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# Independent Risk Factors of Postoperative Lymphatic Leakage in Patients with Gynecological Malignant Tumor: A Single-Center Retrospective Study

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** We aimed this investigation to screen and analyze the risk factors of postoperative lymphatic leakage of gynecological malignant tumors that contribute to the treatment of the diseases.

**Material/Methods:** According to the occurrence of lymphatic leakage after an operation, 655 patients with pelvic lymph node and/or abdominal para-aortic lymph node dissection for gynecological malignant tumor were retrospectively analyzed and divided into a case group and a control group. Univariate and multivariate logistic regression analysis were used to screen the effective independent risk factors and establish a clinical prediction model. The differentiation and calibration of the clinical prediction model were evaluated, and we performed internal and external validation of the model with 207 cases.

**Results:** The surgeons, the number of removed lymph nodes, the field and range of lymph nodes to be removed, the method of drainage, and postoperative infection are the independent risk factors of lymphatic leakage after lymph node dissection for gynecological malignant tumors. The area under the ROC curve of the clinical prediction model was 0.839 ( $P < 0.001$ ), the calibration Hosmer-Lemeshow test shows  $\chi^2 = 4.381$ ,  $P = 0.821$ . Through 10-fold cross-validation, the average correct rate of the prediction model was 0.899, the area under the ROC curve of the external verification group was 0.741, and the calibration Hosmer-Lemeshow test showed  $\chi^2 = 12.728$ ,  $P = 0.122$ .

**Conclusions:** The new logistic prediction model showed a good degree of differentiation and calibration in both the modeling and verification groups, and it can be used for early warning of the occurrence of lymphatic leakage after lymph node dissection.

**Keywords:** Manual Lymphatic Drainage • Postoperative Period • Risk Factors

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## Background

Gynecological malignant tumors seriously affect the physical and mental health of women all over the world. Despite the continuous progress of medical care and the enhancement of women's health awareness, the overall cure rate is not optimal in China [1].

Surgery is still the main treatment for early gynecological malignancies, but a series of complications may occur during the operation, such as infection [2], urinary retention [3], lymphoid cyst [2], thrombosis [4], and pelvic organ injury [5]. Lymphatic leakage is one of the rarest but most harmful complications after gynecological malignant tumor surgery [6]. The ascites with postoperative lymphatic leakage is divided into 2 categories, chylous and lymphatic, determined by the anatomic location of lymphatic injury. Many kinds of postoperative lymphatic leakage have been presented, including lymphatic ascites, lymphocele, lymphorrhea, lymphatic fistula, and some special forms of lymphatic leakage such as chylous ascites (chyloperitoneum), chyloorrhea, chyloretroperitoneum, chylothorax. Loss of fluid, triglyceride, lymphocyte, and immunoglobulin from the leakage of lymphatic vessels can lead to dehydration, nutritional deficiency, and immunologic dysfunction. At the same time, it will also increase the infection rate, even when the microbiological test result is negative [7]. The occurrence of postoperative lymphatic leakage prolongs the patient's hospital stay and increases hospital costs, affects the patient's postoperative recovery and quality of life, and delays follow-up treatment.

We aimed to identify the high-risk factors of postoperative lymphatic leakage in gynecological malignant tumors, and to establish and verify a clinical prediction model.

## Material and Methods

### Sample Size Calculation

Tests for one-sample sensitivity and specificity were performed by PASS to estimate the sample size. A total minimum predicted sample size of 420 (which includes 42 cases with lymphatic leakage) achieves 92% power to detect a change in sensitivity from 0.5 to 0.75 using a two-sided binomial test and 100% power to detect a change in specificity from 0.5 to 0.75 using a two-sided binomial test. The target significance level is 0.05. The actual significance level achieved by the sensitivity test was 0.0436 and the significance of the specificity test was 0.0447. The prevalence of the disease was 0.1.

A total minimum validation sample size of 170 (which includes 17 cases with lymphatic leakage) achieves 87% power to detect a change in sensitivity from 0.5 to 0.838 using a two-sided

binomial test and 100% power to detect a change in specificity from 0.5 to 0.717 using a two-sided binomial test. The target significance level was 0.05. The actual significance level achieved by the sensitivity test was 0.0490 and the significance of the specificity test was 0.0352. The prevalence of the disease was 0.1.

### Clinical Guidelines

The clinical data were abstracted from the medical records of patients with the diagnosis of disease (International Classification of Diseases 10<sup>th</sup> revision, codes N80.0-9). The stage of cervical cancer was determined according to the 2018 FIGO staging system, ovarian cancer was determined according to the 2014 FIGO staging system, and endometrial cancer was determined according to the 2009 FIGO staging system, based on the final pathologic assessment. All patients underwent surgical procedures for pelvic and/or para-aortic lymphadenectomy based on the guidelines of the National Comprehensive Cancer Network (NCCN).

