

Analysis of Risk Factors of Lymphedema After Surgical Treatment in Cervical Cancer: A Case-Control Retrospective Study

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Objective: Cervical cancer is a common malignant tumor in the female reproductive system, surgery is the main radical treatment methods. Lymphedema, as a postoperative complication of cervical cancer, affects the prognosis of patients. Identifying the risk factors for lymphedema after surgery is of great clinical significance for reducing its incidence. This study aims to systematically analyze the related risk factors for lymphedema after cervical cancer surgery.

Methods: Clinical medical data of 701 cervical cancer patients at Meizhou People's Hospital from December 2018 to December 2023 were collected, including age, body mass index (BMI), hypertension, diabetes mellitus, induced abortion, menopause, clinical stage, number of dissected lymph nodes, lymph node metastasis, postoperative complications, postoperative chemotherapy, postoperative radiotherapy, postoperative living habits, and lymphedema. The relationship between lymphedema and clinical features in cervical cancer was analyzed.

Results: A total of 220 (31.4%) patients developed lymphedema and 481 (68.6%) did not. The cervical cancer patients with lymphedema had higher proportions of advanced age, hypertension, menopause, number of dissected lymph nodes ≥ 30 , postoperative radiotherapy, and sitting quietly > 1 hour every day than patients without lymphedema. Logistic regression analysis showed that advanced age (odds ratio (OR): 2.713, 95% confidence interval (CI): 1.560–4.717, $p < 0.001$), menopause (OR: 1.954, 95% CI: 1.091–3.501, $p = 0.024$), pelvic lymph nodes plus para-aortic lymph nodes plus inguinal lymph nodes were dissected (OR: 2.039, 95% CI: 1.297–3.207, $p = 0.002$), number of dissected lymph nodes (≥ 30 vs < 30 , OR: 1.666, 95% CI: 1.105–2.514, $p = 0.015$), postoperative radiotherapy (OR: 3.775, 95% CI: 2.348–6.069, $p < 0.001$), and sitting quietly > 1 hour every day (OR: 14.782, 95% CI: 7.926–27.567, $p < 0.001$) were associated with lymphedema in cervical cancer.

Conclusion: Advanced age, menopause, pelvic lymph nodes plus para-aortic lymph nodes plus inguinal lymph nodes were dissected, number of dissected lymph nodes, postoperative complications, postoperative radiotherapy, and sitting quietly every day were independently associated with lymphedema in cervical cancer patients.

Keywords: cervical cancer, lymphedema, risk factors, clinical features

Introduction

Cervical cancer is a malignant tumor that occurs in the cervix.¹ Cervical cancer, as the fourth most common malignant tumor among women worldwide, seriously threatens their lives and health.² As a populous country, China accounts for a considerable proportion of the global cervical cancer burden, and it is gradually showing a trend of becoming younger.^{3,4} The prevention and treatment of cervical cancer is rather severe.^{3,5} Surgical treatment is an important treatment option for patients with early-stage cervical cancer and some patients with middle and advanced-stage cervical cancer.^{6,7} For example, hysterectomy combined with pelvic lymph node dissection can effectively remove tumor tissues, providing patients with a chance of cure and longer survival period.^{8,9} However, surgical treatment inevitably causes trauma to the patient's body and triggers a series of complications, such as postoperative lymphedema, urinary retention,

infection, and so on.¹⁰ These complications not only affect the postoperative rehabilitation process of patients and reduce their quality of life, but also affect the prognosis and survival rate of patients.¹¹

Postoperative lymphedema in cervical cancer refers to abnormal accumulation of lymph fluid in the interstitial spaces due to the obstruction of lymph fluid return caused by surgery, resulting in a series of symptoms such as swelling, pain, and skin changes.¹² Lymphedema not only significantly affects the quality of life, daily functions, and body image of patients, but may also increase the medical burden.¹³ In addition, long-term lymphedema has a great impact on the mental health of patients, with frequent negative emotions such as anxiety and depression.¹³ The prevalence of lymphedema after cervical cancer surgery varies greatly among populations, ranging from 10% to 70%.^{14,15} Its high incidence and severity have become important factors affecting the postoperative recovery and prognosis of patients with cervical cancer.¹⁶

