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Construction and Validation of a Risk Prediction Model for Lower Limb Lymphedema After Cervical Cancer Surgery: A Prospective Cohort Study

Guorui Zhao[1] | Jiali Xu[2] | Gaoming Liu[3] | Sen Li[2] | Xiang Liu[4] | Jie Long[4]

[1]Department of Thyroid Surgery, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China | [2]Xiangya School of Nursing, Central South University, Changsha, Hunan, China | [3]Department of Lymphedema Rehabilitation Center, Hunan Cancer Hospital—The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan, China | [4]School of Nursing, Hunan University of Chinese Medicine, Changsha, China

Correspondence: Gaoming Liu (liugaoming@hnca.org.cn)

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ABSTRACT

Objective: To analyze various risk factors for lower limb lymphedema (LLL) after cervical cancer surgery, to build a risk prediction model and to verify the model's predictive effect.

Methods: Clinical data were collected from 544 patients who underwent cervical cancer surgery in our hospital from January 2020 to December 2022. LASSO regression was used to screen risk factors for postoperative LLL. Then we established a Cox proportional hazard regression model including several parameters screened by LASSO regression. The final prediction model was visualized, and the nomogram for postoperative LLL risk prediction was finally plotted.

Results: A total of 544 patients undergoing cervical cancer surgery were randomly divided into training and validation sets at a 6:4 ratio. LASSO regression screened out 9 candidate variables. Multivariate Cox regression identified 3 independent risk factors and 1 independent protective factor for postoperative LLL. Statistically significant risk factors included prolonged preoperative static posture (HR = 4.675, $p < 0.001$), pelvic lymph node dissection (HR = 2.261, $p = 0.008$), and radiotherapy within 3 months after the surgery (HR = 1.929, $p = 0.029$). Preoperative labor intensity served as an independent protective factor (HR = 0.536, 95% CI: 0.364–0.790, $p = 0.002$). The other 5 screened variables had no significant correlation with LLL (all $p > 0.05$). A nomogram prediction model was constructed and internally validated. The C-index reached 0.835 in the training set and 0.810 in the validation set. The time-dependent AUC values ranged from 0.882 to 0.887 in the training set and 0.882 to 0.890 in the validation set at 12, 24, and 36 months. Calibration curves showed moderate consistency between predicted and observed LLL risks. Decision curve analysis verified that the model yielded satisfactory clinical net benefit within a wide threshold probability range.

Conclusion: Our risk prediction model has a good prediction effect and can provide a valid reference for clinical medical staff to evaluate the risk of LLL after cervical cancer surgery.

Guorui Zhao and Jiali Xu contributed equally to this work and share the first authorship.

1 | Introduction

Cervical cancer constitutes a significant challenge to women's health within the global cancer burden. According to 2022 data from the International Agency for Research on Cancer, cervical cancer ranks as the third most commonly diagnosed cancer among women worldwide, with approximately 660,000 new cases annually. It is also the third leading cause of cancer-related death in women, resulting in about 350,000 deaths each year [1].

Lower Limb Lymphedema (LLL) in cervical cancer patients is a common postoperative complication due to the destruction of the primary lymphatic system caused by intraoperative lymph node resection, as well as postoperative radiotherapy and chemotherapy. A study [2] has shown that the incidence of postoperative LLL in cervical cancer cases is 1.2%–37.8%. Once LLL occurs, the affected limb may become swelling, hardened, painful, and weak, potentially progressing to elephantiasis. These changes severely impair limb function, restrict social activities, and significantly diminish postoperative quality of life [3]. Furthermore, as LLL is currently incurable, patients must commit to long-term rehabilitation and self-management to mitigate physical disfigurement and symptomatic discomfort, imposing a substantial disease burden on both the individuals and their families [4]. Therefore, early postoperative prevention of LLL is of paramount importance.

Risk prediction models provide an essential basis for implementing personalized preventive measures by effectively identifying key risk factors. In current studies, risk factors are predominantly included using logistic regression analysis, such as age, body mass index (BMI), extent and number of lymph nodes dissected, radiotherapy, chemotherapy, and family history of cervical cancer [5, 6]. As a simple type of risk prediction model, this approach fails to eliminate interaction effects between variables and cannot address the collinearity issue. Chen et al. developed a nomogram that incorporated age, BMI, hypertension, number of lymph nodes dissected, adjuvant radiotherapy and chemotherapy, and prolonged standing time to achieve personalized prediction [7]. The nomogram overcomes the limitation of abstract numerical results from traditional logistic regression and enables intuitive and convenient individualized risk assessment in clinical practice. Therefore, this study aims to employ a prospective cohort design to analyze the risk factors for LLL following cervical cancer surgery and to construct useful and easy prediction models.

2 | Materials and Methods

2.1 | Setting and Participants

Sample collection for this study has been reviewed and approved by the Ethics Committee of Hunan Cancer Hospital (KYJJ-2020-016). We included those patients who underwent cervical cancer surgery in a tertiary cancer hospital in Hunan Province from January 2020 to December 2022 by convenience sampling method. The inclusion criteria were: (1) Patient's age ≥ 18 years; (2) Those meeting the diagnostic criteria for Stage I, II, III, and IV cervical cancer as per the International Federation of Obstetrics and Gynecology (FIGO), and (3) Patients who underwent cervical cancer surgery. The exclusion criteria were: (1) Those with cognitive and communication dysfunction; (2) Patients with other severe diseases; (3) Patients with a history of lower extremity injury or/and surgery before cervical cancer surgery, and (4) Those with cardiogenic, nephrogenic, dystrophic or other edema. All subjects provided informed consent and volunteered to participate.

2.2 | Sample Size Estimation

This study used Cox regression for multivariate analysis, which requires that the number of endpoint events be at least 10 times the number of predictive variables [8]. With 8–10 variables planned for inclusion, 80 LLL events were required. Using a 37.8% LLL incidence after cervical cancer surgery, the minimum sample size was calculated as 212 cases. Adjusting for a 20% loss to follow-up rate, the final required sample size was 265 cases at least. Finally, we included 544 cases. Subsequently, they were divided into 378 and 166 cases in the modeling and verification groups in a 6:4 ratio, respectively.

2.3 | Measures

According to the diagnostic criteria of the International Society of Lymphedema (ISL), a multimodal approach was adopted to ensure a scientific and accurate diagnosis. The diagnosis first used three methods for initial disease screening: (1) Measuring the circumference of both lower limbs: A trained professional used a unified inelastic tape measure. The instep circumference was first measured at the base of the little toe and followed by marking a reference point approximately 2 cm above the lateral malleolus. Limb circumference was measured at 4 cm intervals from the bottom to the upper border of the thigh. A bilateral circumference difference ≥ 2.0 cm was defined as the diagnostic threshold; (2) Human water molecular component detection: The human body component analysis tester was used to detect edema-related objective indicators in patients, like extracellular and segmental water ratios, bioelectrical impedance, with an extracellular water ratio > 0.39 as the diagnostic criterion; (3) Subjective symptoms and signs assessment: The Gynecologic Cancer Lymphedema Questionnaire (GCLQ) was used since it can effectively distinguish the occurrence of LLL in gynecologic cancer survivors, with good sensitivity and specificity [9]. The internal consistency reliability of the GCLQ total score was 0.95 [10]. GCLQ assesses 20 LLL-associated symptoms in the past 4 weeks, including heaviness, overall edema, localized swelling, infection signs, and symptom groups (limited knee movement, general swelling, redness, tightness, groin swelling, heaviness, and pain). A score of ≥ 4 can effectively diagnose LLL. If positive or discordant results are obtained from any of the three assessment modalities, high-frequency ultrasonography is implemented using a Canon Aplio i800 (TUS-AI800) scanner with an 18 MHz and 33 MHz linear transducer. All scans are completed by radiologists with ≥ 5 years of musculoskeletal ultrasound experience. The examination is intended to rule out deep vein thrombosis, lipedema and other limb swelling mimics, and confirm lymphedema via typical sonographic manifestations: increased thickness of subcutaneous tissue, dilated or sclerotic lymphatic vessels, and abundant irregular fluid clefts in the subcutaneous compartment.