### Patients

We retrospectively analyzed the clinical data from 688 patients with primary gynecological malignant tumors who underwent pelvic lymph node and/or abdominal para-aortic lymph node dissection in the Second Xiangya Hospital of Central South University from January 2017 to December 2018. An inclusion criterion was set up, with exclusion criteria and removal criteria as follows. (1) Inclusion criteria were: 1. all patients were diagnosed as having gynecological malignant tumors by preoperative biopsy or postoperative pathological diagnosis (the gynecological malignant tumors included cervical cancer, endometrial cancer, and ovarian cancer); 2. the surgery was performed in the Second Xiangya Hospital of Central South University for gynecological malignant tumors; 3. pelvic lymph node and/or para-aortic lymph node operation; 4. complete case data; 5. American Society of Anesthesia (ASA) grade I-II. (2) Exclusion criteria were: 1. with other malignant tumors; 2. combined disease with pulmonary tuberculosis, filariasis, liver cirrhosis, and nephrotic syndrome; 3. trauma in the past 6 months; 4. taking medicine that may cause lymphatic leakage in the past 6 months, such as calcium channel blocker (CCBs) [8]. (3) Removal criteria were: 1. postoperative abdominal drainage tube fell off spontaneously; 2. unplanned reoperation for organ damage, bleeding, etc; 3. drainage tube not placed; 4. reoperation for pathologic upstaging; 5. performed intraperitoneal hyperthermic perfusion; 6. postoperative radiotherapy; 7. postoperative vesicovaginal fistula.

Several cases were excluded according to the elimination criteria, in which there were 15 cases with a drainage tube that fell off spontaneously, 5 cases that did not have a drainage tube

**Table 1.** Variables and assignments.

Name	Variable parameter	Description
Age	X1	n/a
BMI	X2	n/a
Diabetes	X3	1=yes, 0=no
Previous abdominal and/or pelvic surgery	X4	1=no, 2=once, 3 ≥2 times
Neoadjuvant chemotherapy	X5	1=yes, 0=no
Postoperative chemotherapy	X6	1=yes, 0=no
Preoperative ALB	X7	n/a
Postoperative ALB	X8	n/a
Preoperative HGB	X9	n/a
Postoperative HGB	X10	n/a
Method of operation	X11	1=laparoscopy, 2=robot-assisted laparoscopy, 3=laparotomy
Range of lymph node dissection	X12	1=PLND+PALND, 0=PLND
Numbers of removed lymph node	X13	n/a
Lymph node metastasis	X14	1=yes, 0=no
Drainage method	X15	0=conventional drainage, 1=negative pressure drainage
Postoperative infection	X16	1=yes, 0=no
Pathology result	X17	1=cervical carcinoma, 2=endometrial carcinoma, 3=ovarian carcinoma
Low molecular weight heparin	X18	1=yes, 0=no
Postoperative lymphatic leakage	Y	1=yes, 0=no

placed, 5 cases in which intraperitoneal hyperthermic perfusion was performed, 6 cases in which reoperation for pathologic upstaging was performed, and 2 cases with vesicovaginal fistula. There were 655 effective cases, including 68 cases of postoperative lymphatic leakage and 587 cases of no lymphatic leakage.

### Predictor-Variables

(1) General data were: age, BMI, method of operation (robot-assisted laparoscopy, laparoscopy, and laparotomy), previous abdominal and/or pelvic surgery, diabetes, neoadjuvant chemotherapy, postoperative chemotherapy, range of lymph node dissection, postoperative infection, daily drainage, drainage method, number of the removed lymph nodes in the dissection, use of low molecular weight heparin. (2) Laboratory examination data were: albumin value, hemoglobin value before and after operation; lymph node metastasis; pathology diagnosis and staging; chylous test; triglyceride value, urea nitrogen, and creatinine value of drainage fluid (Table 1).

### Definition and Diagnostic Criteria of Related Factors

At present, there are no recognized diagnostic criteria for lymphatic leakage. In this study, lymphatic leakage was defined as chylous or yellowish fluid drained by pelvic and abdominal drainage tube on or 3 days after surgery on a gynecological malignant tumor, the volume of chylous fluid in ≥200 ml, the chylous test is positive or the triglyceride concentration of drainage fluid is ≥110 ml/dl or ≥1.2 mmol/L, and urinary fistula is excluded [7,9-12]. The diagnosis of postoperative infection is generally made when there is: (1) pain and tenderness in the area contiguous with the infection; (2) an oral temperature of ≥38°C on 2 separate occasions at least 6 hours apart, or of >38.5°C at any time, also supported by leukocytosis of >13 000/mm<sup>3</sup> with >90% bands plus polymorphonuclear leukocytes. Delayed signs included a positive blood culture or positive culture from the wound, operation site, or abscess cavity [13].

## Modeling and Statistical Methods

PASS (NCSS, LLC, USA) was used to perform the sample size calculation. The data analysis and statistical modeling were performed using SPSS (SPSS, Inc., Chicago, IL, USA).

Normally distributed measurement data were assessed using the *t* test, which is represented by the mean±standard deviation ( $\bar{x}\pm s$ ); the measurement data not meeting normal distribution were assessed using the Mann-Whitney U test, which is represented by the quartile; the count data were assessed by the chi-square test or Fisher's exact probability method, expressed in frequency and percentage. Based on the results of the univariate analyses, multivariate logistic regression models were adjusted for risk analyses. The results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was defined as  $P<0.05$ .