The risk factors for lymphedema after cervical cancer treatment are complex and include patient factors (age, obesity, combined chronic diseases, and lifestyle habits),^{14,16–18} disease factors (disease stage and lymph node metastasis),¹⁴ and treatment factors (number of dissected lymph nodes, radiotherapy, and chemotherapy).^{14,17–19} However, Hareyama et al found that these factors have no relation to the risk of developing lymphedema.²⁰ Although lymphedema has a profound impact on the long-term health of patients, there are still many gaps in the current research on its occurrence mechanism and risk factors. Existing studies have not reached a consensus on the role of factors such as different surgical methods and individual differences among patients in the occurrence and development of lymphedema. An in-depth exploration of the risk factors for lymphedema after cervical cancer surgery is not only helpful for the early identification of high-risk populations and the formulation of personalized prevention strategies, but also provides a scientific basis for optimizing surgical techniques and improving adjuvant treatment plans. Therefore, systematically analyzing and clarifying the risk factors of lymphedema after cervical cancer surgery has become a key clinical issue for improving the prognosis of patients and enhancing their quality of life, which is of great significance.

Materials and Methods

Subjects

This study retrospectively analyzed the clinical medical data of 701 patients with cervical cancer who were diagnosed and treated at the Meizhou People's Hospital from December 2018 to December 2023. Patients who underwent surgery from January 2019 to September 2023. The follow-up deadline for this study was December 31, 2024. Lymphedema was regarded as a termination event during follow-up. If the patient did not develop lymphedema, the last follow-up deadline was considered as the cut-off date.

The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for cervical cancer; (2) patients who underwent surgical treatment in our hospital; (3) age ≥ 18 years; and (4) complete medical records. Exclusion criteria were: (1) coexisting with other severe diseases, such as severe organ failure, deep vein thrombosis, peripheral neuropathy or other malignant lesions; (2) patients with other surgical treatment histories; (3) cervical cancer patients who had received preoperative chemotherapy; (4) patients with edema caused by reasons such as cardiogenic, nephrogenic, or malnutrition; and (5) patients with incomplete medical records. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Data Collection

Clinical medical records of patients with cervical cancer were collected, including age, body mass index (BMI), history of hypertension, diabetes mellitus, and induced abortion, menopause, clinical stage, number of dissected lymph nodes, lymph node metastasis, postoperative complications (such as fever, diarrhea, infection, and thrombosis), postoperative chemotherapy, postoperative radiotherapy, postoperative living habits (such as exercise, sitting still), and the locations and stages of lymphedema. BMI was divided into three grades: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–23.9 kg/m²), and overweight (BMI ≥ 24.0 kg/m²).^{21,22} The diagnostic criteria of diabetes mellitus as follows: random serum glucose ≥ 11.1 mmol/L; or fasting blood glucose (FBG) ≥ 7 mmol/L; or blood glucose level at the 2-hour oral glucose tolerance test ≥ 11.1 mmol/L.²³ The diagnostic criteria of hypertension as follows: mean SBP > 140 mmHg and/or mean DBP > 90 mmHg.²⁴

In this study, the number of dissected lymph nodes refers to the total number of pelvic and/or para-aortic lymph nodes that were actually removed during the surgery and confirmed by pathological examination.²⁵

Sit quietly > 1 hour every day means that there is at least one instance within a 24-hour period where the duration of continuous sitting exceeds 60 minutes. If multiple instances of continuous sitting shorter than 60 minutes occur in a day but the cumulative total sitting time exceeds 1 hour, it does not fall under the category defined in this study as sit quietly > 1 hour every day. Additionally, sitting behavior includes but is not limited to sitting for long periods at work, traveling, watching TV, reading, using electronic devices, and other activities that involve a predominantly stationary position. This information was obtained through telephone follow-ups with the patients.

The disease stage of cervical cancer patients were evaluated according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system:²⁶ (1) stage I: the tumor is confined to the cervix; (2) stage II: the tumor extends beyond the uterus but has not reached the lower 1/3 of the vagina or the pelvic wall; (3) stage III: the tumor has spread to the pelvic wall, or involves the lower 1/3 of the vagina, or causes hydronephrosis or renal insufficiency; (4) stage IV: the tumor extends beyond the true pelvic cavity, or invades the bladder and/or rectal mucosa.