A general questionnaire on postoperative LLL risk factors was prepared according to the "6s" evidence model database, and all studies involving the LLL risk factors/influencing factors were selected. Simultaneously, three gynecological oncologists (all chief physicians) and lymphedema specialist nurses (all international lymphedema therapists) were invited. Among them, two chief nurses and one deputy chief nurse revised the questionnaire, while the research team revised the questionnaire three times based on the opinions collected. Consequently, the patients' clinical data and related behavior patterns were investigated (Figure 1). Finally, a pre-survey of 15 patients was carried out, and the difficult entries or statements ambiguous to patients, as well as the time to fill in, were recorded. The questionnaire was further supplemented and improved to form the final questionnaire.

2.4 | Data Collection

To ensure research accuracy, all investigators received standardized training to proficiently operate the Hospital Information System (HIS) and standardize questionnaire administration. Investigators consulted medical records through the hospital's HIS system to obtain the general clinical and tumor-related data of patients who underwent cervical cancer surgery from January 2020 to December 2022. Additionally, patients also reported to the lymphedema clinic at 3, 6, 9, 12, 24, and 36 months postoperatively to observe the occurrence of LLL and collect relevant behavioral data. The GCLQ was distributed online. For patients unable to attend in-person clinic visits, follow-up assessments were conducted via WeChat video. Telephonic follow-up appointments were conducted to supplement and fill in unclear and missing data. The observational follow-up was terminated upon LLL onset. Similarly, follow-up ended if no LLL developed by 36 months after surgery. The patients' personal information was strictly protected during data processing to avoid disclosures.

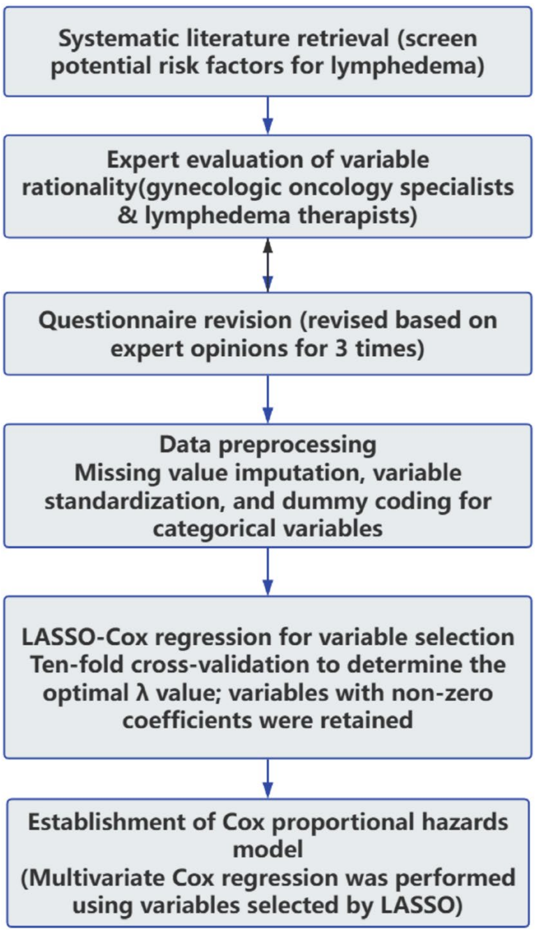


FIGURE 1 | Flowchart of variable selection for postoperative lower limb lymphedema risk prediction model.

2.5 | Data Analysis

All statistical analyses were performed using R 4.5.3 software. Normally distributed continuous data were described as mean ± standard deviation (Mean ± SD), non-normally distributed or heterogeneous data as median and interquartile range [median (IQR)], and count/ordinal data as n (%) with χ^2 test for intergroup comparisons and the Wilcoxon rank-sum test for comparing indicators between patients with and without LLL. Prior to multivariate analysis, LASSO regression (glmnet package) was applied to screen potential LLL risk factors to reduce multicollinearity. Subsequently, Cox proportional hazards regression (survival package) with partial maximum likelihood estimation was performed, with LLL occurrence as the dependent variable. The entry and removal α levels were set at 0.10 and 0.05, respectively, and the overall significance level was 5% ($p<0.05$). A risk scoring model was established based on the results of the Cox regression, with its predictive performance evaluated via ROC curve AUC (with 95% CI) and clinical applicability verified by sensitivity/specificity. The robustness and generalizability of the final prediction model were rigorously assessed via internal validation using 1000 bootstrap resamples. This resampling procedure effectively accounts for overfitting bias and confirms the stability of the model's predictive performance across repeated sampling. Calibration curves were plotted to evaluate the consistency between model-predicted probabilities and the actual observed incidence of postoperative LLL. Decision curve analysis (DCA) was further applied to quantify the net clinical benefit and comprehensively assess the clinical utility of the model. Finally, an intuitive visual nomogram was constructed using the rms package to support precise, individualized clinical risk stratification.

3 | Results

A total of 544 patients who received cervical cancer surgery combined with pelvic lymph node dissection at Hunan Provincial Cancer Hospital from January 2020 to December 2022 were enrolled. Among these patients, 41 (7.5%) had kidney disease, 103 (18.9%) had hypertension, and 42 (7.7%) had hyperlipidemia. Additionally, 16 (2.9%) had a history of drinking. There were 154 (28.3%) patients who developed LLL, and 15 (2.8%) had coronary heart disease. The patient screening flowchart is shown in Figure 2.

The patients were randomly divided into the training set and the validation set in a 6:4 ratio. The training set was used to establish the model, and the validation set was used to test the established model. There were no statistically significant differences in all variables included between the two groups ($p > 0.05$), which indicated that the data grouping was random and reasonable (Table 1). LASSO regression was employed to screen parameters, and the variation characteristics of the coefficients of these variables were shown in Figure 3A. The 10-fold cross-validation method was used for iterative analysis, and a model with excellent performance but the minimum number of variables was obtained when λ was 0.057 (Log λ = −2.864) in

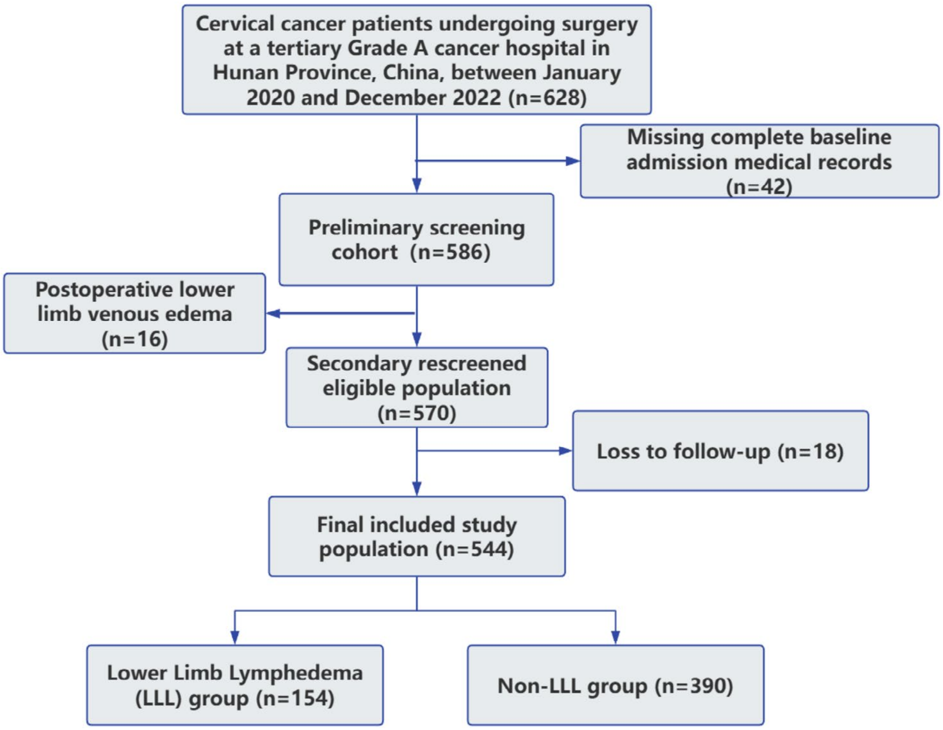


FIGURE 2 | Patient enrollment and screening flowchart.