SPSS was used to perform univariate logistic analysis on the related factors of lymphatic leakage, incorporating significant differences into the multivariate logistic regression analysis, using the stepwise forward method to obtain the final included variables, and calculating the variance expansion factor for the included variables to evaluate each factor for whether there is multicollinearity among the variables, and finally constructing the prediction model of the variables.

Discrimination and calibration are the main indicators for evaluating prediction models. The most widely used measure of discrimination is the consistency statistic, also known as the C statistic (Concordance Statistics). The range of C statistics is 0-1. The closer to 1, the better the model's discrimination; equal to 0.5 means that the model has no predictive ability; less than 0.5 means that the predicted result of the model is exactly the opposite of the actual result. In the 2-class event, the C statistic is the same as the area under the curve (AUC) of the receiver operating characteristic (ROC).

MedCalc software (Belgium) was used to construct the ROC curve and AUC, calculate its Youden index, and screen the optimal boundary value of the ROC curve.

The degree of calibration is an important indicator for evaluating the accuracy of a prediction model for estimating future risk. It reflects the degree of consistency between the predicted risk of the model and the actual risk, so it is also called consistency evaluation. It is usually evaluated by Hosmer-Lemeshow goodness-of-fit test and drawing a calibration graph. SPSS was used to calculate the goodness-of-fit test value and draw a calibration graph for visual display.

R software was used to draw a nomogram of the prediction model.

## Results

### Predictor-Variables and Univariate Analysis

The incidence of postoperative lymphatic leakage was 10.38% in the 655 effective cases. A total of 19 potentially related factors were assessed with univariate analysis. There were 8 variables, including numbers of removed lymph node, range of lymph node dissection, postoperative chemotherapy, preoperative ALB and HGB, method of drainage, postoperative infection, and low molecular weight heparin (all  $P<0.001$ ), which indicated that the difference was statistically significant (**Table 2**).

### Multivariate Analysis

The significant variables were assessed in single-factor regression analysis, and the stepwise forwards method was used to set up dummy variables for disordered multi-category variables. The disordered multi-categorical variables were used in SPSS. Six chief surgeons were divided into 6 groups from A to F. The results of multivariate logistic regression are shown in **Table 3**.

### Regression Models

Five independent risk factors were finally selected. Collinearity analysis indicated that there was no multicollinearity relationship among them, and we established a multi-factor logistic prediction model. The expression was:  $\text{Logit}(P)=1.012\times \text{postoperative infection}+1.934\times \text{the method of drainage}+0.035\times \text{the number of removed lymph nodes}+1.087\times \text{range of dissected lymph nodes}+0.979\times \text{surgeon F}-0.596\times \text{surgeon E}-1.269\times \text{surgeon D}+0.295\times \text{surgeon C}-1.713\times \text{surgeon B}-0.595\times \text{surgeon A}-4.959$ . The nomogram of the prediction model is shown in **Figure 1**. This nomogram is used by locating each factor and getting the score of points on the score scale to which the factor corresponds. The probability corresponding to total score is that of postoperative lymphatic leakage in patients.

### Evaluation of the Logistic Regression Prediction Model

#### 1. Distinction

SPSS was used to summarize the prediction probability of each indicator in the logistic regression prediction model. The indicator includes surgeons (AUC=0.756, 95% CI: 0.696-0.817,  $P<0.01$ ), range of lymph node dissection (AUC=0.597, 95% CI: 0.518-0.675,  $P<0.01$ ), number of removed lymph nodes (AUC=0.638, 95% CI: 0.567-0.710,  $P<0.01$ ), method of drainage (AUC=0.670, 95% CI: 0.612-0.729,  $P<0.01$ ), postoperative infection (AUC=0.635, 95% CI: 0.568-0.702,  $P<0.01$ ), total combining predictor and all the combining predictor, showing AUC=0.839, 95% CI: 0.788-0.889,  $P<0.01$  (**Figure 2A**). The total combining predictor and combining predictor 1 including the factor of range of lymph node

