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ORIGINAL RESEARCH

Development and Validation of a Nomogram to Predict the Risk of Special Uterine Leiomyoma Pathological Types or Leiomyosarcoma in Postmenopausal Women: A Retrospective Study

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Purpose: The aim of this study was to investigate the risk factors of postmenopausal special uterine leiomyoma pathological types or leiomyosarcoma and to develop a nomogram for clinical risk assessment, ultimately to reduce unnecessary surgical interventions and corresponding economic expenses.

Methods: A total of 707 patients with complete information were enrolled from 1 August 2012 to 1 August 2022. Univariate and multivariate logistic regression models were used to analyse the association between variables and special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal patients. A nomogram for special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal patients was developed and validated by bootstrap resampling. The calibration curve was used to assess the accuracy of the model and receiver operating characteristic (ROC) curve and decision curve analysis (DCA) were compared with the clinical experience model.

Results: The increasing trend after menopause, the diameter of the largest uterine fibroid, serum carcinoembryonic antigen 125 concentration, Serum neutrophil to lymphocyte ratio, and Serum phosphorus ion concentration were independent risk factors for special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal patients. We developed a user-friendly nomogram which showed good diagnostic performance (AUC=0.724). The model was consistent and the calibration curve of our cohort was close to the ideal diagonal line. DCA indicated that the model has potential value for clinical application. Furthermore, our model was superior to the previous clinical experience model in terms of ROC and DCA.

Conclusion: We have developed a prediction nomogram for special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal patients. This nomogram could serve as an important warning signal and evaluation method for special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal patients.

Keywords: special uterine leiomyoma pathological types, leiomyosarcoma, postmenopausal women, prediction nomogram, bootstrap

Introduction

Uterine leiomyomas (UL) are the most prevalent noncancerous tumors found in women. Studies have shown that 70–80% of women will receive a diagnosis of this condition at some point in their lives.[1,2] In the United States, hysterectomy and myomectomy are significant surgical procedures, with approximately 433,621 and 34,000 cases performed annually, respectively.[3] Age is a significant factor in the development of UL, with the incidence increasing as women age, peaking around the age of 50,[4] and gradually declining with the onset of menopause. In clinical practice, postmenopausal women usually undergo a gradual reduction in the size of their leiomyomas as a result of declining hormone levels.[5,6] However, some patients may continue to experience growth even after reaching menopause. Ciarmela et al[7] emphasized the

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importance of treatment for both pre-and post-menopausal women, as not all leiomyomas in postmenopausal women will shrink. Peddada et al[8] have documented that the growth rate of ULs may vary at different stages and that shrinkage can occur at any age, not just after menopause.

After menopause, women are at a higher risk of experiencing UL degeneration compared to before menopause. Degenerated ULs typically do not present with noticeable symptoms and require a postoperative pathological diagnosis for confirmation. Currently, more than 20 variations of leiomyomas have been identified.[9,10] The degeneration of UL can be categorized into benign forms, such as hyaline degeneration cystic degeneration, fatty degeneration, and calcification. There are also specific pathological and growth types, such as cellular leiomyoma, lipoleiomyoma,[11] mitotically active leiomyoma, bizarre leiomyoma,[12,13] vascular leiomyoma, epithelioid leiomyoma, intravenous leiomyoma, peritoneal disseminated leiomyoma, smooth muscle tumor of unknown malignant potential[14] and benign metastasizing leiomyoma, as well as leiomyosarcoma.[15] Benign degeneration of UL rarely progresses to malignancy; therefore, conservative treatment can be considered for postmenopausal women. However, surgical treatment is recommended for patients with special uterine leiomyoma pathological types or leiomyosarcoma.

The criteria for performing surgery for UL in postmenopausal women are well-defined. However, there is a lack of effective methods for assessing the nature of UL before surgery, particularly for those with unique pathological types and malignant transformation. Among the available models, a nomogram provides a highly accurate, personalized, evidence-based risk estimate. As a straightforward statistical visualization tool, nomograms have been widely used to predict disease incidence, progression, prognosis, and survival.[16–18] However, there are few predictive models available to estimate the risk of UL degeneration, especially in postmenopausal patients with special uterine leiomyoma pathological types or leiomyosarcoma. To fill this knowledge gap, a retrospective case-control study was conducted in China. The main objective is to decrease unnecessary surgery for postmenopausal women with uterine fibroids, thus reducing patient discomfort and the societal economic burden.[19]

Methods

Our analysis follows Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline[12] (refer to Table S5) and incorporates best practice recommendations for variable selection and model construction when using pre-existing observational datasets. We provide information on model calibration, predictive accuracy, overfitting control, and internal bootstrap validation. A comparison is made between receiver operating characteristic (ROC) curve,[13] decision curve analysis (DCA)[20] of our new model and the clinical experience model. The purpose of these comparisons is to evaluate the performance of our model and illustrate its superiority over existing clinical experience model. By following these guidelines and recommendations, our goal is to provide precise and dependable predictions that will ultimately benefit postmenopausal women with UL.

Study Design and Data Source

This research conducted a retrospective analysis of medical records from Women's Hospital, School of Medicine, Zhejiang University, with a specific focus on patients diagnosed with UL through pathological examination. This study is a retrospective case study and has certain scientific and social value. We anonymously retrieve patient case information, and this study will not bring any additional adverse risks to patients. The researchers will strictly adhere to confidentiality principles. Relevant research information is only accessible to researchers/ethics committees. Therefore, the study was approved by the Institutional Review Board of Women's Hospital, School of Medicine, Zhejiang University, under IRB-20230105-R. The retrospective analysis included 993 patients who underwent surgical procedures (including hysteroscopic myomectomy, laparoscopic myomectomy, or total hysterectomy) at Women's Hospital, School of Medicine, Zhejiang University between August 1, 2012, and August 1, 2022. The final pathological examination of the surgical specimens confirmed the presence of UL, including the identification of special uterine leiomyoma pathological types or leiomyosarcoma (refer to Table S1). Inclusion criteria required a time interval of more than 1 year between the last menstrual period and enrollment, as well as definitive pathological and histological diagnostic results. Taking into account various causes of postmenopausal vaginal bleeding[21,22] exclusion criteria encompassed patients with various

gynecological malignancies, such as ovarian malignancies, cervical malignancies, and endometrial malignancies, with atypical endometrial hyperplasia as well as individuals with unclear imaging information also excluded.

Outcomes

Considering the different treatment approaches for special pathological types and leiomyosarcoma compared to common UL and general degeneration, this article will consider these two as the outcome variables for the study. The researchers utilized clinical codes from the International Classification of Diseases, 11th Revision (ICD-11) to identify cases discharged from the Women's Hospital, School of Medicine, Zhejiang University, with a diagnosis of UL between August 1, 2012, and August 1, 2022. Patients were selected based on predetermined inclusion and exclusion criteria to ensure the study's reliability and validity. The ICD-11[23] codes employed for identification encompassed D25 (uterine leiomyoma), D26 (cervical leiomyoma), and D28.2 (broad ligament leiomyoma). Comprehensive clinical data and laboratory test results for the 993 chosen patients were meticulously documented using the inpatient medical record system, and their upper limb pathology findings were scrutinized. At the Women's Hospital, School of Medicine, Zhejiang University, the pathology results of all patients were evaluated by two pathologists, one of whom was a pathologist and the other a senior pathologist.