TABLE 1 | Comparison of clinical data between training set and validation set.

Items	Total ($n = 544$)	Training set ($n = 334$)	Test set ($n = 210$)	p
Marital status (married/unmarried)	529/15	324/10	205/5	0.493
Hypertension (yes/no)	103/441	67/267	36/174	0.398
Hyperlipidemia (yes/no)	42/502	31/303	11/119	0.085
Coronary heart disease (yes/no)	15/529	11/323	4/206	0.336
Thyroid disease (yes/no)	39/505	27/307	12/198	0.297
Liver disease (yes/no)	83/461	45/289	38/172	0.144
Kidney disease (yes/no)	41/503	21/313	20/190	0.164
Smoking (yes/no)	23/521	16/314	7/207	0.164
Alcohol (yes/no)	16/528	11/323	5/205	0.540
Pathological stage (I/II/III/IV)	324/135/84/1	281/44/6/3	164/42/2/2	0.172
Time since surgery (> 7d/< 7d)	273/271	169/165	104/106	0.807
Pararectal lymph node dissection (yes/no)	270/274	165/169	105/105	0.892
Lower limb lymphedema (yes/no)	154/390	94/240	60/150	0.914
Prolonged preoperative static posture (yes/no)	140/404	86/248	54/156	0.993
Prolonged postoperative static posture (yes/no)	110/434	73/261	37/173	0.231
Preoperative regular exercise (yes/no)	176/368	115/219	61/149	0.191

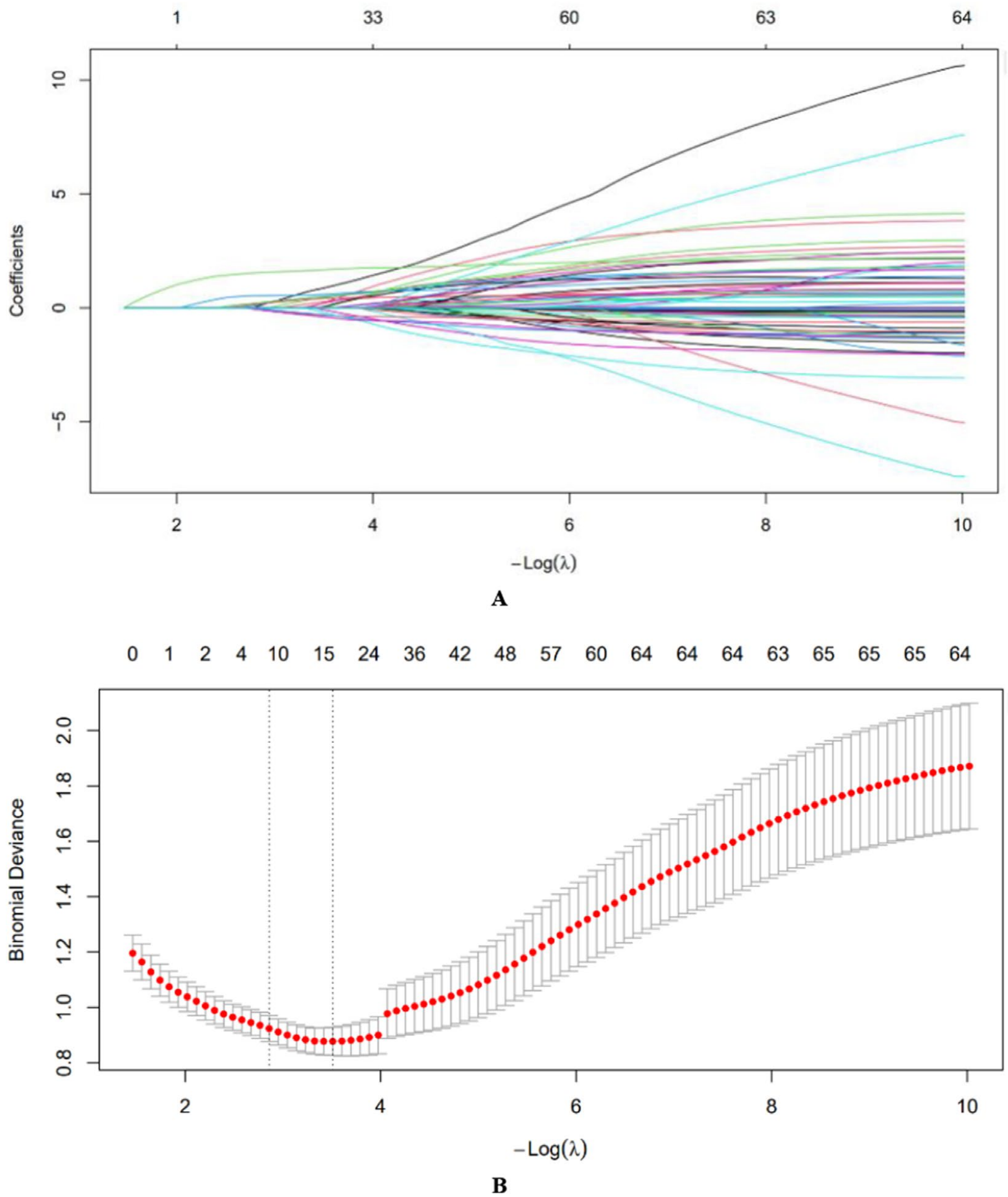


FIGURE 3 | Screening of variables based on Lasso regression. (A) The variation characteristics of the coefficients of variables; (B) the selection process of the optimum value of the parameter λ in the Lasso regression model by cross-validation method.

Figure 3B. The C-index of the training set was 0.835, and that of the validation set was 0.810.

To find the optimal penalty coefficient λ, the λ value corresponding to the minimum cross-validation error was selected, which can effectively reduce overfitting and ensure model stability. A total of 9 candidate predictors were retained after LASSO feature selection, namely smoking, pelvic lymph node dissection, radiotherapy within 3 months after the surgery, chemoradiotherapy within 3 months after the surgery, preoperative labor intensity, prolonged preoperative static posture, regular exercise before the surgery, prolonged postoperative static posture, and regular exercise after the surgery. These variables can effectively predict the occurrence of LLL and provide a reliable reference for clinical practice.

Prior to multivariate Cox regression, the proportional hazards assumption was verified by Pearson correlation analysis between Schoenfeld partial residuals and survival time for all 9 covariates. The correlation test of each covariate yielded $p > 0.05$, indicating no significant time-dependent hazard effects. Meanwhile, Schoenfeld residual scatter plots with fitted linear trends presented nearly horizontal lines without systematic time-varying trends (all corresponding plots are provided as Figure S1 in the supporting information), confirming that all predictors met the proportional hazards assumption for Cox regression. Then, multivariable Cox regression analysis identified three independent risk factors and one independent protective factor for postoperative LLL (all $p < 0.05$). The significant risk factors included prolonged preoperative static posture (HR = 4.675, 95% CI: 2.551–8.566, $p < 0.001$), pelvic lymph node dissection (HR = 2.261, 95% CI: 1.239–4.127, $p = 0.007$), and radiotherapy within 3 months after the surgery (HR = 1.929, 95% CI: 1.068–3.486, $p = 0.029$). Preoperative labor intensity was confirmed as an independent protective factor against postoperative LLL (HR = 0.536, 95% CI: 0.364–0.790, $p = 0.002$). The remaining five LASSO-screened variables exhibited weak associations with the risk of LLL but lacked statistical significance (all $p > 0.05$): smoking (HR = 2.047, 95% CI: 0.798–5.252, $p = 0.136$), chemoradiotherapy within 3 months after the surgery (HR = 1.331, 95% CI: 0.728–2.435, $p = 0.353$), regular exercise before the surgery (HR = 0.629, 95% CI: 0.358–1.106, $p = 0.107$), prolonged postoperative static posture (HR = 1.356, 95% CI: 0.766–2.402, $p = 0.297$), and regular exercise after the surgery (HR = 0.597, 95% CI: 0.349–1.024, $p = 0.061$). Full multivariate Cox regression results for all nine candidate predictors are summarized in Table 2. Furthermore, a nomogram-based Cox prediction model was constructed incorporating all predictive factors selected by LASSO regression (Figure 4). The total number of participants and LLL endpoint events for each subgroup of all predictors are summarized in Table S1.