Diagnosis and Grading of Lymphedema

The diagnostic criteria for lymphedema:

- (1) Clinical symptoms and signs: symmetrical or asymmetrical swelling in one or both lower limbs (from the ankle to the root of the thigh), the perineum, or the lower abdomen, accompanied or not accompanied by a tight or heavy sensation of the skin, and limited mobility.
- (2) Measurement indicators: measurement of the circumferential diameter of both lower limbs: The “5-point marking method” was applied to measure the circumferential diameter of both lower limbs, that is, 2 cm directly above the highest point of the lateral malleolus and directly below the highest point of the patella, 10 cm directly above the upper edge of the patella and 20 cm directly above the upper edge of the patella. A difference of ≥ 2.0 cm between the two sides was considered the diagnostic standard for leptococcal edema. Body composition analysis test: A body composition analysis tester was used to detect intracellular water content, extracellular water content, total body water content, edema index, limb water content and other objective indicators related to edema. If the extracellular water content ratio of fine cells was greater than 0.39, edema was confirmed.²⁷ Magnetic resonance imaging (MRI) and vascular ultrasonography were used to diagnose the regional lymphoid nodules and subcutaneous tissue moisture.
- (3) Exclude lymphedema caused by factors such as cardiogenic edema, nephrogenic edema, hepatogenic edema, deep vein thrombosis of the lower extremities, hypoproteinemia, and local infection.

The classification standards for lymphedema are as follows: (1) grade I: the limb edema can subside on its own, disappearing after rest at night or after raising the limb, there are no obvious skin changes; (2) grade II: the limb edema does not subside on its own, and can be alleviated by raising the limb, the skin shows mild fibrosis; (3) grade III: the limb edema is significant, and does not significantly reduce after raising the limb; the skin shows obvious fibrosis, pigmentation, verrucous hyperplasia and other changes.

Statistical Analysis

SPSS statistical software (version 26.0) was used for data analysis. The χ^2 test was used to evaluate the relationship between lymphedema and clinical features. Logistic regression analyses were used to evaluate factors associated with lymphedema in patients with cervical cancer. $p < 0.05$ was set as statistically significant.

Results

Clinical Features of Patients with Cervical Cancer

There were 443 (63.2%) and 258 (36.8%) patients aged <50 and ≥ 55 years, respectively. The BMI of 373 (53.2%) patients was within the normal range, and 275 (39.2%) were overweight. A total of 145 (20.7%), 67 (9.6%), 327 (46.6%),

and 347 (49.5%) patients had a history of hypertension, diabetes mellitus, induced abortion, and menopause, respectively. There were 581 (82.9%), 93 (13.3%), 22 (3.1%), and 5 (0.7%) patients with squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and neuroendocrine carcinoma, respectively. There were 97 (13.8%), 368 (52.5%), 100 (14.3%), 198 (28.2%), 148 (21.1%), 459 (65.5%), and 95 (13.6%) patients with clinical stage III-IV, number of dissected lymph nodes ≥ 30 , lymph node metastasis, postoperative complications, postoperative chemotherapy, postoperative radiotherapy, and sitting quietly for more than one hour every day, respectively. And pelvic lymph nodes plus para-aortic lymph nodes plus inguinal lymph nodes in 448 (63.9%) patients were dissected (Table 1).

Table 1 The Clinical Features of Patients with Cervical Cancer

Clinical Features	Patients with Cervical Cancer (n=701)
Age (years)	
<55, n (%)	443 (63.2%)
≥ 55 , n (%)	258 (36.8%)
BMI (kg/m^2)	
<18.5, n (%)	53 (7.6%)
18.5–23.9, n (%)	373 (53.2%)
≥ 24.0 , n (%)	275 (39.2%)
History of hypertension	
No, n (%)	556 (79.3%)
Yes, n (%)	145 (20.7%)
History of diabetes mellitus	
No, n (%)	634 (90.4%)
Yes, n (%)	67 (9.6%)
History of induced abortion	
No, n (%)	374 (53.4%)
Yes, n (%)	327 (46.6%)
Menopause	
No, n (%)	300 (42.8%)
Yes, n (%)	347 (49.5%)
Unknown, n (%)	54 (7.7%)
Histopathological types	
Squamous cell carcinoma, n (%)	581 (82.9%)
Adenocarcinoma, n (%)	93 (13.3%)
Adenosquamous carcinoma, n (%)	22 (3.1%)
Neuroendocrine carcinoma, n (%)	5 (0.7%)
Clinical stage	
I, n (%)	351 (50.1%)
II, n (%)	253 (36.1%)
III, n (%)	95 (13.6%)
IV, n (%)	2 (0.3%)
Positions of dissected lymph nodes	
Pelvic lymph nodes + para-aortic lymph nodes + inguinal lymph nodes, n (%)	448 (63.9%)
Pelvic lymph nodes + inguinal lymph nodes, n (%)	227 (32.4%)
Pelvic lymph nodes + para-aortic lymph nodes, n (%)	2 (0.3%)
No lymph nodes were dissected, n (%)	24 (3.4%)
Number of dissected lymph nodes	
<30, n (%)	333 (47.5%)
≥ 30 , n (%)	368 (52.5%)