Predictor Variables

We identified predictor variables based on clinical experience and relevant literature reports,[24–29] as outlined in Table S2. Information related to UL (such as" Menopausal time", "clinical symptoms related to UL", etc). and other medical histories (such as hypertension disease or breast cancer disease, etc). was extracted from inpatient medical records through patient inquiries at the time of admission. Data on "Body mass index", "Number of UL indicated by B-ultrasound", and "The diameter of the largest UL indicated by B-ultrasound" were collected from blood pressure measurements, imaging studies, and patient inquiries. Laboratory indices, such as rate of absolute value of neutrophil and lymphocyte(NLR), estradiol hormone (E2), progestational hormone, testosterone levels, carcinoembryonic antigen 125 (CA125), thyroid stimulating hormone (TSH), lactate dehydrogenase (LDH), total cholesterol, triglycerides, calcium ions, magnesium ions, phosphorus ions, total ferritin levels, transferrin levels, and homocysteine, were obtained from pertinent preoperative reports. All predictive variables were derived from the most recent information recorded in the admission records prior to entry into the cohort. To ensure unbiased data collection, the attending physician, laboratory or imaging physician, and pathologist were all blinded at the time of recording. These measures were implemented to maintain the accuracy and reliability of our study results.

Handling Missing Values and Sample Size Estimation

This research study involved the analysis of data from 993 cases, which underwent thorough scrutiny to ensure the absence of any missing information prior to commencing the analysis (see Figure S1). Subsequently, 707 cases with a complete set of 32 potential variables were chosen for model development, and 5 predictors were ultimately selected from the initial 32 potential variables to construct a multivariate risk prediction model. Among the total 707 patients, 55 individuals exhibited pathological findings indicative of specific types of lesions or malignancies related to the uterus, resulting in an incidence rate of 0.078%. The R package "pmsampsize" was employed for sample size calculation[30] (refer to Table S3), revealing that the maximum sample size required under current conditions is 290. Consequently, the current sample size fulfills the prerequisites for further calculations.

Derivation and Validation of the Models

We employed Cox's proportional hazards models to calculate coefficients for each risk predictor in the cohort. Both univariate and multivariable logistic regression models were used to examine the association between variables and the outcome. In the univariate analysis, preliminary analyses were conducted to identify potential risk factors. All variables demonstrating a bivariate association with with special uterine leiomyoma pathological types or leiomyosarcoma at $P < 0.1$ were included in the multivariable model. A stepwise nomogram model was developed using multivariate logistic regression, employing a stepwise selection process based on the Akaike information criterion (AIC) minimum

principle.[31] The model's discriminatory ability was assessed using ROC analysis, and the calibration curve was used to evaluate the alignment between the model's probability curve and the ideal curve. Furthermore, a Hosmer-Lemeshow test was conducted on the final model to assess its goodness of fit, with a P value greater than 0.05 indicating an acceptable model fit. The accuracy of the model was further validated through bootstrap validation, involving computer resampling for 100 repetitions of simple random sampling with replacement. The model was refitted in each bootstrap replicate and tested on the original sample to estimate the degree of optimism in model performance.

The clinical utility of the model was evaluated using DCA. Additionally, ROC, and DCA were utilized to compare the effectiveness of new predictive models in forecasting Outcomes with previous clinical experience model. By adhering to these rigorous Methods, we aim to provide accurate and reliable predictions for postmenopausal women with UL.

Statistical Analysis

Continuous variables with a normal distribution are analyzed using the *t*-test. Otherwise, the *U*-test is used and described using the median (with a 95% confidence interval). Classification variables are presented as frequencies (percentages) and analyzed using the chi-squared test. A p-value below 0.05 was considered significant. All statistical analyses were performed using SPSS version 26.0 (IBM, New York). Other statistical analyses were performed using R version 3.6.3 software with the packages boot, rmda, pROC, calibrate, RMS, and PredictABEL.

Results

General Characteristics

In our study group, clinical data was collected for 993 individuals from Women's Hospital, School of Medicine, Zhejiang University. Among these, 286 patients were found to have incomplete data, primarily concerning serum indicators. The highest frequency of missing values was noted for serum testosterone, with 134 patients lacking this specific data point (refer to Figure S1). Ultimately, 707 patients were chosen for participation in the study as complete information on the pertinent variables was accessible for subsequent model development (refer to Figure 1 and Table S4).

A total of 707 postmenopausal women were involved in the research, of which 55 had undergone surgery and their postoperative pathology indicated special uterine leiomyoma pathological types or leiomyosarcoma. Table 1 demonstrates that there were no significant disparities between these two groups of postmenopausal women in terms of age at menarche, duration of menopause, history of underlying diseases (such as hypertension, diabetes mellitus, history of breast disease, etc)., CA125, LDH, and other factors. However, it is important to note that distinctions were observed between these two groups of postmenopausal women in terms of the growth trend and size of postmenopausal leiomyoma, which aligns with previous research findings. It is worth noting that there is a certain difference in the concentration of phosphorus in the serum between the two groups of data. Specifically, in the special uterine leiomyoma pathological types or leiomyosarcoma group, the serum phosphorus concentration is lower and has statistical significance.

Risk Factors for UL Among Postmenopausal Women

Table 2 displays the Results of univariate and multivariate logistic regression analyses carried out to ascertain the correlation between variables and UL in postmenopausal women. The research revealed that in postmenopausal patients, the likelihood of developing special uterine leiomyoma pathological types or leiomyosarcoma was significantly higher when the size of the uterine leiomyomas was equal to or greater than 5 cm, as compared to those with fibroids smaller than or equal to 5 cm (odds ratio (OR) = 2.94, 95% CI: 1.62–5.33, P < 0.001). Additionally, if the UL continues to grow after menopause, the postoperative pathology suggests an increased risk of special pathological types or leiomyosarcoma (OR = 1.4, 95% CI: 0.94–2.07, P = 0.094). The research also revealed that postmenopausal patients with a CA125 level of 11.05 nmol/L or higher had a significantly higher risk of special pathological types or leiomyosarcoma (OR = 1.67, 95% CI: 0.94–2.98, P = 0.084). Furthermore, a heightened risk was observed in cases where the neutrophil-to-lymphocyte ratio (NLR) was greater than or equal to 3.12 (OR = 2.14, 95% CI: 1.11–4.11, P = 0.022). Furthermore, the analysis indicated that a serum phosphorus concentration above 1.195 mmol/L was associated with a protective effect (OR = 0.52, 95% CI: 0.27–1.00, P = 0.051), as shown in Table 2. All variables with a bivariate association having a significance level (P) of less than 0.1 were included in the multivariable logistic regression, which also