In the training set, the C-index of the model predicting LLL after cervical cancer surgery was satisfactory. The AUCs of time-dependent ROC (tROC) at 12 months, 24 months, and 36 months were 0.882 (95% CI: 0.833–0.930), 0.887 (95% CI: 0.844–0.931), and 0.882 (95% CI: 0.841–0.923), respectively. In the validation set, the model maintained stable and robust discrimination performance. The tROC curve showed the AUCs at 12, 24, and 36 months were 0.880 (95% CI: 0.818–0.942), 0.890 (95% CI: 0.838–0.943), and 0.882 (95% CI: 0.831–0.933), respectively (Figure 5A,B).

TABLE 2 | Multivariate Cox regression analysis of postoperative LLL.

Items	β	HR (95% CI)	p
Chemoradiotherapy within 3 months after the surgery	0.286	1.331 (0.728–2.435)	0.353
Smoking	0.717	2.047 (0.798–5.252)	0.136
Regular exercise after the surgery	−0.515	0.597 (0.349–1.024)	0.061
Radiotherapy within 3 months after the surgery	0.657	1.929 (1.068–3.486)	0.029
Regular exercise before the surgery	−0.464	0.629 (0.358–1.106)	0.107
Preoperative labor intensity	−0.624	0.535 (0.364–0.789)	0.002
Prolonged postoperative static posture	0.304	1.356 (0.765–2.402)	0.297
Prolonged preoperative static posture	1.542	4.675 (2.551–8.566)	0.000
Pelvic lymph node dissection	0.816	2.261 (1.239–4.127)	0.007

The calibration curves of the training set (Figure 5C–E) and validation set (Figure 5F–H) showed generally acceptable agreement between model-predicted LLL risk probabilities and actual observed outcomes at 12, 24, and 36 months of follow-up. Obvious deviations from the ideal reference line were mainly concentrated in the low predicted risk interval, especially in the 12-month validation plot. In contrast, the clinically critical medium- and high-risk ranges exhibited good fitting consistency across all time points in both cohorts, verifying acceptable overall calibration ability of this prediction nomogram.

The DCA curves further verified the clinical utility of the model (Figure 5I,J). Compared with the default "treat-all" and "treat-none" management strategies, this prediction model delivered a higher net clinical benefit across a wide range of threshold probabilities. In both the training and validation cohorts, applying this model to identify patients at high risk of postoperative LLL could achieve considerable net benefit within the common clinical decision threshold range, demonstrating promising clinical application value.

4 | Discussion

Some studies have demonstrated that early identification and timely intervention are critical to halting the progression of LLL and preventing its irreversible sequelae [11, 12]. In the present prospective cohort, the median follow-up duration was 36 months, and the cumulative incidence of postoperative LLL in patients with cervical cancer reached 28.3%, which is consistent with the epidemiological findings reported in existing studies [7]. The development of LLL after cervical cancer surgery is driven by a combination of oncologic treatment-related injury and modifiable daily behavioral factors. All predictors retained after LASSO regression and incorporated into the final nomogram can be categorized into two domains: behavioral lifestyle factors and treatment-related factors. The behavioral lifestyle factors include smoking, preoperative labor intensity, prolonged preoperative static posture, regular preoperative exercise, prolonged postoperative static posture, and regular postoperative exercise. The treatment-related factors consist of pelvic lymph node dissection, radiotherapy within 3 months after surgery, and chemoradiotherapy within 3 months after surgery. This multi-dimensional predictor panel enables precise early risk stratification and individualized rehabilitation guidance for high-risk populations.

In recent years, Cox analysis and nomogram have been widely used for constructing disease risk prediction models and obtaining good discriminative values [13]. LASSO-regularized Cox proportional hazards regression effectively controls model complexity and mitigates overfitting, rendering it more suitable for clinical prognostic modeling. The nomogram in this study demonstrated good discrimination and calibration, with AUC values of 0.880, 0.890, and 0.882 at 12, 24, and 36 months on the validation set, and a C-index of 0.810. Using this nomogram, clinical healthcare providers can quickly and accurately identify high-risk patients, deliver health education and behavioral

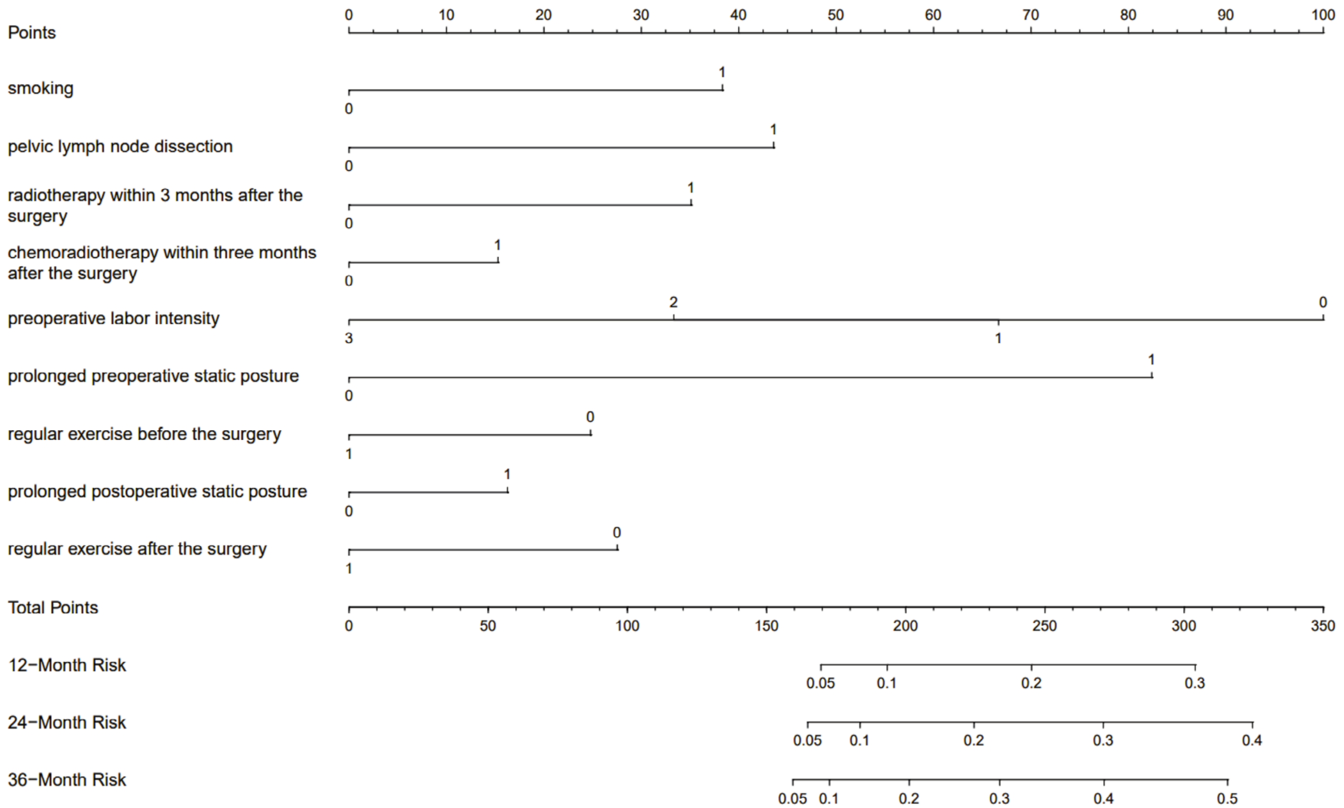
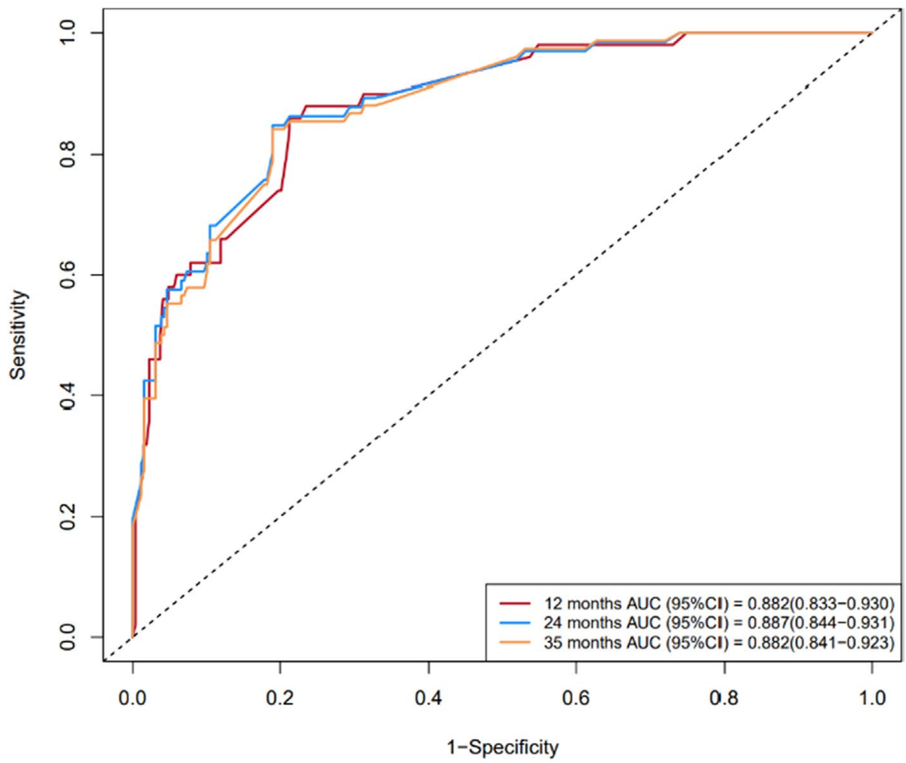