(Continued)

Table I (Continued).

Clinical Features	Patients with Cervical Cancer (n=701)
Lymph node metastasis	
No, n (%)	601 (85.7%)
Yes, n (%)	100 (14.3%)
Postoperative complication	
No, n (%)	503 (71.8%)
Yes, n (%)	198 (28.2%)
Postoperative chemotherapy	
No, n (%)	553 (78.9%)
Yes, n (%)	148 (21.1%)
Postoperative radiotherapy	
No, n (%)	242 (34.5%)
Yes, n (%)	459 (65.5%)
Sit quietly for more than one hour every day	
No, n (%)	606 (86.4%)
Yes, n (%)	95 (13.6%)
Lymphedema	
No, n (%)	481 (68.6%)
Yes, n (%)	220 (31.4%)

The Distribution of the Locations and Stages of Lymphedema

In this study, 220 (31.4%) patients developed lymphedema, whereas 481 (68.6%) patients did not. Among the patients with lymphedema, 92 (42%) had lower extremity lymphedema, 72 (33%) had perineum and lower extremity lymphedema, and 41 (18%) had perineum lymphedema alone. These three sites were the most common sites at which lymphedema occurs (Figure 1A). According to the stage distribution of lymphedema, the number of patients with stages I, II, and II lymphedema was the highest, and their combined proportion accounted for approximately 98% (Figure 1B).

Comparison of Clinical Features in Cervical Cancer Patients with and without Lymphedema

The cervical cancer patients with lymphedema had higher proportions of advanced age (≥ 55 years old) (58.6% vs 26.8%, $\chi^2=65.703$, $p<0.001$), history of hypertension (26.4% vs 18.1%, $\chi^2=6.303$, $p=0.016$), menopause (68.6% vs 40.7%, $\chi^2=49.798$, $p<0.001$), pelvic lymph nodes plus para-aortic lymph nodes plus inguinal lymph nodes were dissected (76.4% vs 58.2%, $\chi^2=27.463$, $p<0.001$), number of dissected lymph nodes ≥ 30 (62.7% vs 47.8%, $\chi^2=13.457$, $p<0.001$),

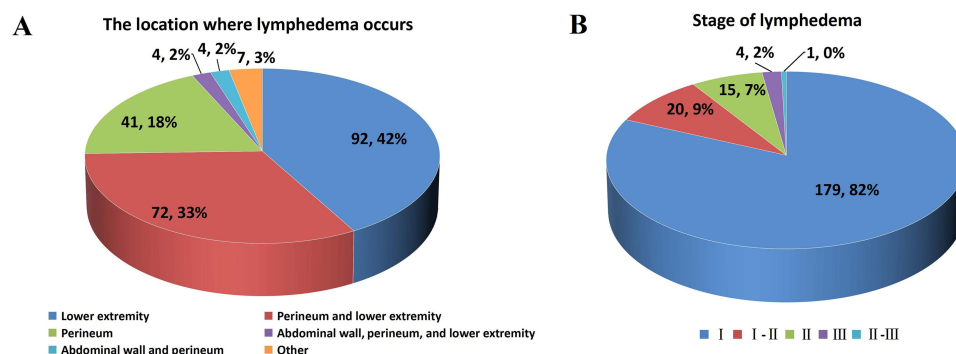


Figure 1 The distributions of the locations (A) and stages (B) of lymphedema.

postoperative radiotherapy (82.7% vs 57.6%, $\chi^2=42.204$, $p<0.001$), and sitting quietly for more than one hour every day (33.6% vs 4.4%, $\chi^2=110.395$, $p<0.001$) than patients without lymphedema. There were no statistically significant differences in BMI, history of diabetes mellitus, history of induced abortion, histopathological types, clinical stage, lymph node metastasis, postoperative complications, or postoperative chemotherapy between the patients with and without lymphedema (Table 2).