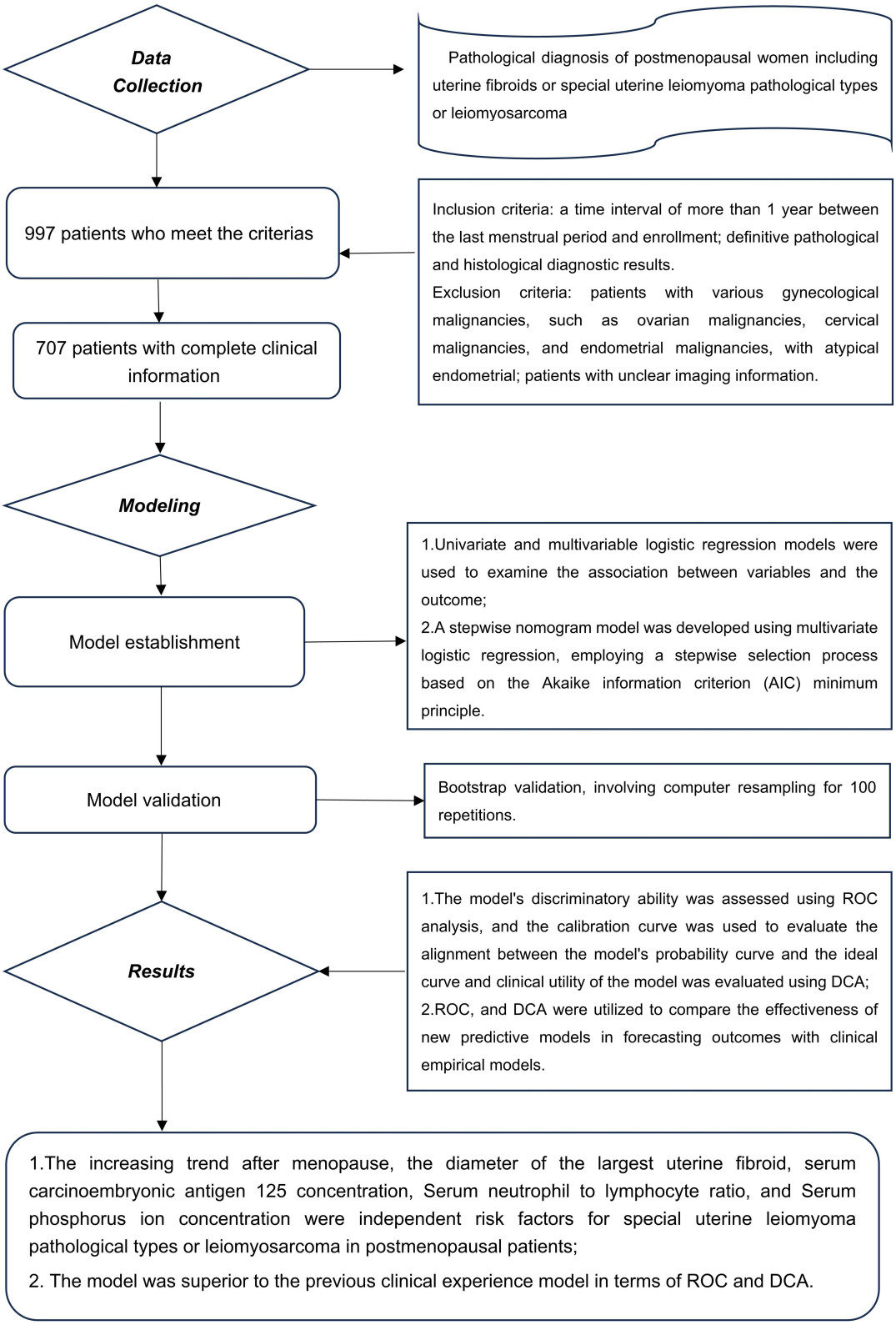

Figure 1 Flow chart of this study.

produced the adjusted ORs shown in Table 2. In the multivariable model, following the principle of AIC minimum, 5 factors were ultimately selected to construct the model. These factors include the increasing trend after menopause, the diameter of the largest uterine fibroid, CA125, NLR, and Serum phosphorus ion concentration.

Table 1 Baseline Characteristics of the Enrolled Participants

Variables	Patients with Pathology Suggestive Only of UL (n=652)	Patients with Pathology Suggestive of Special Uterine Leiomyoma Pathological types or Leiomyosarcoma (n=55)	test	P
Menopausal time≥10 years (n(%))	251 (38.5%)	23 (41.8%)	p	
Have clinical symptoms related to UL (n(%))	179 (27.5%)	13 (23.6%)	p	
The discovery time of UL after menopause after menopause (n(%))	423 (64.9%)	33 (60.0%)	p	
The changing trend of UL after menopause (n(%))			p	*
Discreased or stable	313 (48.0%)	16 (29.1%)		
Increased	217 (33.3%)	25 (45.5%)		
Unknown	122 (18.7%)	14 (25.5%)		
Have a history of hysteromyoma related surgery	20 (3.1%)	0(0.0%)	p	
Age of menarche (Mean (95% CI))	15.22 (15.09–15.35)	14.76 (14.37–15.15)	u	
Gravidity (n(%))			p	
0	5 (0.8%)	1 (1.8%)		
1	67 (10.3%)	4 (7.3%)		
2	207 (31.7%)	30 (54.5%)		
3	216 (33.1%)	13 (23.6%)		
4	95 (14.6%)	3 (5.5%)		
5	42 (6.4%)	4 (7.3%)		
6	12 (1.8%)	0 (0.0%)		
7	6(0.9%)	0 (0.0%)		
8	2(0.3%)	0 (0.0%)		
Parity (n(%))			p	
0	9 (1.4%)	2 (3.6%)		
1	375 (57.5%)	30 (54.5%)		
2	194 (29.8%)	19 (34.5%)		
3	58 (8.9%)	2 (3.6%)		
4	12 (1.8%)	2 (3.6%)		
5	3 (0.5%)	0 (0.0%)		
8	1 (0.2%)	0 (0.0%)		
Have a confirmed hypertension disease (n(%))	235 (36.0%)	27 (49.1%)	p	
Have a confirmed diabetes disease (n(%))	59 (9.0%)	6 (10.9%)	p	
Have a confirmed thyroid diseases (n(%))	40 (6.1%)	3 (5.5%)	p	

(*Continued*)

Table 1 (Continued).