FIGURE 4 | Training set-based nomogram for prediction of lower limb lymphedema risk in patients after cervical cancer surgery. For each patient, locate the point score for each of the 9 independent risk variables. Sum the corresponding scores of all variables to obtain the total points. Then, draw a vertical line downward from the total points axis to the final prediction scale, so as to determine the individual predicted probability of developing postoperative LLL at different follow-up time points.

guidance based on patients' existing modifiable risk factors, and enhance patients' awareness of the risk and harm associated with lymphedema.

Pelvic lymph node dissection is one of the most important causes of LLL. Our Cox multivariable results showed that patients who underwent pelvic lymph node dissection had an approximately 2.26-times higher risk of LLL than those who did not. Because it terminates the limb lymphatic return pathway, resulting in the obstruction of the lower limb lymphatic return as well as protein and cell metabolite accumulation in the extracellular space of tissues. This affects the lymphatic system's ability to transport tissue fluid, resulting in impaired lymphatic system functions and lymphedema [14]. Besides, surgical modalities including sentinel lymph node biopsy, as well as the extent and number of lymph nodes removed, are also closely correlated with the risk of lymphedema [15, 16]. A study of 147 patients with gynecologic malignancies identified the number of lymph nodes dissected and the removal of deep circumflex iliac lymph nodes as major risk factors for LLL [17]. For patients with extensive pelvic lymph node dissections, we recommend providing education regarding the signs and symptoms of lymphedema and guidance for LLL prevention prior to discharge. This includes training in simple lower limb lymphatic drainage and the use of postoperative compression stockings, along with offering self-management education via video tutorials or digital health applications. Patients should be advised to remain vigilant and seek medical attention promptly if symptoms occur.

In our study, both prolonged static posture before surgery and prolonged identical posture after surgery were independent risk factors for LLL, which aligns with the findings of a previous relevant study [18]. The reason may be that prolonged same position might increase the lymph load in the lower extremities and affect lymphatic reflux. Hence, prolonged standing without exercise elevates leg and baseline extracellular water volumes [19, 20]. Mahjong playing and square dancing are popular pastimes in China; however, people who play mahjong tend to sit and stand for extended times, while square dancing people generally stand for > 2 h a day, thereby causing or aggravating LLL. While exploring the influence of exercise on LLL, we found that regular exercise before surgery can reduce the incidence of LLL. Presently, the mechanism of regular exercise in promoting lymphatic reflux is still unclear. Lymphatic pumps, muscle contraction, arterial pulsation, and chest negative pressure might be the driving forces of lymphatic reflux [21]. Simultaneously, joint flexion and extension can stimulate lymph nodes, enhance their function, and promote lymphatic vessels' operation [22]. Thus, patients should wear pressure products during regular exercise as the resulting reaction force exerts pressure on deep blood vessels and lymphatics, thereby promoting the filling and discharge of lymph fluid and blood. Clinicians should deliver targeted health education to guide patients to avoid prolonged static positions both preoperatively and postoperatively, reduce lower-extremity lymphatic burden via regular physical activity and alternating sitting and standing, and ultimately improve lymphatic reflux function.



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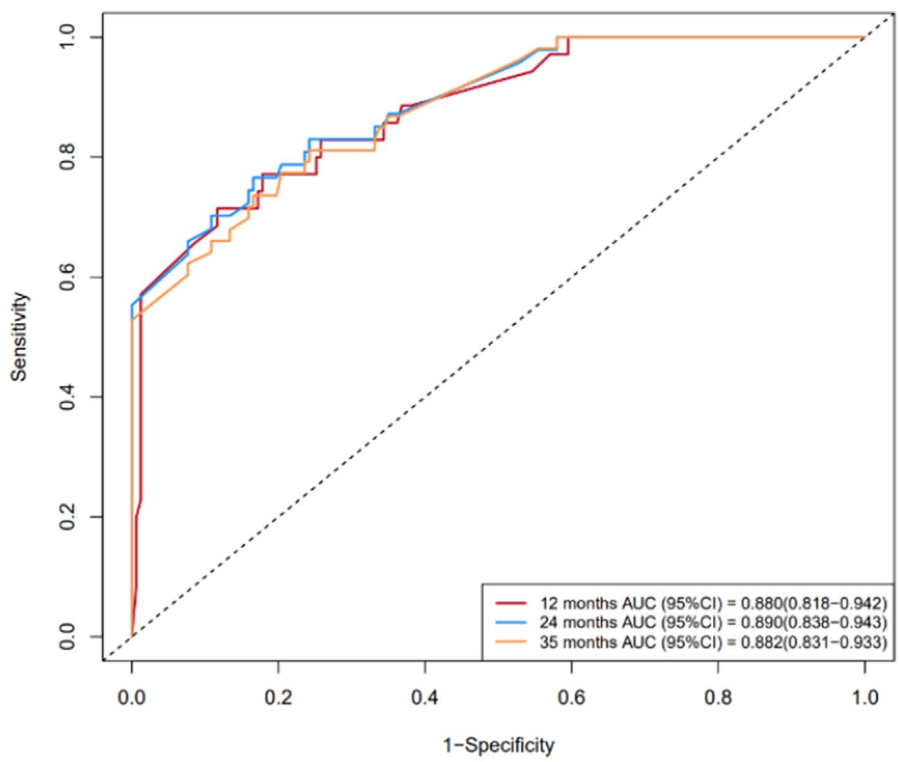
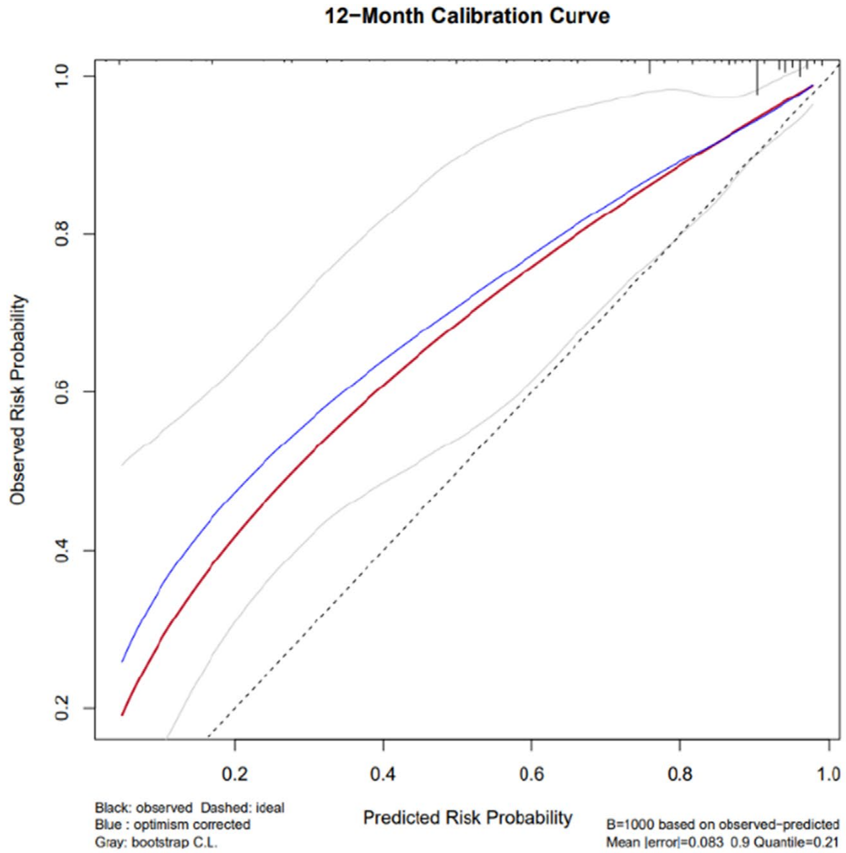


