Establishment and Evaluation of a Nomogram For Prediction of Peritoneal Metastasis in Gastric Cancer

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Research

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Abstract

Background Peritoneal metastasis is a critical way of metastasis for gastric cancer, patients with which tend to have poor prognosis. Laparoscopy or laparotomy is still major approach to diagnose peritoneal metastasis presently. This study was aimed to explore the factors affecting peritoneal metastasis of gastric cancer and establish a nomogram to predict that preoperatively.

Methods 1002 gastric cancer patients who underwent surgery without distant organ metastasis was collected in the study. The nomogram was built with variables selected by univariate logistical regression and LASSO, and evaluated with internal and external validation ROC curve.

Results Three factors including carbohydrate antigen 125, carbohydrate antigen 242 and serosal invasion or not of primary tumor were enrolled in the nomogram. The AUC value was0.922 (95%CI 0.897~0.947) in internal validation and 0.934 (95%CI 0.852~1.000) in external validation.

Conclusions This study developed a nomogram with risk factors easily accessible before surgery in patients with gastric cancer, which can predict the probability of peritoneal metastasis well and would be helpful for clinicians to make appropriate therapy strategies.

Introduction

Gastric cancer is one of the most malignant tumor in the world. According to global cancer statistics, more than 950,000 new gastric cancer cases and more than 720,000 deaths occurred in 2012[1]. Peritoneal metastasis (PM) is an important way of metastasis for gastric cancer. Gastric cancer patients with PM tend to lose the chance of surgery and have poor prognosis. Diagnosis of PM depends mainly on laparotomy or laparoscopy at present, which may bring unnecessary operative wound for patients with PM. There has been a lack of a good preoperative diagnostic approach to predict PM so far. Though computed tomography (CT) and positron emission tomography combined with CT (PET-CT) can be used to predict PM, they are less satisfactory because of low sensitivity (<50%) [2]. Studies have been conducted to find risk factors associated with PM such as tumor size, lymph node metastasis, Borrmann classifications, serum carbohydrate antigen 125(CA125) and so on [3-4]. MASAKI OHI et.al performed a combined ROC analysis using independent clinical predictors including tumor type, histopathology, serum carbohydrate antigen 19-9(CA19-9) and lymphocyte counts for predicting PM with an AUC value of 0.882[5]. Mimi Kim et.al developed a CT-based model to predict PM with an AUC value of 0.903[6]. Nomogram model is a novel tool for prediction widely used in many fields because it can visualize the outcome of logistic regression model to make it easy to use in clinical practice. By far there has been few studies to develop a nomogram to predict PM. This study was aimed to establish a nomogram for noninvasive prediction of PM based on data of preoperative clinical features and laboratory test indexes of blood.

Patients And Methods

Patients:

1002 patients with gastric cancer undergoing surgery without blood diseases, rheumatic diseases, acute cardiopulmonary diseases, severe infection and other tumor diseases were enrolled at Xinhua hospital affiliated to Shanghai Jiaotong University School of Medicine between January 1st, 2013 and January 1st, 2020. No patients received chemotherapy, radiotherapy and endoscopic therapy before surgery. No patients had received gastrectomy and had blood disease 1 month before surgery. All patients were classified according to the International Union against Cancer TNM Classification (Eight Edition): 272 patients had stage I disease, 172 stage II, 435 stage III and 123 stage IV. Patients with stage IV had no organ metastasis but PM. PM was diagnosed by laparotomy when metastasis nodules were found in the peritoneal cavity, postoperative pathology which confirmed metastasis nodules in the peritoneum, PET-CT or CT.