Variables	Patients with Pathology Suggestive Only of UL (n=652)	Patients with Pathology Suggestive of Special Uterine Leiomyoma Pathological types or Leiomyosarcoma (n=55)	test	P
Have a confirmed breast cancer disease (n(%))	24 (3.7%)	1 (1.8%)	p	
Have a history of tamoxifen use (n(%))	8 (1.2%)	0 (0.0%)	p	
Number of UL indicated by B-ultrasound > =2 (n(%))	361 (55.4%)	34 (61.8%)	p	
The diameter of the largest UL indicated by B-ultrasound ≥5cm(n(%))	250 (38.3%)	36 (65.5%)	p	***
Estradiol hormone (E2) (n(%))			p	
<100pmol/L	631 (96.8%)	51 (92.7%)		
100–300pmol/L	14 (2.1%)	3 (5.5%)		
>300pmol/L	7 (1.1%)	1 (1.8%)		
Progestational hormone value ≥ 2.2nmol/L(n(%))	9 (1.4%)	2 (3.6%)	p	
Testosterone value ≥1.2nmol/L (n(%))	36 (5.5%)	5 (9.1%)	p	
Body mass index(BMI) (Mean(95% CI))	23.79 (23.52–24.04)	24.58 (23.60–25.54)	u	
Rate of absolute value of platelet and lymphocyte (PLR) (Mean(95% CI))	137.59 (134.07–141.12)	137.25 (124.870149.64)	u	
Rate of absolute value of neutrophil and lymphocyte(NLR) (Mean(95% CI))	2.34 (2.24–2.43)	2.59 (2.27–2.91)	u	
Carcinoembryonic antigen 125 (CA125) (Mean(95% CI))	12.15 (11.59–12.71)	14.36 (11.48–17.24)	u	
Thyroid stimulating hormoneat value(TSH) (Mean(95% CI))	1.74 (1.66–1.83)	1.71 (1.41–2.01)	u	
Lactic dehydrogenase value(LDH) (Mean(95% CI))	188.65 (186.17–191.13)	194.13 (180.38–207.88)	u	
Triglyceride value(TC) (Mean(95% CI))	1.89 (1.79–1.99)	2.1 (1.73–2.47)	u	
Total cholesterol index(TG) (Mean(95% CI))	5.3 (5.23–5.38)	5.41 (5.07–5.74)	u	
Calcium ion concentration(Ca) (Mean(95% CI))	2.33 (2.32–2.34)	2.31 (2.29–2.34)	u	
Concentration of magnesium(Mg) (Mean(95% CI))	0.85 (0.85–0.86)	0.85 (0.83–0.87)	u	
Phosphorus ion concentration(Ph) (Mean(95% CI))	1.34 (0.96–1.73)	1.11 (1.07–1.15)	u	*
Total ferritin value(TF) (Mean(95% CI))	14.77 (14.41–15.13)	14.16 (13.00–15.32)	u	
Transferrin value(trf) (Mean(95% CI))	2.47 (2.44–2.50)	2.47 (2.40–2.54)	u	
Homocysteine value(Hcy) (Mean(95% CI))	11.1 (10.80–11.40)	10.96 (10.08–11.84)	u	

Notes: p: Chi square test, u: Mann–Whitney test; *P ≤ 0.05, ***P ≤ 0.001.

Nomogram for UL Among Postmenopausal Women

We conducted an analysis of 32 clinical variables to investigate their correlation with the risk of special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal women. Out of the original 32 variables, five were excluded, namely the increasing trend after menopause, the diameter of the largest uterine fibroid, CA125, NLR, and Serum phosphorus ion concentration. In our research, the stepwise selection model was computed as: −3.5523 + 0.3354*trend (the increasing trend after menopause) + 1.0769*size (the diameter of the largest uterine fibroid) + 0.7611*NLR + 0.513*CA125 - 0.6609*Ph (serum phosphorus ion concentration).

Table 2 Association of UL with Selected Variables in Bivariate Analysis and in Multivariable Models

Characteristics	OR(uni)	CI(uni)	P(uni)	OR(multi)	CI(multi)	P(multi)
Body mass index(BMI)	1.11	0.64–1.93	0.705			
Have a confirmed breast cancer disease	0.48	0.06–3.65	0.482			
Calcium ion concentration(Ca)	0.64	0.37–1.12	0.119			
Carcinoembryonic antigen 125 (CA125)	1.97	1.12–3.47	0.019	1.67	0.94–2.98	0.084
Have clinical symptoms related to UL	0.82	0.43–1.56	0.542			
Have a confirmed diabetes disease	1.23	0.51–3	0.647			
Estradiol hormone (E2)	1.67	0.76–3.65	0.2			
The discovery time of UL after menopause after menopause	0.81	0.46–1.43	0.469			
Gravidity	0.46	0.2–1.04	0.061			
Have a confirmed hypertension disease	1.71	0.98–2.97	0.057			
Homocysteine value(Hcy)	1.75	0.97–3.16	0.065			
Lactic dehydrogenase value(LDH)	0.97	0.7–1.35	0.87			
Menopause.period 10	1.15	0.66–2.01	0.628			
Age of menarche	0.77	0.43–1.37	0.365			
Concentration of magnesium(Mg)	1.01	0.67–1.53	0.946			
Rate of absolute value of neutrophil and lymphocyte(NLR)	2.32	1.25–4.31	0.008	2.14	1.11–4.11	0.022
Number of UL indicated by B-ultrasound > =2	1.31	0.74–2.3	0.356			
Progesterone at value ≥ 2.2nmol/	2.7	0.57–12.81	0.212			
Parity	0.61	0.22–1.74	0.359			
Phosphorus ion concentration(Ph)	0.5	0.27–0.96	0.037	0.52	0.27–1	0.051
Rate of absolute value of platelet and lymphocyte (PLR)	1.1	0.76–1.6	0.618			
Have a history of hysteromyoma related surgery	0	0-Inf	0.986			
The diameter of the largest UL indicated by B-ultrasound ≥5cm	3.05	1.71–5.43	<0.001	2.94	1.62–5.33	<0.001
Have a history of tamoxifen use	0	0-Inf	0.987			
Triglyceride value(TC)	1.52	0.87–2.64	0.14			
Total ferritin value(TF)	0.84	0.48–1.46	0.535			
Total cholesterol index(TG)	1.02	0.59–1.76	0.951			
Have a confirmed thyroid diseases	0.88	0.26–2.95	0.839			
The changing trend of UL after menopause	1.52	1.07–2.16	0.018	1.4	0.94–2.07	0.094
Transferrin value(trf)	1.35	0.78–2.35	0.285			
Thyroid stimulating hormoneat value(TSH)	1.67	0.51–5.46	0.395			
Testosterone value ≥1.2nmol/L	1.71	0.64–4.55	0.282			

This model was developed using a rigorous stepwise selection process based on the principle of minimizing the AIC, and it incorporates the variables that are most significantly linked to special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal women. By employing this model, our aim is to provide clinicians and patients with accurate and reliable predictions for managing UL, especially for special pathological types or leiomyosarcoma. The likelihood of UL for special pathological types or leiomyosarcoma in postmenopausal women can be estimated using the stepwise nomogram outlined in Figure 2.