Table 2 Comparison of Clinical Features in Cervical Cancer Patients with and without Lymphedema

Clinical Features	Patients without Lymphedema (n=481)	Patients with Lymphedema (n=220)	p (χ^2)
Age (years)			
<55, n (%)	352 (73.2%)	91 (41.4%)	<0.001 ($\chi^2=65.703$)
≥55, n (%)	129 (26.8%)	129 (58.6%)	
BMI (kg/m ²)			
<18.5, n (%)	39 (8.1%)	14 (6.4%)	0.681 ($\chi^2=0.730$)
18.5–23.9, n (%)	256 (53.2%)	117 (53.2%)	
≥24.0, n (%)	186 (38.7%)	89 (40.5%)	
History of hypertension			
No, n (%)	394 (81.9%)	162 (73.6%)	0.016 ($\chi^2=6.303$)
Yes, n (%)	87 (18.1%)	58 (26.4%)	
History of diabetes mellitus			
No, n (%)	436 (90.6%)	198 (90.0%)	0.890 ($\chi^2=0.073$)
Yes, n (%)	45 (9.4%)	22 (10.0%)	
History of induced abortion			
No, n (%)	256 (53.2%)	118 (53.6%)	0.935 ($\chi^2=0.010$)
Yes, n (%)	225 (46.8%)	102 (46.4%)	
Menopause			
No, n (%)	247 (51.4%)	53 (24.1%)	<0.001 ($\chi^2=49.798$)
Yes, n (%)	196 (40.7%)	151 (68.6%)	
Histopathological types			
Squamous cell carcinoma	389 (80.9%)	192 (87.3%)	0.196 ($\chi^2=4.566$)
Adenocarcinoma	72 (15.0%)	21 (9.5%)	
Adenosquamous carcinoma	16 (3.3%)	6 (2.7%)	
Neuroendocrine carcinoma	4 (0.8%)	1 (0.5%)	
Clinical stage			
I-II, n (%)	417 (86.7%)	187 (85.0%)	0.557 ($\chi^2=0.363$)
III-IV, n (%)	64 (13.3%)	33 (15.0%)	
Positions of dissected lymph nodes			
Pelvic lymph nodes + para-aortic lymph nodes + inguinal lymph nodes	280 (58.2%)	168 (76.4%)	<0.001 ($\chi^2=27.463$)
Pelvic lymph nodes + inguinal lymph nodes	176 (36.6%)	51 (23.2%)	
Pelvic lymph nodes + para-aortic lymph nodes	1 (0.2%)	1 (0.5%)	
No lymph nodes were dissected	24 (5.0%)	0 (0)	
Number of dissected lymph nodes			
<30, n (%)	251 (52.2%)	82 (37.3%)	<0.001 ($\chi^2=13.457$)
≥30, n (%)	230 (47.8%)	138 (62.7%)	
Lymph node metastasis			
No, n (%)	416 (86.5%)	185 (84.1%)	0.416 ($\chi^2=0.708$)
Yes, n (%)	65 (13.5%)	35 (15.9%)	
Postoperative complication			
No, n (%)	356 (74.0%)	147 (66.8%)	0.058 ($\chi^2=3.855$)
Yes, n (%)	125 (26.0%)	73 (33.2%)	

(Continued)

Table 2 (Continued).

Clinical Features	Patients without Lymphedema (n=481)	Patients with Lymphedema (n=220)	p (χ^2)
Postoperative chemotherapy			
No, n (%)	383 (79.6%)	170 (77.3%)	0.486
Yes, n (%)	98 (20.4%)	50 (22.7%)	($\chi^2=0.502$)
Postoperative radiotherapy			
No, n (%)	204 (42.4%)	38 (17.3%)	<0.001
Yes, n (%)	277 (57.6%)	182 (82.7%)	($\chi^2=42.204$)
Sit quietly for more than one hour every day			
No, n (%)	460 (95.6%)	146 (66.4%)	<0.001
Yes, n (%)	21 (4.4%)	74 (33.6%)	($\chi^2=110.395$)

Note: The bolded values indicate $p < 0.05$.