Objective clinical factors:

The patients' data recorded included sex, age, clinical features (including hemorrhage of alimentary tract or not, hypertension or not and diabetes or not), primary tumor data (including macroscopic type, tumor location, degree of tumor differentiation, tumor size and serosal invasion or not) and preoperative laboratory data of blood (including blood routine examination, liver and kidney function, coagulation function and tumor markers). Macroscopic type was classified into ulcer type, protrusion type and infiltration type. Tumor location was categorized into cardia/fundus, body/antrum and pylorus. Degree of tumor differentiation was classified into poorly, moderate and well differentiation.

Statistical analysis and variables selection:

The correlation between variables (including clinicopathological features and preoperative laboratory data of blood) and PM was analyzed by chi-square test for categorical variables, t test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables. The variables with significant statistical difference were further analyzed by univariate logistic regression to select variables as group 1. The analysis above were carried out via SPSS Statistics Software version 19.0. Next, extract complete data of variables of group 1 excluding the missing value, where LASSO (the least absolute shrinkage and selection operator) was utilized to select variables as group 2. Then the complete data of variables of group 2 extracted from original data set was divided into train set (n=782，PM positive rate was 11.1%) and test set (n=100) by stratified sampling according to peritoneal metastasis or not. The final variables as group 3 were selected by LASSO and 10-folds cross validation in train set to be used for nomogram. The analysis above were carried out via R software version 4.0.2. All p-values were two-sided and $p<0.05$ was considered statistically significant.

LASSO is a penalized regression approach that estimates the regression coefficients by maximizing the log-likelihood function (or the sum of square residuals) with the constraint that the sum of the absolute values of the regression coefficients proposed by Tibshirani in 1996[7]. LASSO can be applied to delete

unnecessary covariates and select variables as it can constrain many components to exactly 0 automatically.

Development and evaluation of nomogram:

A nomogram model was developed on the basis of variables of group 3 and evaluated by receiver operating characteristic (ROC) curve and the area under the curve (AUC) values via R software version 4.0.2. In the nomogram, the regression coefficients of variables were proportionally converted to a specific number within 0 to 100 point scale. Internal validation, external validation and 10-folds cross validation were performed respectively to evaluate the accuracy and generalization capability of the nomogram model.

Results

The correlations between PM and the clinicopathological features.

The age in 1002 patients involved in the study was between 22 and 90 with average age of 62.89, which was not related to PM (P=0.446). PM was associated significantly with hemorrhage of alimentary tract, gross pathological type, tumor location and degree of tumor differentiation (table 1). There were 140 cases of tubular adenocarcinoma, 12 cases of mucinous adenocarcinoma, 18 cases of signet-ring cell carcinoma, 585 cases of adenocarcinoma, 202 cases of mixed pathological types, 31 cases of other pathological types and 14 cases of unidentified pathological types in the patients. Considering that definite histopathologic type is difficult to determinate preoperatively, the association between PM and it was not analyzed in this study.

Table1 Correlations between peritoneal metastasis and clinicopathological features in gastric cancer

		Peritoneal metastasis		Total Number	χ^2 value	P value
		Yes	No			
Sex	Male	77(11.1%)	618(88.9%)	1002	3.015	0.083
	Female	46(15%)	261(85%)			
Hemorrhage of alimentary tract	Yes	13(7.7%)	155(92.3%)	1002	3.859	0.049
	No	110(13.2%)	724(86.8%)			
Hypertension	Yes	32(10.6%)	269(89.4%)	1002	1.080	0.299
	No	91(13%)	610(87%)			
Diabetes	Yes	10(10.2%)	88(89.8%)	1002	0.433	0.511
	No	113(12.5%)	791(87.5%)			
Macroscopic type	Ulcer	93(11.3%)	729(88.7%)	1002	9.944	0.007
	Protrusion	12(11.5%)	92(88.5%)			
	Infiltration	18(23.7%)	58(76.3%)			
Tumor location	Cardia/Fundus	19(11.7%)	144(88.3%)	1002	7.764	0.021
	Body/Antrum	96(11.8%)	716(88.2%)			
	Pylorus	8(29.6%)	19(70.4%)			
Degree of tumor differentiation	Poorly	74(11.2%)	585(88.8%)	909	25.553	<0.001
	Moderate	3(1.3%)	227(98.7%)			
	Well	0(0%)	20(100%)			
Serosal Invasion	Yes	2(0.4%)	455(99.6%)	1002	109.338	<0.001
	No	121(22.2%)	424(77.8%)			

Variables selection for prediction of PM.