For each postmenopausal patient, the higher the total score, the higher the risk of special UL pathological types or leiomyosarcoma in postmenopausal women. In addition, the Hosmer-Lemeshow test showed that the model was a good fit (P = 0.7864684). The performance of this nomogram was measured using ROC analysis, and the area under the ROC curve (AUC) of this model was 0.724, indicating good diagnostic performance (Figure 3).

Model Validation

We conducted additional validation of the stepwise nomogram through internal bootstrap validation with 100 resamples. The ROC curve indicated an optimism of 0.03090277 for the AUC of the stepwise model after 100 repeated bootstrap measurements. As a result, the validated AUC of the final model is (0.7241355–0.03090227). This rigorous validation approach aims to provide healthcare professionals and patients with dependable and precise predictions for managing UL in postmenopausal women. Additionally, the predicted probabilities derived from the stepwise diagnostic pattern closely corresponded with the clinical outcomes (see Figure 4). Also, The Brier indicated an optimism of −0.002205831 of the stepwise model after 100 repeated bootstrap measurements. As a result, the validated Brier of the final model is (0.068 – (−0.002205831)). Overall, our model demonstrates a strong fit and calibration to the ideal curve. Furthermore, the model displays robust consistency, and our calibration curve closely approximates the ideal diagonal line. The decision curve depicted in Figure 5 illustrates the potential clinical utility of this model.

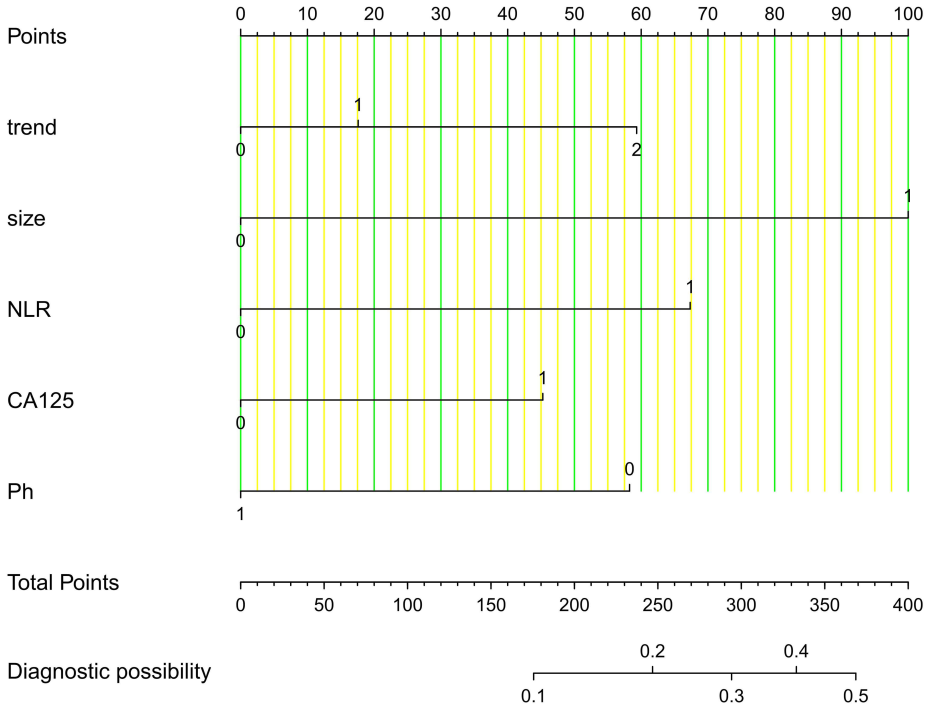

Figure 2 Nomogram prediction of UL for special pathological types or leiomyosarcoma in postmenopausal women trend: the increasing trend after menopause, size: the diameter of the largest uterine fibroid, CA125: serum carcinoembryonic antigen 125 concentration, NLR: Serum neutrophil to lymphocyte ratio, Ph: Serum phosphorus ion concentration.

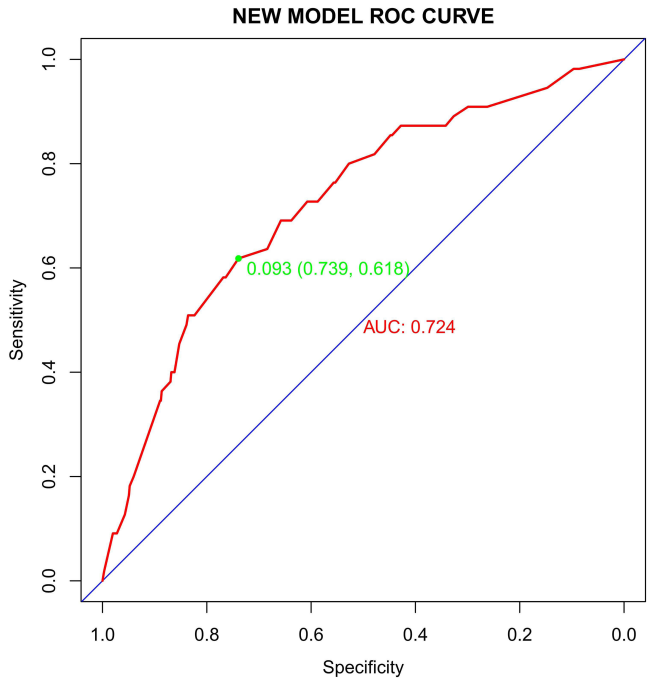

Figure 3 Receiver operating characteristic curve.
Abbreviation: AUC, Area under the receiver operating characteristic curve.

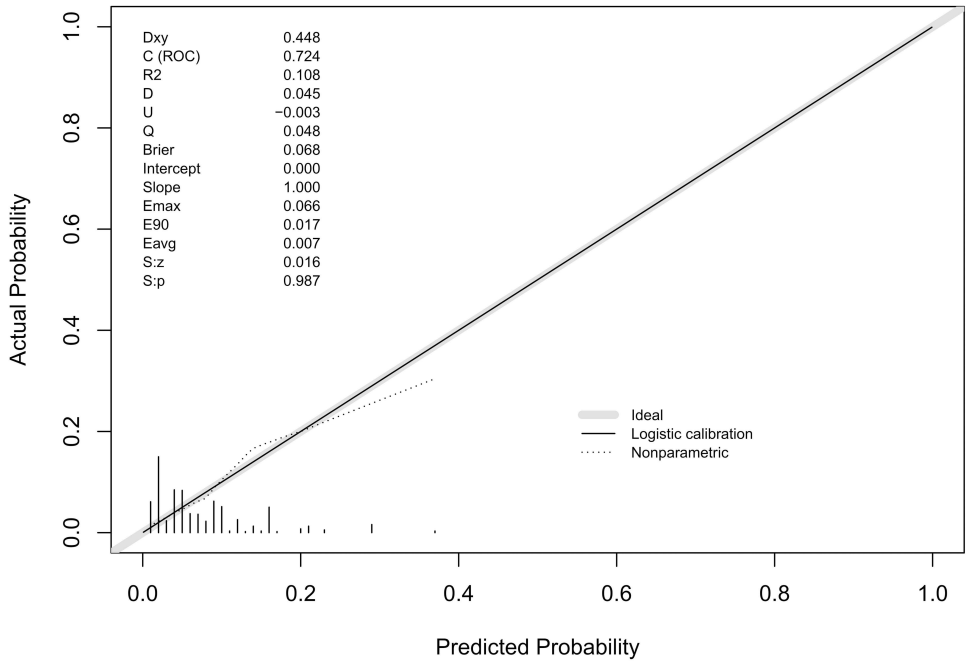

Figure 4 Calibration plot for predicted probability of special uterine leiomyoma pathological types or leiomyosarcoma. When the solid black line (Logistic calibration) was closer to the grey line (ideal model), the prediction accuracy of the nomogram was better.

