Original Article

Risk factors for lower extremity lymphedema after cervical cancer treatment: a systematic review and meta-analysis

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Background: The main risk factors for the development of lower extremity lymphedema after cervical cancer treatment are controversial. Our aim was to evaluate the main risk factors of lower extremity lymphedema after cervical cancer treatment.

Methods: We searched the English database PubMed, Embase, Medline, Central and the Chinese database CNKI to obtain relevant studies. Inclusion criteria: (I) the subjects were cervical cancer patients receiving treatment; (II) cohort studies or case-control studies; (III) exposure factors were not limited; (IV) the outcome was lower extremity lymphedema after treatment; (V) the odds ratio (OR) value and 95% confidence interval of exposure factors can be obtained. The chi-square test was used to test for heterogeneity. The Egger test was used to test for publication bias. OR (95% CI) was calculated using inverse variance.

Results: A total of 12 retrospective studies with a total of 3,401 patients were included in this literature review. The incidence of lower extremity lymphedema after cervical cancer treatment was between 12.6% and 43.1%. Meta-analysis results demonstrated that the main risk factors were: body mass index (BMI) (OR =1.37, 95% CI: 1.10–1.71, P=0.005), age (OR =1.68, 95% CI: 1.07–2.64, P=0.02), International Federation of Gynecology and Obstetrics (FIGO) stage (OR =1.50, 95% CI: 1.24–1.82, P<0.001), radiotherapy (OR =2.87, 95% CI: 1.71–4.82, P<0.001), lymph node (LN) dissection (OR =3.24, 95% CI: 1.44–7.31, P=0.005), and the number of LNs dissected (OR =2.34, 95% CI: 1.80–3.05, P<0.001). Egger's test showed that there was no publication bias among the literatures (P>0.05).

Conclusions: BMI, age, FIGO stage, radiotherapy, LN dissection and the number of LNs removed are the main risk factors for lower extremity lymphedema after cervical cancer treatment. When treating patients with cervical cancer, effective interventions should be sought to reduce the risk of lower extremity edema.

Keywords: Cervical cancer; lower extremity lymphedema; meta-analysis; risk factors

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Introduction

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer death in women. It has high incidence and mortality rates, inferior only to those for breast cancer. According to the latest data released by the International Agency for Research on Cancer of the World Health Organization, there were 604,000 new cases of cervical cancer and 342,000 deaths worldwide in 2020 (1).

With continuous progress in cervical cancer treatment and the popularization of screening technology, the survival rate and survival time of cervical cancer patients have been improved to a certain extent, so medical staff now need to pay more attention to patients' quality of life after treatment.

Early-stage cervical cancer is mainly treated by surgery, often accompanied by pelvic lymphadenectomy. The standard treatment for advanced cervical cancer is radiotherapy and chemotherapy (2,3), which, although having a good therapeutic effect, can affect lymphatic drainage and result in lower extremity lymphedema (4). Lymphedema is defined as dysfunction of the lymphatic system and is diagnosed by subjective or objective methods. When the body tissue contains excessive protein-rich interstitial fluid, it leads to increased limb volume. Lower limb lymphedema is characterized by swelling, unilateral or bilateral, heaviness, pain, pruritus, numbness, skin changes, infection, etc. The condition affects the patient's activities of daily life, and seriously affects quality of life (5,6).

Understanding the risk factors of lower limb lymphedema is of great significance to the clinical outcome of cervical cancer patients, but current research conclusions on the main risk factors are inconsistent (7,8). A study pointed out (9) that body mass index (BMI) and receiving radiotherapy are risk factors for lower extremity edema after cervical cancer treatment. International Federation of Gynecology and Obstetrics (FIGO) stage was not associated with lymph node metastasis and lower extremity edema. Another study (10) pointed out that radiotherapy, FIGO staging, lymph node metastasis, and lymph node dissection are risk factors for lower extremity edema after cervical cancer treatment. We believe the existence of such differences is related to the small sample size and inconsistent diagnostic criteria for lower extremity edema. A meta-analysis is necessary. Therefore, we performed a meta-analysis of studies from China and abroad with the aim of providing clinicians some certainty on the best postoperative management of these patients. We present the following article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1256/rc).