The results with significant statistical difference (P<0.05) of univariate logistic regression analysis of PM were demonstrated in Figure 2. There was ultimately 39 variables associated significantly with PM. NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), FGP (fibrinogen/platelet ratio) and MONOL (monocyte/lymphocyte ratio) were also analyzed in univariate logistic regression but all of them were not related to PM significantly. Levels of serum CA199 and CA125 as well as serosal invasion was finially chosen to establish the nomogram via LASSO.

The nomogram for prediction of PM.

The nomogram was demonstrated in figure 3 with three variables selected above. The probability of PM of gastric cancer patients can be obtained through calculating the total score of the point of every variable. Furthermore, ROC curve was developed to estimate the predictive accuracy of the model (Figure 4) with AUC value of 0.922 (95%CI 0.897~0.947) in train set and that of 0.934 (95%CI 0.852~1.000) in test set, which indicated the nomogram model had good generalization capability. The optimal cut off point of PM was 64, where the sensitivity was 87.2% and the specificity was 85.6% in ROC curve analyses. 10-folds cross validation was performed in train set showed AUC value was 0.924 implying the model didn't over-fit the train set.

Discussion

As one of important types of metastasis, PM is associated with poor prognosis in gastric cancer., the median survival time of patients with which was 3-6 months[8]. Gastric cancer with PM was regarded as unresectable. At present laparotomy or laparoscopy is still the major approach to diagnose PM. PET-CT is also valuable for prediction of PM but it can't be commonly used because of the high cost. As for CT, poor sensitivity limits its application to detect PM. In order to detect PM non-invasively and easily, a nomogram was established to predict PM based on variables including level of serum CA125 and CA242 as well as serosal invasion or not selected from clinicopathological features and preoperative laboratory test data of blood in this study. The variables are so accessible preoperatively by blood test and ultrasound gastroscopy that the nomgram can be applied to clinical practice. The model had good performance for prediction with AUC value of 0.922 (95%CI 0.897~0.947) in train set and that of 0.934 (95%CI 0.852~1.000) in test set.

From the results of univariate logistic regression, we can see a lot of factors involved with PM. Gastric cancer in pylorus with infiltrative type and poorly degree of differentiation had more probability to occur PM. In addition, tumor size and serosal invasion were positively associated with PM. Patients with gastric cancer are often accompanied by malnutrition and bleeding therefore the outcome that Hb, MCV, MCH, MCHC, HCT, RBC, PAB, Alb, TP, A/G related negatively to PM was easily explained. It is well-known that "seed and soil" theory is the most popular explanation for the mechanism of PM, which compares the microenvironment of the metastatic sites to "soil" and the cancer cells to "seed" [9]. Accumulating evidences have indicated inflammation plays an important role in carcinogenesis and plenty of immune cell such as lymphocytes, neutrophils, eosinophils and so on are involved in gastric cancer microenvironment [10]. As shown in this study, L, L%, EO and BASO were negatively associated with high risk of PM while N% was positively associated with that. RDW and AST/ALT have been identified as independent prognostic factors for gastric cancer patients and relevant factors to inflammation [11-12]. On the other hand, growing researches have proved the close association between hemostasis abnormalities and gastric cancer [13]. Cancer cells can activate the clotting system directly and function like a coagulant. PCT, Dimer, Fg, PLT, FDP, PT and APTT were obviously connected with PM in this study. TBIL is considered as a strong endogenous antioxidant linked with low risk of cancer and was decreased along with the progress of TNM stage of gastric cancer, consistent with which this study implied TBIL was a risk factor for PM [14].