Two Model Comparison

In clinical practice, we often assess the likelihood of special UL pathological types or leiomyosarcoma in postmenopausal women based on clinical symptoms related to UL, changing trend of UL after menopause, and diameter of the largest UL indicated by B-ultrasound, and use this as the basis for surgery. To evaluate the effectiveness of our 5-factor model compared to the previous clinical experience model, we conducted a study of 707 patients. Figures 6 and 7 show

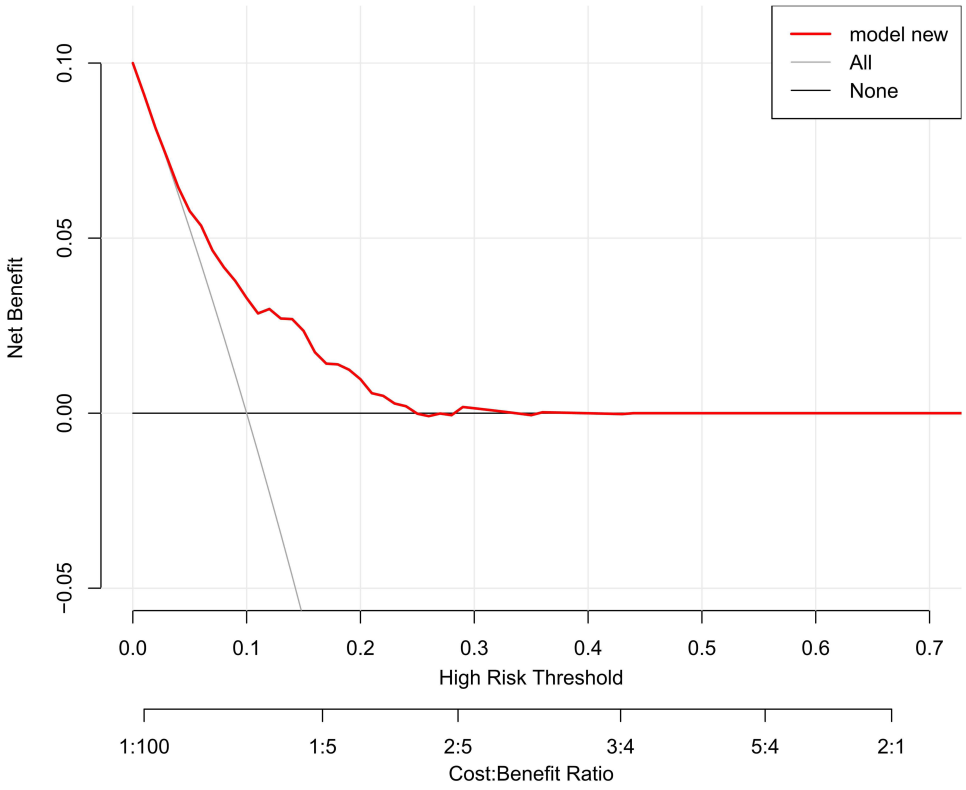

Figure 5 DCA for the prediction model. Red solid line: Prediction model; the gray line: Assume all postmenopausal patients have special uterine leiomyoma pathological types or leiomyosarcoma. Solid horizontal line: Assume no postmenopausal patients have special uterine leiomyoma pathological types or leiomyosarcoma. The graph indicates the expected net benefit per patient relative to the nomogram prediction of special uterine leiomyoma pathological types or leiomyosarcoma; model new: new 5 factor model.

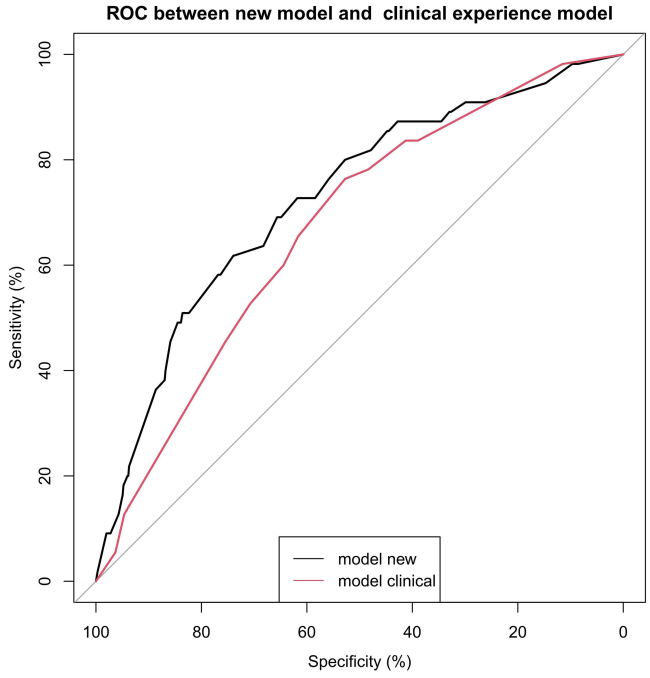

Figure 6 Comparison chart of AUC curve between our 5 factors model and clinical experience model. Black solid line: the AUC of new 5 factor model; Red solid line: the AUC of clinical experience model; model new: new 5 factor (changing trend after menopause, the diameter of the largest UL indicated by B-ultrasound, CA125, NLR, and Serum phosphorus ion concentration) model; model clinical: clinical experience (clinical symptoms related to UL, changing trend of UL after menopause, and diameter of the largest UL indicated by B-ultrasound) model.