**Table 2.** Clinical data of the 2 groups of patients in the modeling population.

	Numbers of lymphatic leakage (%)	Numbers of no-lymphatic leakage (%)	t/ $\chi^2$	P value
Age (years)			-1.396	0.163
$\bar{x}\pm s$ (age)	48.47 $\pm$ 8.81	50.03 $\pm$ 8.69		
Range (age)	24-69	24-74		
BMI (kg/m <sup>2</sup> )	23.27 $\pm$ 3.64	23.26 $\pm$ 3.37	0.039	0.969
Previous abdominal and/or pelvic surgery			0.148	0.938
No	45 (66.2%)	375 (64.1%)		
Once	21 (30.9%)	193 (32.7%)		
$\geq 2$ times	2 (2.9%)	19 (3.2%)		
Neoadjuvant chemotherapy	8 (11.8%)	136 (23.2%)	4.621	0.043*
Postoperative chemotherapy	13 (19.12%)	115 (19.59%)	0.01	1.000
Preoperative ALB (g/L)	39.60 $\pm$ 4.08	40.66 $\pm$ 3.47	-2.352	0.019*
Postoperative ALB (g/L)	31.70 $\pm$ 3.15	32.46 $\pm$ 3.15	-1.883	0.060
Preoperative HGB (g/L)	116.41 $\pm$ 15.12	120.76 $\pm$ 14.95	-2.268	0.023*
Postoperative HGB (g/L)	107.5 $\pm$ 14.48	106.59 $\pm$ 13.90	0.506	0.613
Diabetes	4 (5.9%)	42 (7.2%)	1 (Fisher test)	
Method of operation			1.005	0.605
Laparoscopy	47 (69.1%)	383 (65.2%)		
Robot-assisted laparoscopy	11 (16.2%)	88 (15.0%)		
Laparotomy	10 (14.7%)	116 (19.8%)		
Range of lymph node dissection			27.323	<0.001*
PLND	50 (73.5%)	545 (92.8%)		
PLND+PALND	18 (26.5%)	42 (7.1%)		
Numbers of removed lymph node	28.04 $\pm$ 9.71	23.76 $\pm$ 8.55	3.851	<0.001*
Lymph node metastasis			0.000	1
Yes	6 (8.8%)	52 (8.9%)		
No	62 (91.2%)	535 (91.1%)		
Method of drainage			28.970	<0.001*
Conventional drainage	8 (11.8%)	269 (45.8%)		
Negative pressure drainage	60 (88.2%)	318 (54.2%)		
Postoperative infection			17.687	<0.001*
Yes	49 (72.1%)	265 (45.1%)		
No	19 (27.9%)	322 (54.9%)		
Pathology result			0.23 (Fisher test)	

**Table 2 continued.** Clinical data of the 2 groups of patients in the modeling population.

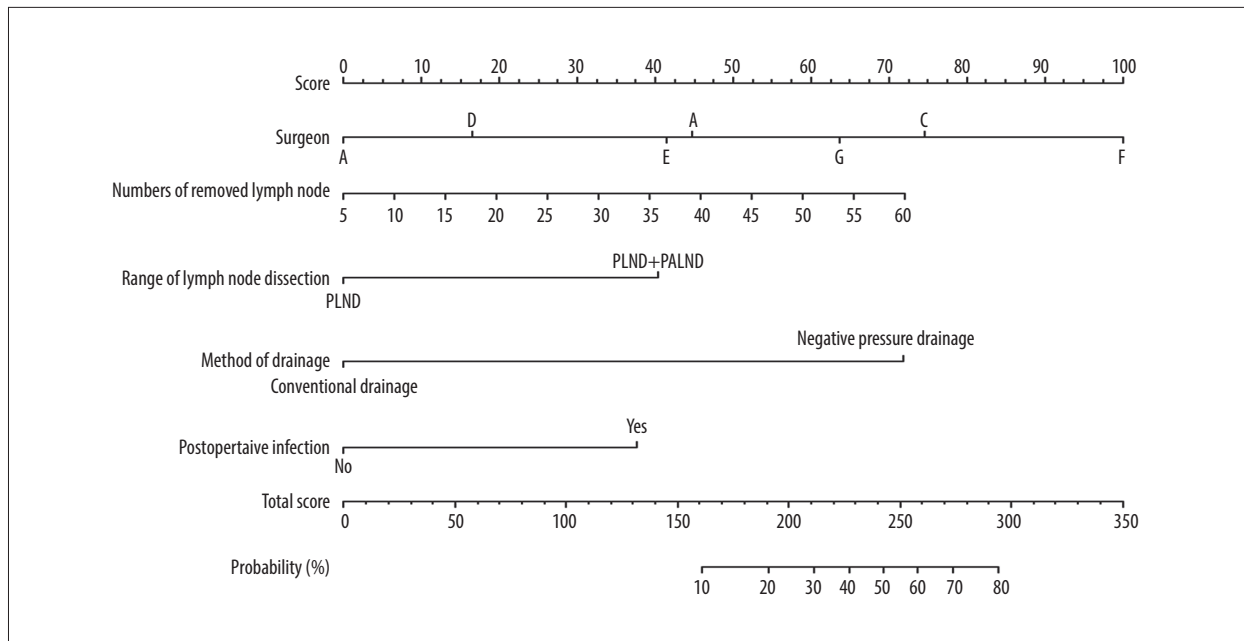
	Numbers of lymphatic leakage (%)	Numbers of no-lymphatic leakage (%)	t/ $\chi^2$	P value
Cervical cancer	39 (57.3%)	366 (62.4%)		
Squamous cell carcinoma	29	342		
Adenocarcinoma	7	12		
Adenosquamous carcinoma	3	6		
Carcinosarcoma	0	2		
Neuroendocrine carcinoma	0	4		
Endometrial cancer	28 (41.2%)	219 (37.3%)		
Adenocarcinoma	26	184		
Serous carcinoma	2	10		
Carcinosarcoma	0	10		
Clear cell carcinoma	0	5		
Ovarian cancer	1 (1.5%)	2 (0.3%)		
Serous adenocarcinoma	1	1		
Endometrioid adenocarcinoma	0	1		
Low molecular weight heparin			13.851	<0.001*
Low molecular weight heparin	30 (44.1%)	137 (23.3%)		
No-low molecular weight heparin	38 (55.9%)	450 (76.7%)		
Total	68	587		

\*  $P < 0.05$ , The difference was statistically significant.