Methods

Literature retrieval

The English database PubMed, Embase, Medline, Central and the Chinese database CNKI were searched for studies in Chinese and English from database establishment time to March 2022. The retrieval method was medical subject words combined with free words. Search terms and subjects included "cervical cancer OR cervical neoplasm" AND "lymphedema OR lower limb lymphedema OR lower extremity lymphedema" AND "risk factor.

Literature screening

Inclusion criteria: (I) patients treated for cervical cancer; (II) cohort study or case-control study; (III) subject exposure factors are not limited; (IV) the observed outcome of the study was lower extremity lymphedema after treatment; (V) odds ratio (OR) and 95% confidence interval (CI) of the risk factors could be ascertained indirectly or directly from the study.

Exclusion criteria: (I) lymphedema <6 months after surgery or radiotherapy; (II) case reports; (III) republished studies; (IV) incomplete data for analysis.

Data extraction

Based on the inclusion and exclusion criteria, two researchers independently screened and determined the final included studies, and extracted the data according to a predetermined table. The main data extracted included (I) basic information such as title, publication date, authors' name, etc.; (II) research type, research population, intervention measures, outcome indicators, etc.; (III) research methods, subject characteristics, data results. Questions or differences in the process of literature screening and extraction were resolved through discussion with a third researcher.

Literature quality evaluation

The quality of the observational studies was evaluated by the Newcastle-Ottawa Scale (NOS), which is divided into the NOS evaluation criteria of a cohort study and the NOS evaluation criteria of a case-control study. It is further divided into three blocks (population selection, comparability, exposure evaluation or result evaluation), comprising 8 items and scoring by a star system. The total score of a cohort study is 13 stars, and the total score of a disease case-control study is 9 stars. Two researchers independently evaluated the quality of the included literature and then cross-checked it. If there were any differences, an agreement was reached after discussion with the third researcher.

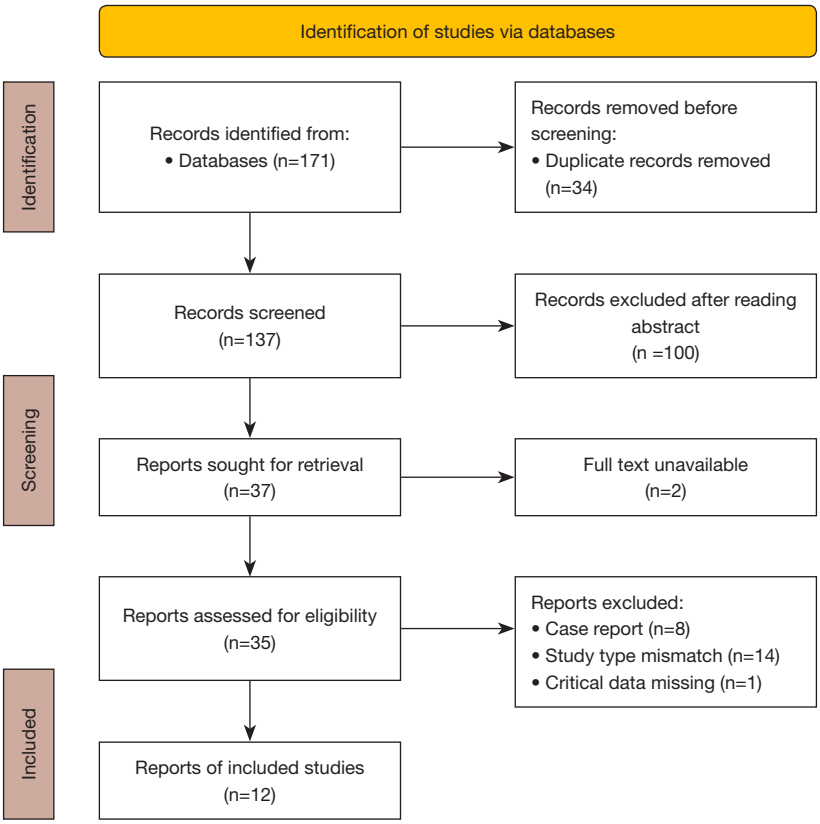

Figure 1 Flowchart of document screening process.