Logistic Regression Analysis of Risk Factors of Lymphedema in Patients with Cervical Cancer

In univariate logistic regression analysis, advanced age (odds ratio (OR): 3.868, 95% confidence interval (CI): 2.765–5.411, $p < 0.001$), history of hypertension (OR: 1.621, 95% CI: 1.110–2.369, $p = 0.013$), menopause (OR: 3.590, 95% CI: 2.493–5.171, $p < 0.001$), pelvic lymph nodes plus para-aortic lymph nodes plus inguinal lymph nodes were dissected (OR: 2.319, 95% CI: 1.618–3.324, $p < 0.001$), number of dissected lymph nodes (≥ 30 vs < 30 , OR: 1.837, 95% CI: 1.325–2.546, $p < 0.001$), postoperative radiotherapy (OR: 3.527, 95% CI: 2.380–5.228, $p < 0.001$), and sitting quietly for more than one hour every day (OR: 11.102, 95% CI: 6.606–18.658, $p < 0.001$) were associated with lymphedema in cervical cancer patients (Table 3).

Multivariate analysis showed that advanced age (OR: 2.713, 95% CI: 1.560–4.717, $p < 0.001$), menopause (OR: 1.954, 95% CI: 1.091–3.501, $p = 0.024$), pelvic lymph nodes plus para-aortic lymph nodes plus inguinal lymph nodes were dissected (OR: 2.039, 95% CI: 1.297–3.207, $p = 0.002$), number of dissected lymph nodes (≥ 30 vs < 30 , OR: 1.666, 95% CI: 1.105–2.514, $p = 0.015$), postoperative radiotherapy (OR: 3.775, 95% CI: 2.348–6.069, $p < 0.001$), and sitting quietly for more than one hour every day (OR: 14.782, 95% CI: 7.926–27.567, $p < 0.001$) were independently associated with lymphedema in cervical cancer patients (Table 3).

Table 3 Logistic Regression Analysis of Risk Factors of Lymphedema in Patients with Cervical Cancer

Variables	Univariate		Multivariate	
	OR (95% CI)	p values	OR (95% CI)	p values
Age (≥ 55 vs < 55 , years old)	3.868 (2.765–5.411)	< 0.001	2.713 (1.560–4.717)	<0.001
History of hypertension (yes vs no)	1.621 (1.110–2.369)	0.013	1.377 (0.856–2.217)	0.188
Menopause (yes vs no)	3.590 (2.493–5.171)	< 0.001	1.954 (1.091–3.501)	0.024
Positions of dissected lymph nodes (Pelvic lymph nodes + para-aortic lymph nodes + inguinal lymph nodes vs other)	2.319 (1.618–3.324)	< 0.001	2.039 (1.297–3.207)	0.002
Number of dissected lymph nodes (≥ 30 vs < 30)	1.837 (1.325–2.546)	< 0.001	1.666 (1.105–2.514)	0.015
Postoperative radiotherapy (yes vs no)	3.527 (2.380–5.228)	< 0.001	3.775 (2.348–6.069)	<0.001
Sit quietly for more than one hour every day (yes vs no)	11.102 (6.606–18.658)	< 0.001	14.782 (7.926–27.567)	<0.001

Note: The bolded values indicate $p < 0.05$.

Abbreviations: OR, odds ratio; CI, confidence interval.

Discussion

Surgical treatment is the main radical method for early and locally advanced cervical cancer.²⁸ However, while surgery brings therapeutic benefits, it may also cause a series of complications. Postoperative lymphedema is one of the more common and challenging ones.¹⁵ Mild lymphedema may only present as slight swelling and discomfort in the limb, while severe lymphedema can cause limb dysfunction, recurrent infections, skin fibrosis, and even disability, significantly impacting the quality of life of the patient.²⁹ Identifying the risk factors for lymphedema after surgery is of great clinical significance for reducing its incidence.³⁰ At present, there is no unified conclusion regarding the risk factors of postoperative lymphedema in cervical cancer. In particular, the causal associations between the demographic and sociological characteristics of patients, disease and treatment factors, lifestyle and behavioral patterns and the occurrence of postoperative lymphedema need to be further clarified. In this study, advanced age, menopause, number of dissected lymph nodes, postoperative complication, postoperative radiotherapy, and sitting quietly for more than one hour every day were independently associated with lymphedema in cervical cancer patients.