**Table 3.** Multivariate logistic regression results.

	B	Standard error	P value	Exp(B)	95% CI
Reference group $\alpha$			0.001*		
Surgeon A	-0.595	0.528		0.601	0.214-1.693
Surgeon B	-1.713	0.722		0.180	0.044-0.742
Surgeon C	0.295	0.487		1.343	0.517-3.490
Surgeon D	-1.269	0.859		0.281	0.052-1.516
Surgeon E	-0.596	0.594		0.551	0.172-1.763
Surgeon F	0.979	0.542		2.662	0.921-7.700
Range of lymph node dissection	1.087	0.395	0.006*	2.965	1.367-6.432
Numbers of removed lymph node	0.035	0.016	0.031*	1.036	1.003-1.069
Method of drainage	1.934	0.435	<0.001*	6.914	2.946-16.228
Postoperative infection	1.012	0.324	0.002*	2.751	1.459-5.188
Normal	-4.959	0.745	<0.001*	0.007	

The reference group  $\alpha$  is surgeon G, \*  $P < 0.05$ , the difference was statistically significant.



**Figure 1.** Nomogram of the postoperative lymphatic leakage prediction model for visual display.

dissection, numbers of removed lymph node and postoperative infection (**Figure 2B**) shows AUC=0.725, 95% CI: 0.665-0.785,  $P<0.01$ . The total combining predictor and combining predictor 2 including the surgeons, factor of range of lymph node dissection, number of removed lymph nodes and postoperative infection (**Figure 2C**) shows AUC=0.798, 95% CI: 0.742-0.853,  $P<0.01$ . The total combining predictor and combining predictor 3 including the method of drainage, factor of range of lymph node dissection, numbers of removed lymph node and postoperative infection (**Figure 2D**) shows AUC=0.798, 95% CI: 0.74-0.857,  $P<0.01$ . MedCalc was used to calculate the predicted probability of the total joint predictor of the combined indicators, to construct the ROC curve, and calculate its AUC.

## 2. Calibration

The prediction probabilities of all individuals were calculated by statistical methods, ranked from small to large, and divided into 10 equal parts. The predicted probability was taken as the abscissa and the actual probability as the ordinate, the Hosmer-Lemeshow goodness-of-fit test showed  $\chi^2=4.381$ ,  $P=0.821$  (**Figure 2G**), meaning that the predicted value of the prediction model is no different from the observed value. The calibration chart of the nomogram is shown in **Figure 2F**.

## Validation of the Prediction Model

At 8 A.M. on the third day after the operation, 207 effective cases with 44 cases with lymphatic leakage and 163 cases without lymphatic leakage were collected who underwent pelvic lymph node and/or para-abdominal aortic lymph node

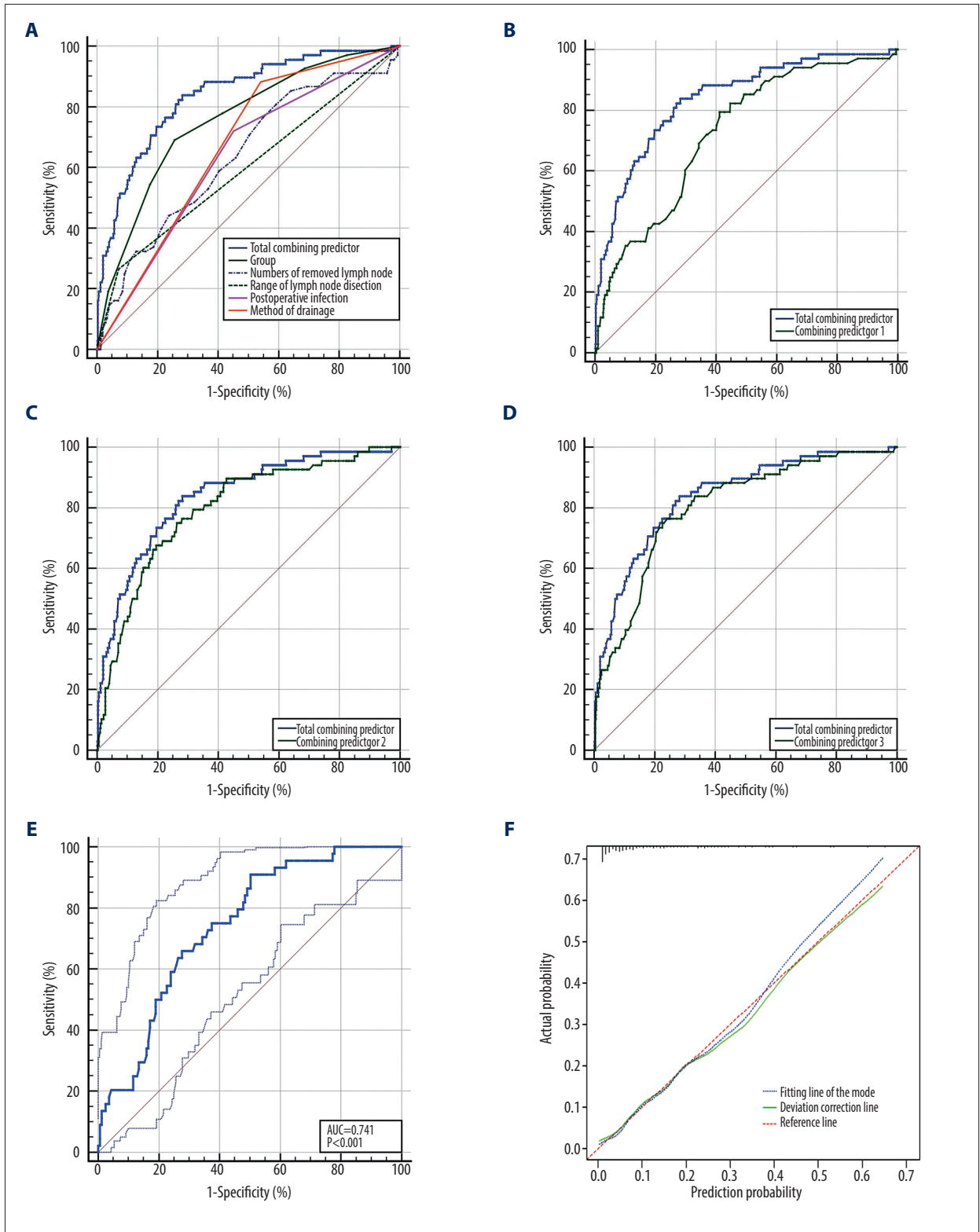
dissection at the Second Xiangya Hospital of Central South University from January to August 2019 for gynecological malignant tumors according to the criteria.