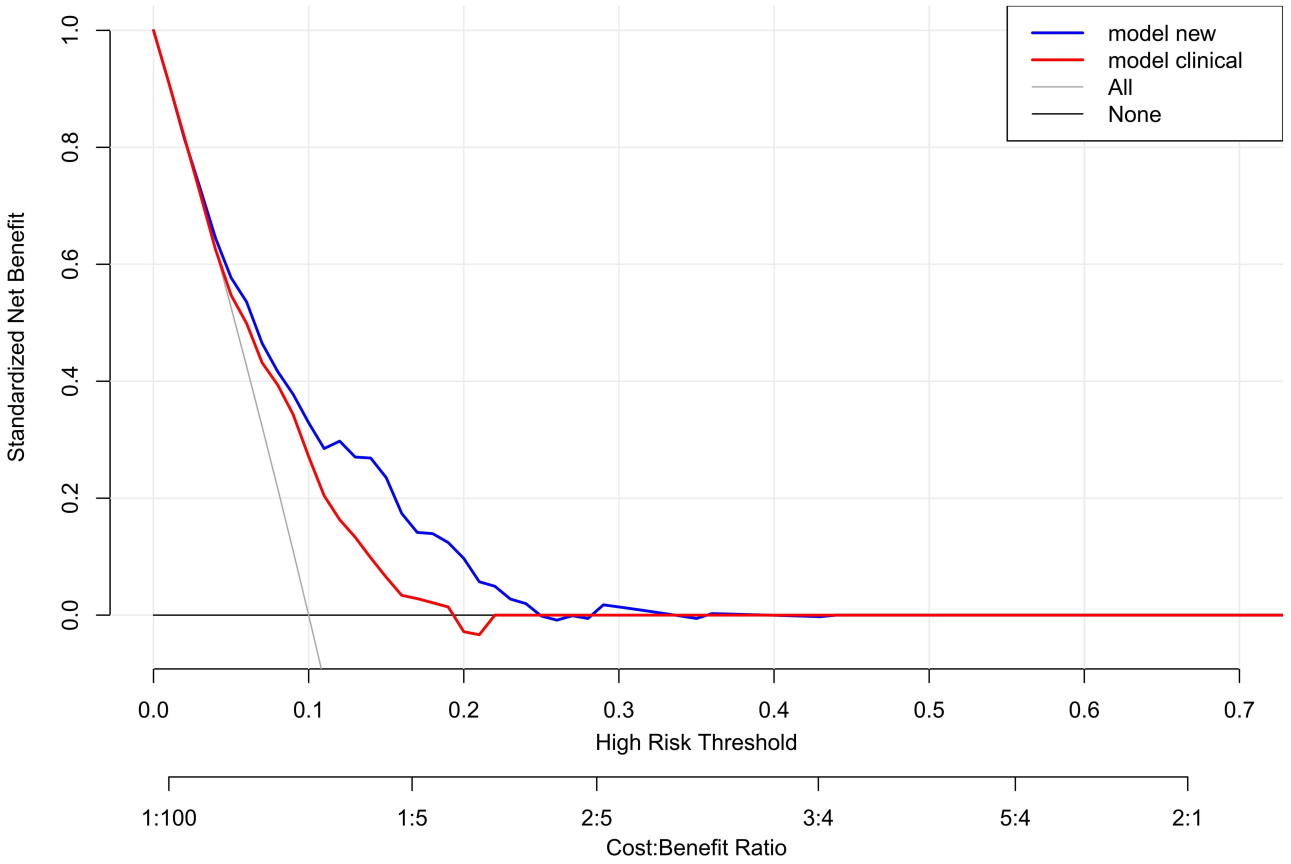

Figure 7 DCA between our 5-factor model (model new) and clinical-experience model (model clinical). Blue solid line: the DCA of new 5 factor model; Red solid line: the DCA of clinical model; model new: new 5 factor (changing trend after menopause, the diameter of the largest UL indicated by B-ultrasound, CA125, NLR, and Serum phosphorus ion concentration) model; model clinical: clinical experience (clinical symptoms related to UL, changing trend of UL after menopause, and diameter of the largest UL indicated by B-ultrasound) model.

that our model has advantages in ROC (P=0.04317) and DCA. By demonstrating the superior performance of our model in predicting special uterine leiomyoma pathological types or leiomyosarcoma in postmenopausal women, we aim to provide clinicians with a reliable and effective tool for decision making in surgical management.

Discussion

Surgical intervention has been found to be an effective approach for managing UL in postmenopausal women, particularly those who exhibit escalating postmenopausal fibroids, associated clinical symptoms, and substantial fibroid sizes. While surgery presents a viable treatment option, it is imperative to conduct a comprehensive evaluation of patients prior to surgical intervention, taking into account the physical and psychological impact of surgery, particularly in postmenopausal women, as well as the socioeconomic implications of the procedure.

In this investigation, an analysis was conducted on 32 potential variables associated with UL in 707 postmenopausal women who had undergone surgical procedures for hysteromyoma (myomectomy or hysterectomy). Stepwise regression was employed to select five variables for inclusion in the nomogram. The nomogram exhibited favorable diagnostic performance (AUC = 0.724) and underwent internal validation using the bootstrap sampling method. Additionally, the predictive model demonstrated enhanced performance in a clinical context, as evidenced by the results of DCA. Notably, in comparison to the previous clinical experience model in terms of AUC and DCA, the constructed prediction model displayed significant advantages in predicting the outcomes of special uterine leiomyoma pathological types or leiomyosarcoma.

After menopause, serum estrogen and progesterone levels decrease significantly, leading to a reduced likelihood of UL growth. Therefore, only a few cases of UL have been reported in postmenopausal women.[32–34] Interestingly, researchers[35] have found no discernible difference in the expression of sex steroid hormone receptors between

postmenopausal UL that required surgery and those that did not. These findings suggest that sex steroid hormones may play a less significant role in the growth of postmenopausal UL. In general, we believe that an increase in postmenopausal uterine leiomyoma size is indicative of special pathological types or leiomyosarcoma. This study found that uterine fibroid enlargement in postmenopausal women is indeed a risk factor for fibroids, and therefore must be considered when determining the need for surgery. However, because of the vast expanse of China, there are regional variations in the prevalence of uterine fibroids. As a result, some women have not paid attention to the trend of uterine fibroid growth, which may, to some extent, affect the determination of the surgical indications for uterine fibroids.

According to this investigation, it is advisable to consider the changing trend of UL after menopause in conjunction with the fibroid diameter. Various research studies have indicated the significant role of myoma size in predicting uterine smooth muscle tumors. For instance, a retrospective analysis of 31 patients with uterine sarcomas suggested that a larger tumor size (>8.0 cm) was an independent risk factor (P = 0.048).[27] Another study involving 15 patients with uterine smooth muscle tumors demonstrated that tumors larger than 7 cm may serve as a predictive factor (OR= 0.973, P = 0.08).[36] However, conflicting results have been reported in some studies. For example, in Chen's study, which involved 66 patients with uterine smooth muscle tumors, no significant difference in size was found between uterine smooth muscle tumors and UL (9.6 cm vs 8.5 cm, P = 0.40).[37] Our study evaluated the size of the largest fibroid in the uterus using ultrasound. We found that when the fibroid diameter is ≥ 5cm, there is a significantly higher likelihood of postoperative special UL pathological types or leiomyosarcoma (OR = 2.94).

