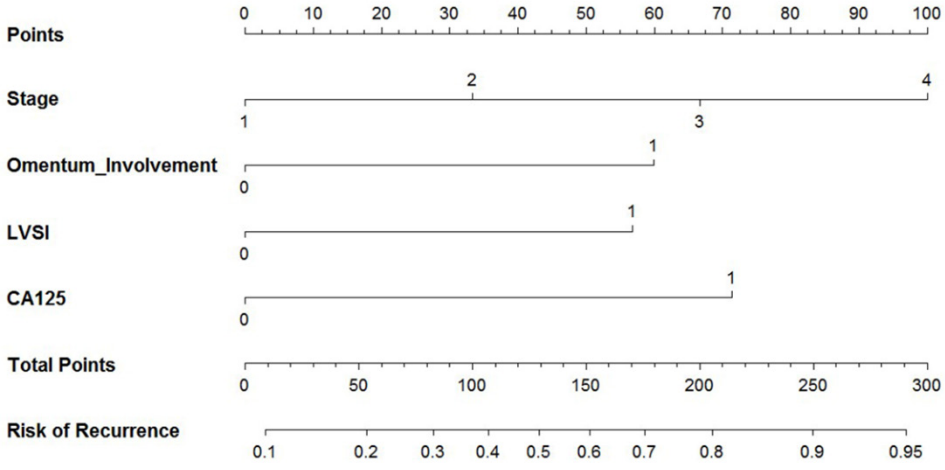


Table 5. Scoring system of predicting the recurrence of ovarian cancer.

Predictors	Scores
FIGO stages	
I	0
II	33
III	66.5
IV	100
LVSI	
No	0
Yes	57
Omentum Involvement	
No	0
Yes	60
CA125	
No	0
Yes	71.5

According to the specific score, we could infer the probability of recurrence (**Table 6**). Meanwhile, the bootsharp was used to internally verify the nomogram model. As shown in Tab.6, the score of 129 points was considered to be the cutoff for the 50% chance of recurrence. Patients whose score was greater than 129 points are more prone to relapse. According to the result of the binary logistic regression model, the accuracy of calculated prediction was 81.7% (**Table 7**). The Emax and Eavg of the bootsharp were 0.035 and 0.007 respectively. The P value of the U-test is S:p =0.975(**Fig.4a**). The AUC of this model is 0.863 (**Fig.4b**). The decision curve analysis (DCA) revealed that compared with TNM models, the hybrid model was more superior in predicting the recurrent rate of patients (**Fig. 4c**).

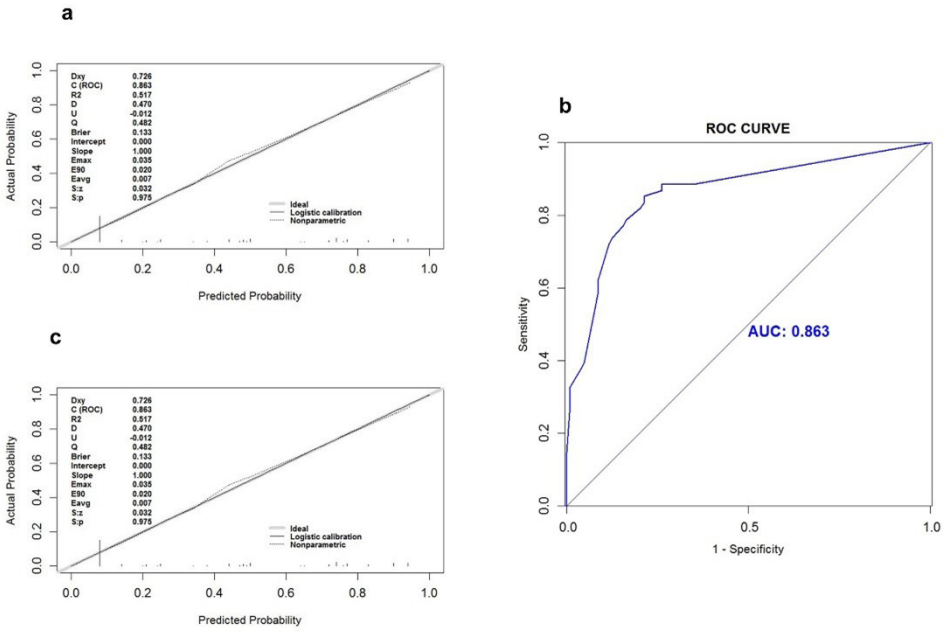
Table 6. The corresponding relation between recurrence rate and scores.

Recurrent rate	Scores
0.20	54
0.30	83
0.40	107
0.50	128.5
0.60	151.5
0.70	176
0.80	205
0.90	249

Table 7. The accuracy of calculated prediction.

Observed	Predicted		
	No-recurrence	Recurrence	Percentage correction
No recurrence	88	13	87.1
Recurrence	17	46	73.0
Overall			81.7

Figure 4.



DISCUSSION

Most studies focused on the overall survival prediction of patients with ovarian cancer [9-11], researches on the recurrence prediction model were rarely reported. Accurate prediction of the possibility of cancer recurrence after surgery is very important for patients. Here, we defined the recurrence of ovarian cancer based on the combination of radiographic imaging, symptoms, clinical examination, and biopsy [9,12-14]. In our study, we used four significant clinical factors to establish a user-friendly and non-invasion model to predict the recurrence rate of ovarian cancer.

FIGO stage is reported to play an important role in the prediction of recurrence of ovarian cancer [11]. In our study, we also found FIGO stage was a significant factor influencing the recurrence of ovarian cancer.

In accordance with many other researches on the relationship between the level of serum CA125 and the recurrence or the prognosis of ovarian cancer, our study confirmed that a high level of serum CA125 correlated with an increased risk of recurrence, which was demonstrated by the OR value of 3.440(1.361~8.695) in the logistic analysis and its high weight in the nomogram. So we inferred patients with a high initial level of serum CA125 were more prone to relapse than those with a low level.

According to the binary logistic regression analysis, omentum involvement and LVSI also showed a prominent correlation with ovarian cancer relapse. On the basis of above-mentioned four significant clinical factors, a nomogram was developed and the validation of this model by calibration curve proved the model to be highly fit and accurate for the prediction of recurrence of ovarian cancer.

Considering the limitation of the database, it is relatively hard to find enough extra data to further validate the nomogram. With the application of the “rms” package, we successfully compared the difference between the actual probability and predicted probability based on nonparametric statistics and visually depicted the deviation by the calibrated curve of logistic calibration. The Maximum Deviation (Emax) and the Average Deviation (Eavg) described the deviation between actuality and ideality. Those values should be as small as possible, in our model those values (Emax: 0.035 and Eavg: 0.007) perfectly meet the criterion. The P value of the U-test is presented by S:p. This value should be more than 0.05 if the data of the calibrated model is originated from the same sample. In our study, the value of S:p was 0.975, which demonstrated the effectiveness of our model. The area under the ROC curve was 0.863, which was bigger than 0.5. All of these parameters confirmed the accuracy of our model.

Although the theoretical accuracy of our model was as high as 81.7%, there are some defects in the prediction of more complicated cases due to the limitations of a small amount of validated data. In order to improve the reliability of our model, data in different hospitals were needed to be collected and retrospective or prospective studies should be analyzed.

Supplementary Materials

None

Acknowledgments

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Statement of Ethics

The study was approved by an ethics committee of JiNan University. We have obtained informed consent from during the treatment and got consent to publish the case from the study participant.

Conflict of Interest Statement

There were no competing interests among authors

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