### 1. The Internal Verification

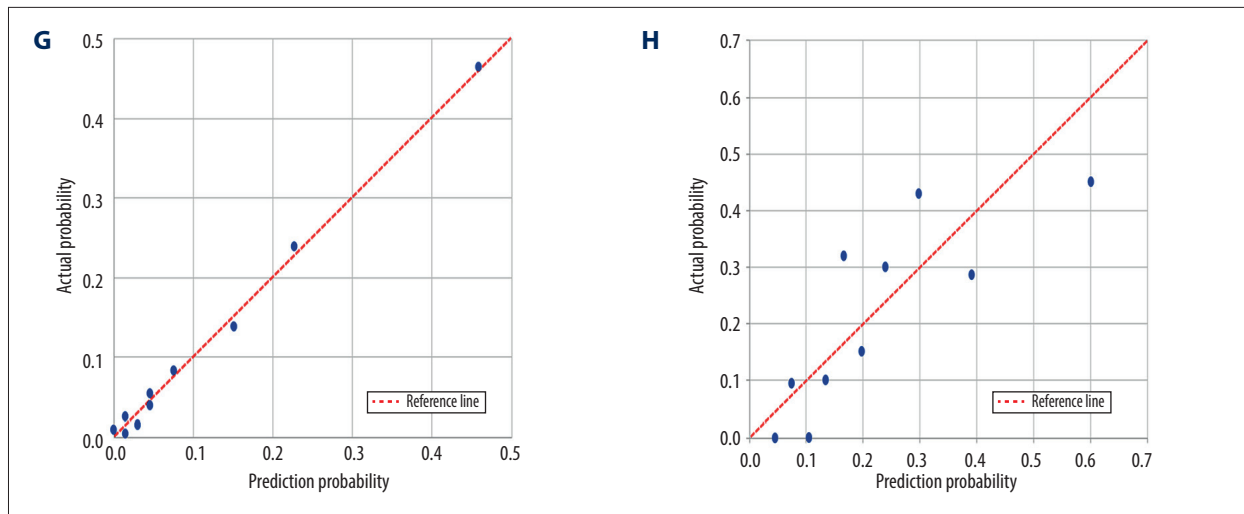
The cross-validation method, also known as the K-fold test, was used for internal verification. The principle is that the modeling group is randomly divided into 10 parts, 1 is taken as the verification group with the other 9 parts taken as the modeling group. Each test will get a correct rate, and the correct rate of the 10 results is taken as the average value to get an accurate estimate of the model. R software was used in this study to perform 10-fold cross-validation, and we finally calculated that the average accuracy was 0.899, indicating that the model was stable in the modeling population.

### 2. The External Verification

**Distinction:** R software was used to calculate the prediction probability and actual incidence of the validation model, and MedCalc software was used to draw the ROC curve. The area under the curve was 0.741 (95% CI: 0.675-0.799),  $P<0.01$ , and the AUC value was between 0.60 and 0.75, indicating that in the verified population, the resolution of the prediction model is acceptable and can effectively separate the lymphatic leakage group from the non-lymphatic leakage group. The maximum value of the Youden index was 0.406, the sensitivity was 90.91%, and the specificity was 49.69%, as shown in **Figure 2E**. Therefore, it can be considered that the external verification of the prediction model is acceptable.