B

FIGURE 5 | Assessment of the risk prediction model for lower limb lymphedema. (A) The time dependent receiver operating characteristic (ROC) curve of the model in the training set at 12 months, 24 months and 36 months. (B) The time dependent ROC curve of the model in the validation set at 12 months, 24 months and 36 months. (C) The calibration curve of the model in the training set at 12 months. (D) The calibration curve of the model in the training set at 24 months. (E) The calibration curve of the model in the training set at 36 months. (F) The calibration curve of the model in the validation set at 12 months. (G) The calibration curve of the model in the validation set at 24 months. (H) The calibration curve of the model in the validation set at 36 months. (I) Decision curve analysis (DCA) of the model in the training set. (J) DCA of the model in the validation set.



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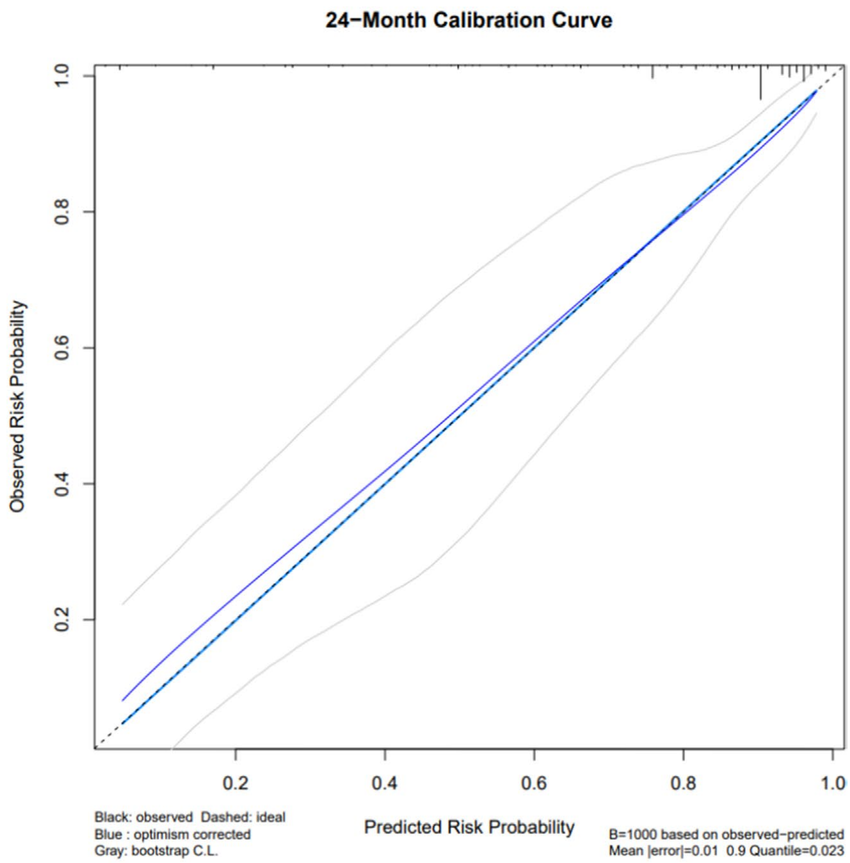

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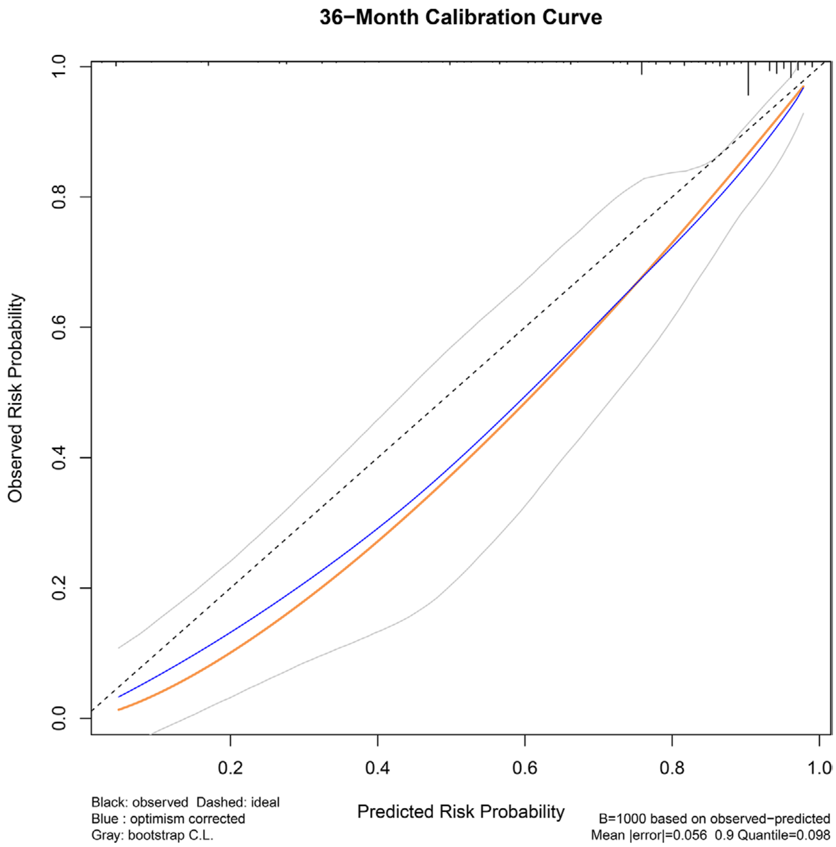