Stepwise regression is commonly applied to variables selection of prediction model in most studies, with which the model is prone to over-fit data and lose some important variables. Considering the disadvantages of that, LASSO was performed to select the variables in this study. The 10-folds cross validation showed AUC value was 0.924 barely different from AUC value of 0.922 in internal validation in train set, which indicated the model was not over-saturated. This study still had some potential limitations: this study was a single center retrospective study and the number of patients with PM was small. The sample size should be expanded and the nomogram needs further external validation from other medical centers.

In conclusion, our study established a nomgram to improve prediction of peritoneal metastasis in gastric cancer preoperatively with variables available routinely as a potential alternative diagnostic method in clinical practice.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Xinhua hospital affiliated to Shanghai Jiaotong University School of Medicine (No.XHEC-D-2020-176). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The raw data used to support the findings of this study are available from the corresponding author upon request.

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Authors' contributions

Zheng Jin designed the study, collected the data, analyzed the data and write the manuscript. Shi Weibin was also the designer of the study and revised the manuscript. All authors read and approved the final manuscript.

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Figures

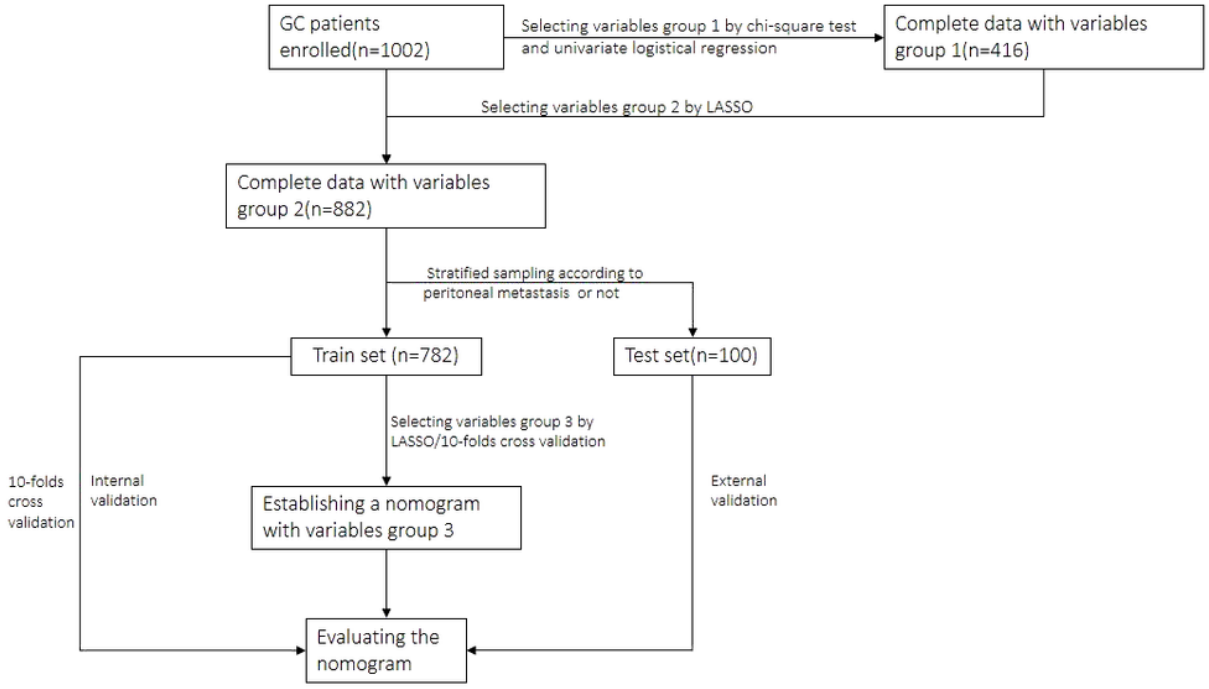

Figure 1

The procedure of variables selection and development and evaluation of the nomogram.