**Figure 2.** (A) ROC curve of total combining predictor, the surgeons, the numbers of removed lymph node, the range of lymph node dissection, the postoperative infection, and the method of drainage. (B) ROC curve of total combining predictor and combining predictor 1. (C) ROC curve of total combining predictor and combining predictor 2. (D) ROC curve of total combining predictor and combining predictor 3. (E) ROC curve of the prediction factor in the validation group (the reference group alpha is the surgeon G,  $AUC=0.741$ ,  $P<0.05$ , the difference was statistically significant). (F) Calibration chart of the nomogram. (G) Scatter plot of the model calibration degree in modeling group ( $\chi^2=4.381$ ,  $P=0.821$ ). (H) Scatter plot of the model calibration degree in validation group ( $\chi^2=12.728$ ,  $P=0.122$ ).

**Calibration:** R software was used to obtain the prediction probability of the verified population, and the Hosmer-Lemeshow goodness-of-fit test was calculated as  $\chi^2=12.728$ ,  $P=0.122$  (Figure 2H), indicating that the predicted value of the prediction model is no different from the observed value. We used the predicted probability of the prediction model as the abscissa, and the actual occurrence probability of the observation as the ordinate. The 10 scatter plots on the scatter plot fluctuate around the reference line, which is not an obvious deviation from the reference line,  $P$  value  $>0.05$ , indicating that the predicted probability of occurrence is in good agreement with the actual probability of occurrence. According to the formula, the Brier score was calculated to be 0.15, less than 0.25, which also proves that the consistency of the prediction model in the verification group was acceptable.

## Discussion

Lymphatic leakage is a rare but harmful complication after surgery of gynecological malignancies. We conducted statistical analysis on the electronic medical records from January 2017 to December 2018, screened out independent risk factors for postoperative lymphatic leakage in gynecological malignancies, and established a prediction model. The results showed that the surgeons, the number of removed lymph nodes, the range of lymph nodes removed, the drainage method, and postoperative infection were independent risk factors. However, the patient's age, BMI, and previous history of abdominal surgery

were not associated with the occurrence of postoperative lymphatic leakage.

The skill of practicing surgeons varied widely, and greater skill was associated with fewer postoperative complications [14]. In the previously published literature, few articles mention the influence of a surgeon's skills on the occurrence of postoperative lymphatic leakage. Some literature only discusses the effects of related factors with the same surgeon [15]. Favero et al [16] proposed that the careful separation of anatomical structures during the operation and the use of sutures to clamp blood vessels and major lymphatic vessels during the operation can prevent the occurrence of postoperative lymphatic leakage, believing that the use of unipolar coagulation and ultrasonic scalpel may increase the incidence of lymphatic leakage. Yilmaz et al [17] reported that in liver transplantation cases, the use of the LigaSure vascular closure system has a greater risk of postoperative lymphatic leakage than the traditional suture technique. Some doctors pointed out that due to the thin wall of the lymphatic vessel and the lack of coagulation mechanism of the vascular system, the use of an ultrasonic scalpel to close the lymphatic vessel during the operation makes the lymphatic vessel poorly close or increases the postoperative lumen pressure, which leads to an increased probability of lymphatic leakage. Our research shows that the area under the curve of the total combined predictive factors increased by 3.6% ( $P<0.05$ ) after the surgeon factor was included in the prediction model, which indicates that the surgeon group is an independent risk factor of postoperative lymphatic

leakage in gynecological malignancies. Therefore, the surgical skills of the surgeon play a critical role in the occurrence of postoperative lymphatic leakage, and the surgeons who have an oncology fellowship may have reduced lymphatic leakage. Some specific factors may be explored further affecting lymphatic leakage through the surgical methods and techniques, and intraoperative data. Discovery of more surgical and surgeon-related factors will improve quality of life of patients.

With the progress of laparoscopic technology and the improvement of equipment, doctors pay more attention to the resection of abdominal aortic lymph nodes. Some guidelines also recommend abdominal para-aortic lymph node dissection for certain gynecological malignancies, such as staging surgery for early-stage endometrial cancer and ovarian cancer surgery. Our study found that lymphatic leakage after pelvic add para-aortic lymph node dissection was 1.37 times higher than after pelvic lymph node dissection, which is similar to the findings of Solmaz U et al [18] and Yuqing Zhao et al [15]. It is hard to avoid damage of the lymphatic vessels in the chyle cistern, and the field of removed lymph nodes is too wide and/or the body's lymphatic drainage is blocked, which may make the incidence of lymphatic leakage higher. Some methods should be adopted, such as sentinel lymph node biopsy, to reduce the occurrence.

The research also shows that the number of the removed lymph nodes in the operation is also a risk factor, which is similar to the reports of Assumpcao et al [19], Lu et al [20], and Gupta et al [21]. However, there are also reports in the literature that the number of removed lymph nodes has no relationship with the occurrence of lymphatic leakage [14,22]. This may be due to the individual differences of patients; in addition, different doctors have different surgical skills with using different surgical methods, and the surgical field of view may affect the number of lymph node dissections. Removal of a greater number of lymph nodes is associated with greater risk of lymphatic vessel damage and a higher risk of lymphatic leakage.