Lee et al revealed that advanced age is a risk factor for postoperative lymphedema in patients with cervical cancer.¹⁹ Most studies suggest that in elderly patients with cervical cancer, due to the decline in physiological functions and activity levels, the recovery ability and compensatory ability of lymphatic vessels after surgery decreases, lymphatic return slows, and the incidence of edema increases.¹⁴ However, Yoshihara et al found that age <50 years was a risk factor for lower limb lymphedema in patients with gynecological cancer after treatment.³¹ Some studies have found that obesity/high BMI is a risk factor for lower limb lymphedema after cervical cancer surgery.^{17,18} Generally, cervical cancer patients with a high BMI have a greater risk of developing lymphedema. Such patients require more blood and lymph to meet their physiological needs, and adipose tissue can weaken the function of lymphatic circulation.³² However, this study did not find a relationship between BMI and lymphedema in patients with cervical cancer after treatment. The occurrence of inconsistent results might be due to factors such as differences in population, the accuracy of BMI measurement, and variations in the number of cases included in the study. Therefore, further studies are required to determine the relationship between the demographic characteristics of the patients and lymphedema.

Few studies have examined the relationship between physical conditions such as menopause, hypertension, diabetes, and postoperative lymphedema in patients with cervical cancer. Chen et al found that hypertension was a risk factor for postoperative lymphedema in patients with cervical cancer.¹⁶ This study found that menopause was a risk factor for postoperative lymphedema in patients with cervical cancer, however, no similar correlation was found in history of hypertension and diabetes mellitus. The inconsistent research results may be caused by the differences in the populations and sample sizes included in different studies.

Studies have found that lymph node dissection was a risk factor for postoperative lymphedema in patients with cervical cancer.¹⁹ Rebegea et al revealed that number of dissected lymph nodes ≥ 10 was an associated risk factor of lower limb lymphedema in cervical cancer.¹⁷ Armbrust et al showed that number of dissected lymph nodes >20 was an associated risk factor for lower limb lymphedema in patients with cervical and endometrial cancer.³³ Kuroda et al found that the risk of lower extremity lymphedema in postoperative cervical cancer patients with ≥ 20 pelvic lymph node dissections was 2.34 times that of those in patients with <20.³² Pelvic lymph node dissection disrupts the lymphatic circulation pathway, restricts the lymphatic fluid return and accumulates in the interstitial tissue spaces.³⁴ Sentinel lymph nodes refer to the first batch of lymph nodes that invade cancer cells have lymph node metastasis. If the biopsy of the sentinel lymph nodes is negative, it indicates that the tumor has not spread to other lymph nodes.³⁵ Therefore, a sentinel lymph node biopsy should be performed before dissecting lymph nodes. In patients with negative sentinel lymph node biopsy results, pelvic lymph node dissection should be avoided to reduce the incidence of lower extremity lymphedema.³⁶

Some studies have suggested that lymphedema is more common in patients undergoing radiotherapy or chemotherapy.³⁷ Several studies showed that postoperative radiotherapy was a risk factor for postoperative lower extremity lymphedema in cervical cancer patients,³⁸ patients with cervical and endometrial carcinoma,³³ and ovarian and uterine cancer patients.³⁹ Radiotherapy can cause severe trauma to lymphatic circulation, leading to inflammation, stenosis, occlusion of lymphatic vessels or fibrosis of the surrounding connective tissue, resulting in restricted lymphatic

circulation and lymphedema.^{40,41} Liu et al found that postoperative chemoradiotherapy was a risk factor for lower limb lymphedema after cervical cancer surgery.¹⁸

In addition, the relationship between other postoperative complications and lymphedema has rarely been studied relatively rarely at present. Liu et al found that the occurrence of postoperative complications was a risk factor for lower limb lymphedema after cervical cancer surgery.¹⁸ In this study, postoperative complications were independently associated with lymphedema in cervical cancer patients. Our results were consistent with these results. Rebegea et al revealed that lymph node metastasis was an associated risk factor of lower limb lymphedema in cervical cancer.¹⁷ Some studies suggested that lymph node metastasis is not correlation with lower extremity lymphedema.²⁰ Studies have found that postoperative chemotherapy was a risk factor for postoperative lymphedema in cervical cancer.¹⁹ Some studies have suggested that postoperative chemotherapy was not associated with lower extremity lymphedema.²⁰ In this study, lymph node metastasis was not associated with lymphedema in cervical cancer patients.