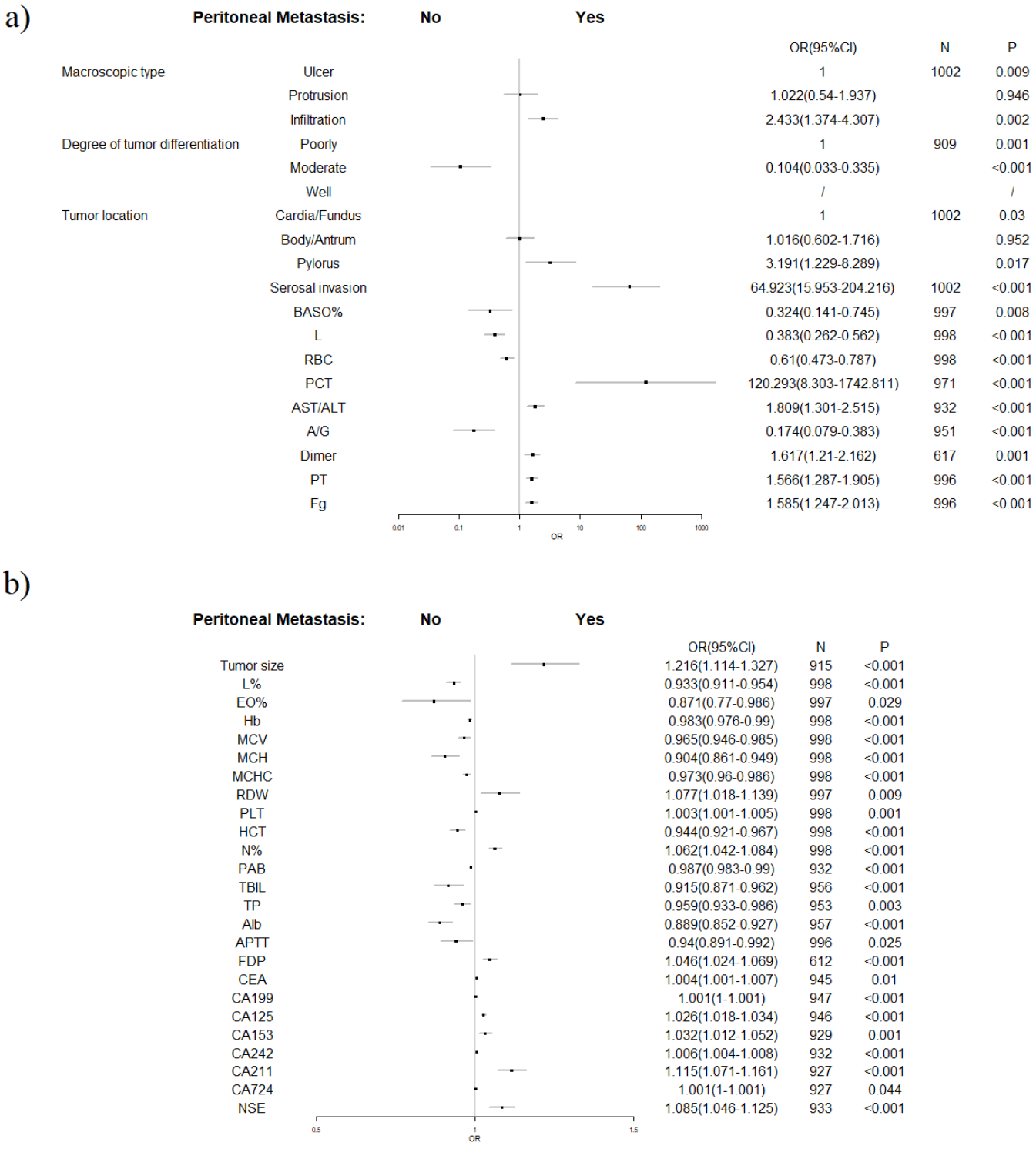

Figure 2

Univariate logistic regression analysis of peritoneal metastasis in gastric cancer. BASO%, Basophil ratio; L, lymphocyte count; L%, lymphocyte ratio; RBC, red blood cell count; PCT, thrombocytocrit; AST/ALT, proportion of aspartate aminotransferase to alanine aminotransferase; A/G, proportion of albumin to globulin; PT, prothrombin time; APTT, activated partial thromboplastin time; Fg, fibrinogen; EO%, eosinophil ratio; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin;

MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell volume distribution width; RBC red blood cell count; PLT, platelet count; HCT, hematocrit; N% neutrophil ratio; PAB, prealbumin; Alb albumin; TP, total protein; TIBL, total bilirubin level; FDP, fibrinogen degradation products; CEA, carcinoma embryonic antigen; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153; CA242, carbohydrate antigen 242; CA211, carbohydrate antigen 211; CA724, carbohydrate antigen 724; NSE, neuron-specificenolase.

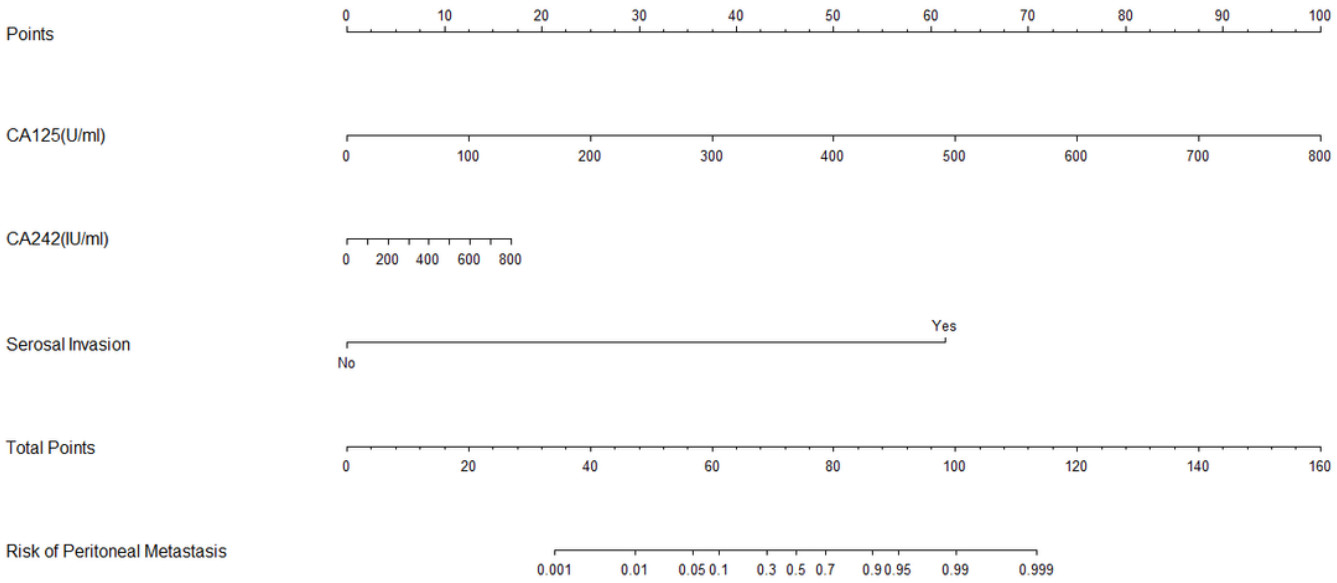

Figure 3

A nomogram for prediction of peritoneal metastasis.