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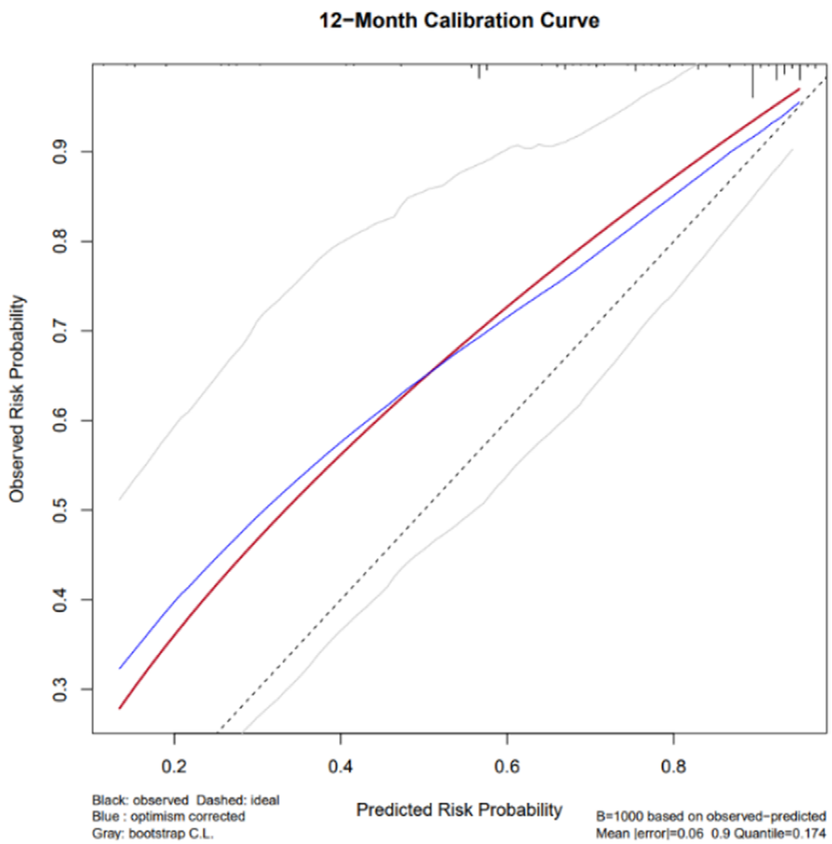

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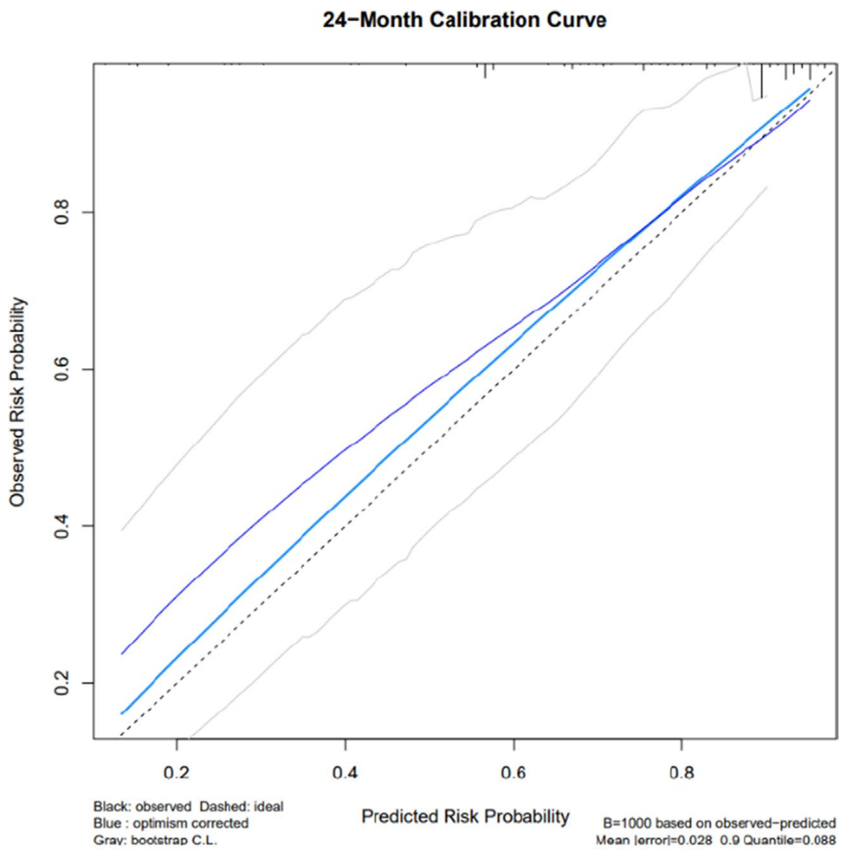

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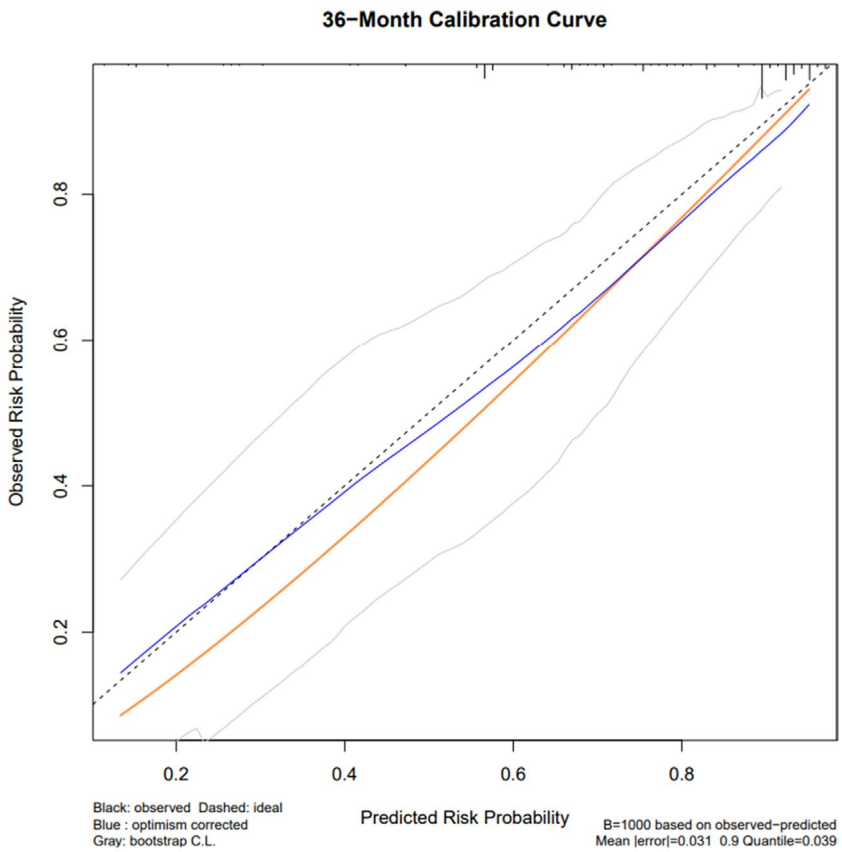

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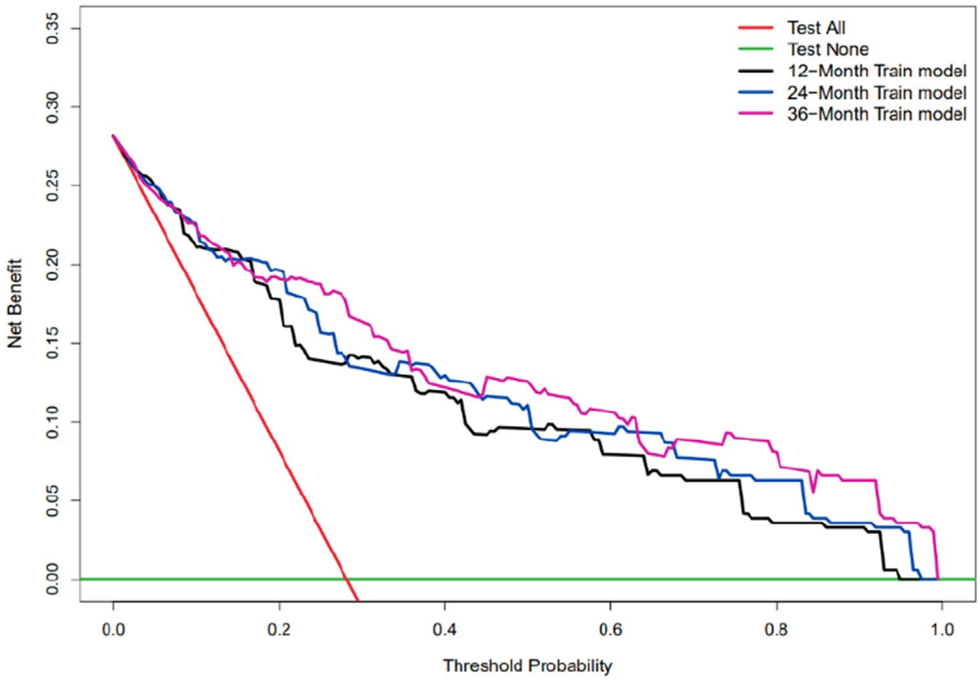