Previous studies have rarely discussed the effect of postoperative drainage on the occurrence of postoperative lymphatic leakage. Here, we compared the effects of an indwelling negative-pressure drainage tube or ordinary drainage tube on postoperative lymphatic leakage. The results showed that the risk of lymphatic leakage after the use of a negative-pressure drainage tube was 2.70 times greater than that of the ordinary drainage tube. Moreover, when the factor of drainage method was incorporated into the overall prediction model, the combined area under the curve of the predictor increased by 4.1%. There are also reports [23] that the postoperative use of a negative-pressure drain can significantly reduce the occurrence of postoperative lymphatic leakage, promote wound healing, and have a better therapeutic effect on patients who

have already developed lymphatic leakage, which was the postoperative treatment of the head and neck. However, the low pressure may promote local tissue damage near the lymphatic vessels to form a fistula. Therefore, the factors affecting risk of lymphatic leakage are whether a negative-pressure drainage tube is used, whether a negative pressure value is maintained in an appropriate range, and whether the negative pressure value is too low, especially after abdominal surgery. These problems warrant clinical exploration.

Our study found that postoperative infection is also an independent risk factor. Manzella et al [24] proposed that lymphatic inflammation leads to increased pressure in the lymphatic lumen, and the increase of inflammatory factors increases the permeability of the lymphatic vessel wall, leading to the occurrence of lymphatic leakage. When there is infection, the local lymphatic circulation increases, causing some of the small lymphatic vessels damaged during the operation to rupture spontaneously, the ligatures are prone to slippage during the operation, and the burned scabs fall off, leading to lymphatic leakage. The high content of triglycerides in the lymphatic ascites increases the risk of postoperative infection. Antibiotics should be used to prevent infection while controlling lymphatic leakage, and the placement time of the drainage tube should be extended for patients with postoperative infection.

This study is the first to report that the surgeons and the method of drainage are independent risk factors for postoperative lymphatic leakage in gynecological malignancies. Other research groups have reported that the number of removed lymph nodes, the range of lymph nodes to be removed, and postoperative infection were the high-risk factors. The use of a decision rule based on this prediction model could contribute to timely intervention to improve patient outcomes (Figure 1). For example, a patient underwent the operation by surgeon A, with PLND+PALND, and a total of 30 lymph nodes were removed, negative-pressure drainage was used, and postoperative infection occurred. According to the model, we can find that the score of surgeon A is 45, PLND+PALND is 40, a total of 30 removed lymph nodes is 32, using negative-pressure drainage is 70, postoperative infection occurred is 37. The sum in the total score is 224, corresponding to a probability of 40%. Thus, the patient may have an approximately 40% chance of postoperative lymphatic leakage.

The model enables doctors to quickly decide the next treatment plan and provide patients with better diagnosis and treatment suggestions. The method is simple and easy to implement and is easy to promote and apply in clinical practice.

As this study was a retrospective analysis, it will inevitably lead to biased information. By the strict inclusion criteria and adequate clinical samples collected as far as possible, the study

group and the control group could reflect the true incidence. Surgical procedure is a factor associated with lymphatic leakage, for the operative procedure details differed among surgeons. Some further indicators, such as further refining the dietary factors, surgery method, surgery procedure, surgery time, intraoperative use, the exact amount of bleeding, fluid volume, surgical energy equipment, and the use of hemostatic material, should be evaluated. Our study used data from a single center and small sample. Future research should include an expanded sample size, collect clinical data from multiple centers, and further adjust and improve the clinical prediction model. With the growing amount of data, coefficients and parameters of the model will also change.

Due to the complexity and uncertainty of electronic medical records with structured and unstructured clinical data, there may be a certain correlation among the data. It is difficult to completely remove the correlation between related variables, and there is confounding bias. In this study, we have taken the first single-factor logistic analysis of each factor, and then performed logistic multivariate analysis. Finally, among variables in multicollinearity analysis, it is important to avoid confounding bias as much as possible in the clinical prediction model. Several indicators show that the predicted value of the clinical prediction model is in good agreement with the actual observation value, which shows that the model is clinically useful and can benefit these patients.

## Conclusions

The surgeons, the number of removed lymph nodes, the field and range of lymph nodes to be removed, the method of drainage, and postoperative infection are the independent risk factors of lymphatic leakage after lymph node dissection for gynecological malignant tumors.

Through retrospective analysis of clinical data using statistical methods, an individualized prediction model of lymphatic leakage after lymph node dissection for gynecological malignancies was established. It has good discrimination and calibration in the modeling population and the verification population, and can provide early warning for the prevention and early diagnosis of lymphatic leakage after lymph node dissection of a gynecological malignant tumor.

## Ethics Approval and Consent to Participate

The experimental protocol was approved and ethics approval was given by the Ethics Committee of the Second Xiangya Hospital of Central South University (Approval number: PIAS-XXM-20191203. Version1.1. Date: December 3, 2019).

## Conflict of Interest

None.

## Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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