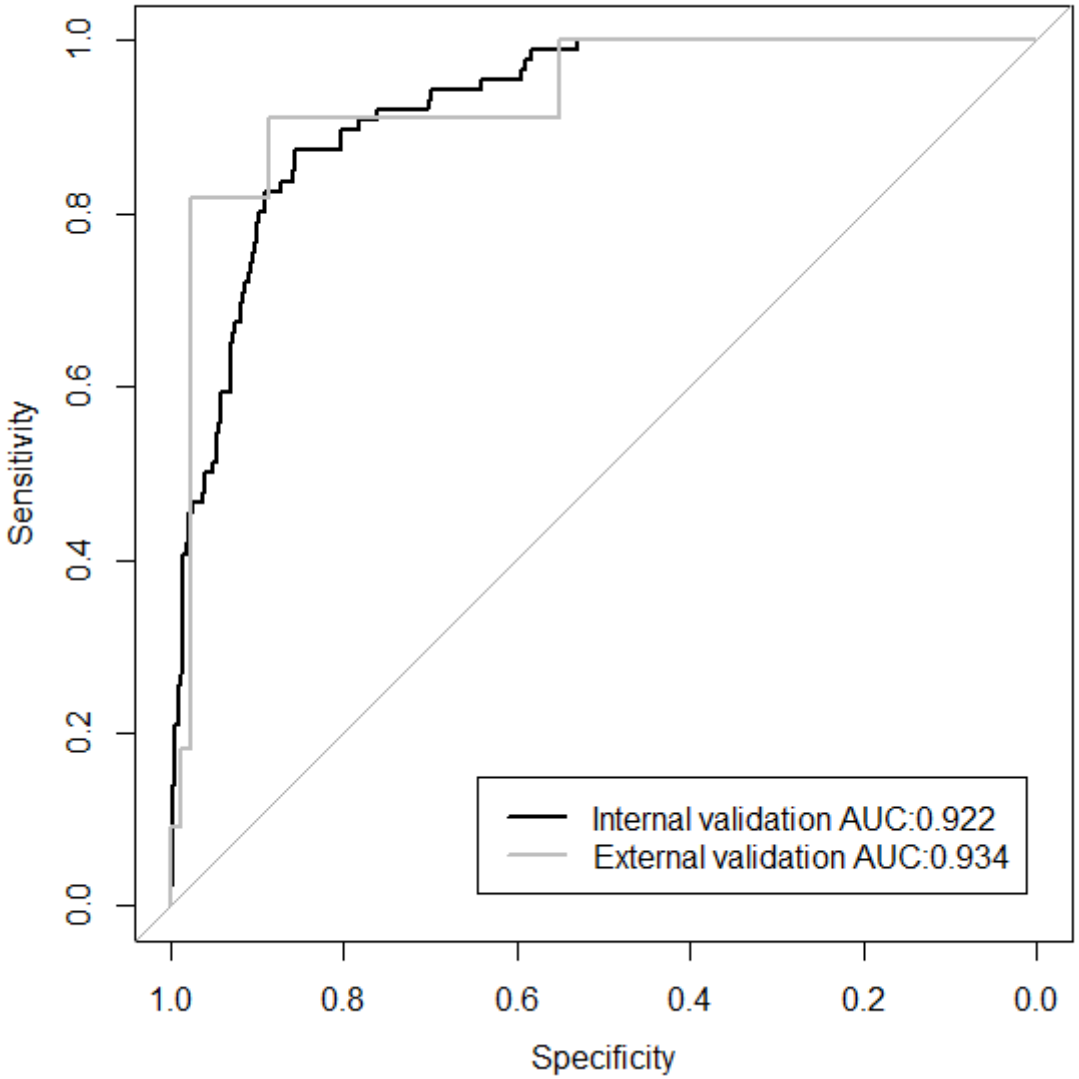

Figure 4

A receiver operating characteristics (ROC) curve of the nomogram for prediction peritoneal metastasis in internal and external validation respectively.