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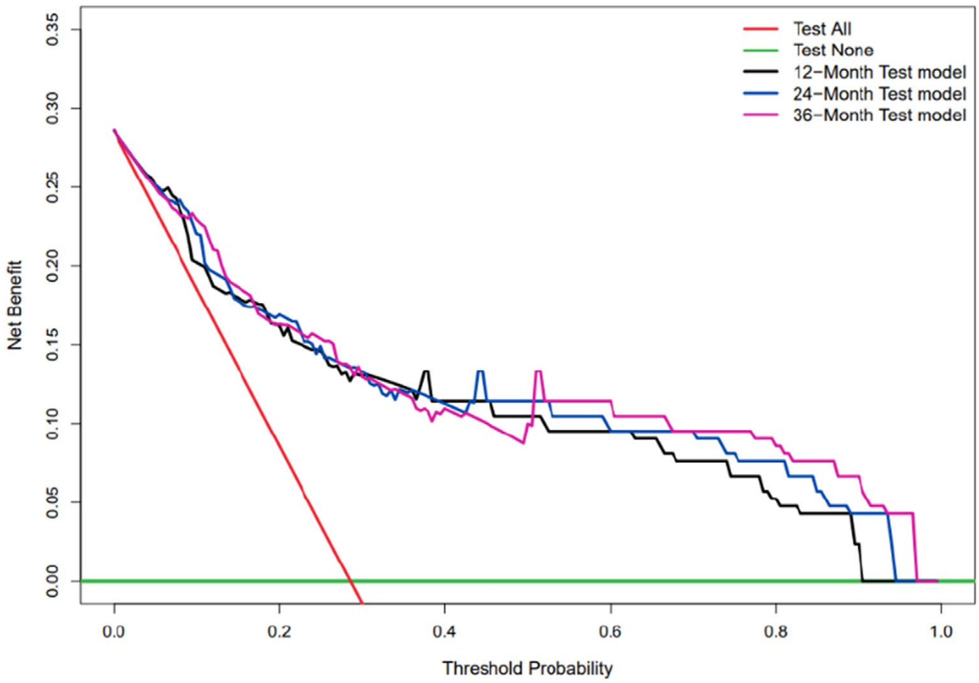

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FIGURE 5 | (Continued)

In this prospective cohort study, all physical activity-related variables—preoperative labor intensity, regular preoperative exercise, and regular postoperative exercise—exhibited consistent protective trends against postoperative LLL, among which preoperative labor intensity was identified as an independent protective factor (HR =0.536, 95% CI: 0.364–0.790, $p=0.002$). The biological plausibility of this protective association primarily lies in the skeletal muscle pump mechanism of the lower extremities: long-term regular physical activity promotes centripetal lymphatic flow through rhythmic skeletal muscle contraction, reduces interstitial fluid stasis, and preserves the intrinsic contractile function of collecting lymphatic vessels as well as the compensatory capacity of collateral lymphatic circulation [23]; as a marker of cumulative habitual physical exposure, preoperative labor intensity may enhance the baseline functional reserve of the pelvic and lower limb lymphatic system prior to surgical trauma, which can partially offset lymphatic drainage impairment induced by pelvic lymphadenectomy and adjuvant radiotherapy. Our findings are concordant with accumulating clinical evidence, as a recent systematic review and meta-analysis of 17 randomized controlled trials confirmed that structured exercise interventions safely reduce the incidence of cancer-related lymphedema without increasing adverse events [24] and a randomized controlled trial enrolling cervical cancer patients undergoing pelvic lymphadenectomy further demonstrated that postoperative progressive resistance exercise training effectively reduces the 6-month incidence of LLL [25], corroborating the preventive value of perioperative physical activity. Collectively, these findings support the implementation of a full perioperative LLL prevention strategy integrating preoperative physical activity optimization to augment lymphatic functional reserve and postoperative individualized exercise guidance to promote lymphatic drainage; the borderline statistical significance of regular exercise variables in our cohort may be attributed to limited sample size, self-reported exercise exposure with heterogeneous compliance, and insufficient stratification of exercise intensity and duration, which warrants further validation in large-scale prospective studies with objective physical activity monitoring.

Since chemotherapy and radiotherapy are currently administered to an increasing number of patients with cervical cancer, their impact on LLL is becoming more pronounced. However, in clinical practice, medical staff and patients do not pay attention to lymphedema post-chemoradiotherapy. Radiotherapy can lead to pelvic lymphatic occlusion, dermal fibrosis, lymphatic vessel atrophy, and impaired collateral circulation in the irradiated area, and these effects may be aggravated by higher radiation doses [26]. Therefore, helical tomotherapy (TOMO) should be used extensively as a precision radiotherapy method as it can achieve a sharp drop in dose around the tumor and better protect the lymphatic system compared to other traditional methods [27, 28]. In addition, Utsugi et al. reported that adjuvant chemotherapy containing docetaxel or paclitaxel significantly increases LLL risk, possibly by inducing capillary hyperpermeability and dermal sclerosis [29]. Also, chemotherapy may lead to bone marrow suppression, gastrointestinal toxicity, liver and kidney dysfunction, hypoalbuminemia, and malnutrition, thereby increasing the load on the lymphatic system [30]. Notably, nutritional support should also be strengthened while chemoradiotherapy is being administered to improve treatment tolerance and reduce toxic side effects.

In the present study, smoking was associated with an increased risk of postoperative LLL, though this association did not achieve statistical significance in multivariate Cox regression (HR = 2.048, 95% CI: 0.799–5.252, p = 0.136). Pathophysiologically, toxic components in tobacco smoke can induce inflammatory activation and prothrombotic phenotypic shifts in lymphatic endothelial cells, impair endothelial barrier integrity, and reduce lymphatic vessel contractility and drainage capacity [31]; for cervical cancer patients with surgically disrupted pelvic lymphatic pathways and additional radiotherapy exposure, such smoking-induced endothelial dysfunction further compromises the compensatory capacity of the residual lymphatic system, thereby exacerbating interstitial fluid retention and elevating LLL susceptibility. Clinically, this adverse association has also been verified in other pelvic malignancy populations receiving combined surgery and radiotherapy. A cohort study of prostate cancer patients undergoing postoperative radiotherapy identified smoking as a potential predictor of LLL, with smokers exhibiting a markedly elevated edema risk among those receiving pelvic lymph node dissection [32], which is consistent with the effect direction observed in our cohort. The lack of statistical significance in the present study is likely attributable to the relatively low prevalence of active smokers and limited statistical power for this variable. Clinically, these findings support the integration of preoperative smoking cessation counseling into routine perioperative LLL prevention protocols, particularly for patients scheduled for extensive pelvic lymphadenectomy.

5 | Conclusions

In summary, early identification of LLL risk factors preoperatively is crucial to improving the quality of life of cervical cancer patients postoperatively. With this model, clinicians can conveniently assess individual LLL risk in cervical cancer patients before or at admission, offer accurate risk assessment and counseling at the first postoperative visit, and perform dynamic risk monitoring during the perioperative and follow-up phases. However, our limitation was that the model was built and verified in one hospital with a limited sample size. Hence, multicenter, large-sample studies are needed to provide more accurate data for clinical use in the future.

Author Contributions

Gaoming Liu: supervision, resources, writing – review and editing. **Guorui Zhao:** conceptualization, writing – original draft, writing – review and editing, formal analysis. **Jie Long:** methodology, project administration. **Xiang Liu:** methodology, project administration. **Jiali Xu:** conceptualization, validation, writing – review and editing. **Sen Li:** methodology, writing – review and editing.

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Ethics Statement

Sample collection for this study has been reviewed and approved by the Ethics Committee of Hunan Cancer Hospital (KYJJ-2020-016). The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Distribution of candidate predictors and corresponding LLL event counts in the training set ($n = 334$). **Figure S1:** Schoenfeld residual plots for proportional hazards assumption validation of each predictor in the multivariate Cox regression model.