In this study, we found a total of 5 predictors, namely trend, size, CA125, NLR, and Ph. The tumor marker CA 125 is mainly used to supplement the detection of malignant tumors, such as serous ovarian cancer, breast cancer, and other types of malignancies. Nevertheless, recent research indicates that elevated levels of CA 125 can also be observed in benign gynecological conditions such as endometriosis, ovarian cysts, and during the early stages of pregnancy.[38,39] Currently, there have been numerous research investigations examining the correlation between CA125 and uterine fibroids and leiomyosarcoma. Juang's study revealed that the preoperative serum CA125 levels in 42 patients with uterine leiomyosarcoma were significantly higher compared to those in the control group, which comprised 84 patients with leiomyoma.[40] Additionally, Kim and her co-authors documented specific inherent connections between serum CA125 levels and uterine leiomyosarcoma.[41] The relationship between CA125 and uterine fibroids remains not fully understood. While some studies have found no increase in CA125 levels among patients with uterine fibroids,[42,43] others have reported elevated levels.[44,45] However, there is limited research supporting the use of CA125 serum concentration for diagnostic differentiation in this context. This research used a threshold of 11.05 nmol/L for further examination, which was determined based on the distribution of CA125 values within the sampled cases. In the final model, CA125 was identified as a contributing factor, and the likelihood of abnormal uterine fibroid pathology was found to increase when the preoperative CA125 concentration in postmenopausal women was ≥11.05 nmol/L (OR = 1.67).

NLR is a commonly employed inflammatory marker in blood, serving as a diagnostic and prognostic indicator for a range of medical conditions.[46–48] Recent research has highlighted the diagnostic and prognostic significance of NLR in different types of cancerous tumors.[49–52] Investigations into gynecologic malignancies have revealed that a high NLR is correlated with unfavorable clinical outcomes in ovarian, endometrial, and cervical cancers, as well as uterine sarcoma.[64–68] Various studies have underscored the diagnostic relevance of an elevated NLR in the identification of uterine leiomyosarcoma. However, discrepancies in NLR cutoff values among studies may be attributed to limitations in sample size, which have ranged from 2.1 to 2.8. In the context of benign gynecological conditions, the NLR also demonstrates clinical significance. Presently, scholars posit that the activation of neutrophils contributes to the recruitment of various cell types involved in both acute and chronic inflammation, thereby initiating pro-inflammatory effects.[53,54] It is established that uterine fibroids may be linked to genetic factors, chromosomal abnormalities, and other determinants.[55,56] Several investigations[57,58] have indicated the pivotal role of inflammation in the genesis of uterine fibroids, fibroid fibrosis, and disease progression. In their research, Olga Sevostyanova et al[59] identified a correlation between fluctuations in lymphocyte counts, the release of pro-inflammatory mediators, and infertility in women of reproductive age with uterine fibroids. A recent study[60] has demonstrated the utility of employing the neutrophil-to-lymphocyte ratio for evaluating the inflammatory response in uterine fibroids. Additionally, a study focusing on uterine fibroids[61] identified a significant difference in NLR between patients with fibroid diameters exceeding 5 cm and those with diameters below 5 cm. By analyzing the NLR data in all cases, a threshold value of 3.12 was established to categorize the

NLR of all patients into binary categories. In the final predictive model, an NLR equal to or exceeding 3.12 is associated with an increased likelihood of postoperative pathological abnormalities (OR=2.14).

This study has, for the first time, established a connection between the concentration of phosphate ions in the serum and the characteristics of uterine fibroids in postmenopausal women. A serum phosphate ion concentration of ≥1.195 mmol/L is linked to a reduced risk of uterine fibroids (OR=0.52). Phosphorus is an essential constituent of the human body, found in all cells. The normal range of phosphorus in the bloodstream is 0.9 to 1.6 mmol/L. It plays a crucial role in various fundamental physiological functions such as energy metabolism, ion transport, enzyme catalysis, signal transduction, and the maintenance of cellular structure and function. Inadequate or deficient levels of serum phosphorus directly impact the cellular oxidative phosphorylation process, leading to a series of physiological and pathological changes. Reduced blood phosphorus levels also impede ATP synthesis, subsequently suppressing the activity of various immune cells. This includes a reduction in the phagocytic function of white blood cells, which results in immune dysfunction, exacerbates inflammatory responses, and increases susceptibility to infection.[62] Currently, there is a lack of scholarly research on the relationship between phosphorus levels and uterine fibroids. In clinical practice, there has been minimal emphasis on serum phosphorus levels. This study has, for the first time, revealed a potential protective association between elevated serum phosphorus levels and uterine fibroids (OR=0.52) in postmenopausal women, indicating potential diagnostic significance. Further investigation is required to delve into this finding.

The current investigation possesses several notable strengths. Firstly, the nomogram exhibited commendable performance in assessing the risk of special UL pathological types or leiomyosarcoma, thereby facilitating more precise personalized clinical decision-making and monitoring. Secondly, to the best of our knowledge, our study represents the pioneering effort to focus on predicting the risk of distinct UL pathological types or leiomyosarcoma, thereby laying the groundwork for personalized treatment approaches. Lastly, the nomogram's robustness was validated through internal bootstrap validation and demonstrated a favorable net benefit in the decision curve analysis. Furthermore, our predictive model offers enhanced accuracy and clinical applicability in comparison to the clinical experience model.

However, our study has several limitations. First, we only used internal verification methods to assess the clinical applicability of the nomograms without external validation. Second, the retrospective nature of the study inevitably introduces internal bias. Finally, the samples from our cohorts can only be considered representative of the population of Southeast China, and we aim to conduct external validation in a multicenter study.

Conclusion

In Conclusion, the increasing trend after menopause, the diameter of the largest uterine fibroid, serum carcinoembryonic antigen 125 concentration, Serum neutrophil to lymphocyte ratio, and Serum phosphorus ion concentration are independent risk factors for special UL pathological types or leiomyosarcoma in postmenopausal women. This study has developed an easy-to-use and economically impactful nomogram model to predict special UL pathological types or leiomyosarcoma in postmenopausal women. In addition, this model offers more advantages than the clinical experience model. The novel nomogram could offer predictive guidance for managing uterine leiomyomas in postmenopausal women. The visual and personalized model of five predictors provides clinicians with a simple and intuitive tool for early detection and identification of special UL pathological types or leiomyosarcoma in postmenopausal women. This may be crucial in reducing the physical and mental trauma, as well as the social and economic pressure, experienced by postmenopausal women after hysteromyoma surgery.

Data Sharing Statement

The data used for analysis is fully available in the manuscript file without restriction.

Ethics Approval and Consent to Participate

This study is a retrospective case study. We anonymously retrieve patient case information, and will not bring any additional adverse risks to patients. The researchers will strictly adhere to confidentiality principles. Relevant research information is only accessible to researchers/ethics committees. Therefore, the study was approved by the Institutional Review Board of Women's Hospital, School of Medicine, Zhejiang University, under IRB-20230105-R.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts in this work.

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