This study suggests that advanced age, menopause, number of dissected lymph nodes, postoperative complication, postoperative radiotherapy, and sitting quietly for more than one hour every day are independently associated with lymphedema in cervical cancer patients. With the development of precision medicine, the treatment of cervical cancer has gradually shifted from the traditional treatment model to personalized treatment centered on individual patient characteristics. This transformation is not only based on the clinical and pathological features of the tumor, but also incorporates multi-dimensional information such as molecular biology and genetics, aiming to improve treatment efficacy while minimizing adverse reactions to the greatest extent. Based on the identified correlation factors in this study, precision medicine can be applied to the management of lymphedema in the following aspects. Firstly, for older patients, gene testing and other methods can be used to assess the expression levels of genes related to the lymphatic system in the patient, predict the risk of postoperative lymphedema, and formulate individualized prevention plans according to the risk level. Secondly, for postmenopausal patients, hormone levels in the body can be detected, combined with the specific situation of the patient, to formulate individualized hormone regulation plans to reduce the risk of lymphedema. Additionally, for patients with a large number of lymph node resections, higher postoperative complication risks, or those who need postoperative radiotherapy, multi-omics testing can be used to evaluate individual differences and predict the risk of postoperative lymphedema, and formulate individualized treatment and care plans. In addition, some non-coding RNAs are considered to have the potential as targets for tumor treatment.^{30,42} Non-coding RNAs are expected to become a new type of biomarker and therapeutic target for lymphedema in patients with cervical cancer.

This study provides valuable reference information for predicting postoperative lymphedema in patients with cervical cancer. However, it inevitably has some limitations. First of all, postoperative lymphedema in cervical cancer is a chronic progressive disease with a long onset duration. Studies have reported that the incidence of lower extremity lymphedema is highest within one year after gynecological tumor surgery. Some patients with gynecological tumors may develop delayed lower extremity lymphedema, and some may develop it 10–20 years after treatment.³¹ Most studies have focused on lymphedema that occurs during the early stages of follow-up. Therefore, a considerable number of patients with delayed lymphedema may have been missed during diagnosis. The same problem was encountered in the present study. Second, some factors that might affect patient prognosis were not included in the analysis, such as specific regimens and doses of radiotherapy and chemotherapy, disease-free survival period, location and pattern of recurrence, and post-recurrence treatment information. Finally, as this was a single-center retrospective study, the sample size was limited, and inevitably, there was a sample bias and confounding bias. Therefore, more research is needed in the next step to provide valuable information for effectively identifying high-risk patients with lymphedema after cervical cancer surgery, thereby strengthening clinical guidance for high-risk patients and reducing the incidence of lymphedema.

Postoperative lymphedema after cervical cancer surgery is an important complication that affects the quality of life of patients. Its occurrence mechanism involves multiple biological processes such as disruption of lymph circulation, tissue fibrosis, and inflammatory response. Although traditional risk assessment based on clinical and pathological features can identify some high-risk factors, it is difficult to explain the differences among individuals. The development of multi-omics technologies (genomics, transcriptomics, proteomics, metabolomics) provides a new perspective for in-depth analysis of these individual differences.⁴³ By integrating multi-level molecular data, it is possible to achieve precise prediction of lymphedema risk and systematic explanation of the mechanism. Exploring new potential diagnostic and

therapeutic targets based on molecular classification, non-coding RNA, and metabolites, establishing precise/individualized diagnosis and treatment methods, optimizing patient care and targeted treatment pathways, is of great significance for cancer treatment.^{44,45} It is one of the important aspects for future research in this field.

Conclusions

Advanced age, menopause, number of dissected lymph nodes, postoperative complications, postoperative radiotherapy, and sitting quietly for more than one hour every day were independently associated with lymphedema in cervical cancer patients. In clinical practice, it is necessary to comprehensively assess the patient's condition to predict the risk of lymphedema occurrence, and develop individualized prevention strategies for high-risk patients to reduce the incidence of lymphedema. Meanwhile, the conclusions drawn from this study required further verification through multi-center, large-sample, prospective studies. In the future, more in-depth mechanism research and intervention measures exploration can be conducted based on these risk factors, providing a more solid theoretical basis and practical guidance for the prevention and treatment of lymphedema after surgery in cervical cancer.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals, and all the informed consent forms of the participants had been signed. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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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 declare that they have no competing interests in this work.

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