Statistical analysis

We used Cochrane software RevMan5.4 to statistically analyze all data. OR (95% CI) was calculated using Inverse Variance. The Chi-square test was used to test heterogeneity between studies. When the I^2 corrected by degrees of freedom was >50%, it was considered to be heterogeneous, and the random-effects model was used. When the I^2 corrected by degrees of freedom was ≤50%, it was considered there was no heterogeneity, and the fixed-effects model was adopted. Potential publication bias was estimated by Egger test. Two-sided P<0.05 indicated statistical significance.

Results

Literature retrieval

In this study, 171 relevant studies were obtained and then deduplicated by EndNote X9 management software. The researchers then screened the literature according to the predetermined inclusion and exclusion criteria and read the full text as further screening. Finally, 12 studies were included. The specific screening process and results are shown in *Figure 1*.

Literature quality evaluation

The basic information of the included studies is shown in *Table 1*. Of them, 6 articles were in English. The research populations were from the USA, Japan, South Korea, the Czech Republic and Romania. The other 6 articles were in Chinese, and the research population was Chinese. All studies were published between 2010 and 2022, so were relatively new, and they were all retrospective. The incidence of lower extremity lymphedema after treatment of cervical cancer ranged from 12.6% to 43.1%. All studies had evaluated the risk factors of lower extremity lymphedema after cervical cancer treatment, including BMI,

Table 1 Basic characteristics of the included literature

Study	Country	Research type	Test method	Edema criteria	Sample size	Incidence rate	Treatment	Risk factors
Halaska *et al.*, 2010 (9)	Czech Republic	Cohort study	Self-reporting questionnaire, clinical testing	Subjective judgment	60	25.80%	Surgery and radiotherapy	BMI, radiotherapy
Kim *et al.*, 2012 (10)	South Korea	Cohort study	Clinical examination	CTCAE3.0	596	12.60%	Surgery and radiotherapy	BMI, age, radiotherapy, FIGO stage, LN metastasis, LN dissection
Mendivil *et al.*, 2016 (11)	America	Cohort study	Clinical examination	CTCAE4.0	30	18.80%	Surgery and radiotherapy	BMI, FIGO staging, radiotherapy
Ohba *et al.*, 2011 (12)	Japan	Cohort study	Clinical examination	Subjective judgment	155	20.00%	Surgery, radiotherapy, and chemotherapy	BMI, age, radiotherapy, chemotherapy, FIGO stage, LN metastasis
Rebegea *et al.*, 2020 (13)	Romania	Cohort study	Clinical examination	NR	186	15.05%	Surgery, radiotherapy, and chemotherapy	Age
Yamazaki *et al.*, 2015 (14)	Japan	Cohort study	NR	NR	398	NR	Surgery, radiotherapy, and chemotherapy	FIGO staging, radiotherapy, chemotherapy, LN dissection
Liu *et al.*, 2021 (15)	China	Case control study	Self-reporting	GCLQ	109	43.10%	Surgery, radiotherapy, and chemotherapy	BMI, age, FIGO stage, chemotherapy, number of LNs dissected
Sun *et al.*, 2015 (16)	China	Cohort study	Self-reporting	GCLQ	218	19.30%	Surgery, radiotherapy, and chemotherapy	Radiotherapy, chemotherapy, LN dissection
Wang *et al.*, 2015 (17)	China	Cohort study	Self-reporting	GCLQ	492	20.93%	Surgery, radiotherapy, and chemotherapy	Age, FIGO stage, radiotherapy, chemotherapy, LN dissection
Yin *et al.*, 2021 (18)	China	Case control study	Self-reporting	GCLQ	110	33.64%	Surgery, radiotherapy, and chemotherapy	BMI, age, FIGO stage, number of LNs dissected
Zhang *et al.*, 2021 (19)	China	Case control study	Self-reporting	GCLQ	949	22.60%	Surgery	BMI, age, FIGO stage, radiotherapy, LN dissection, number of LNs dissected
Zhou, 2022 (20)	China	Case control study	Self-reporting	GCLQ	98	33.67%	Surgery, radiotherapy, and chemotherapy	BMI, age, FIGO stage

BMI, body mass index; CTCAE, common terminology criteria for adverse events; FIGO, International Federation of Gynecology and Obstetrics; GCLQ, gynecological cancerlymphedema questionnaire; LN, lymph node; NR, not reported.

age, International Federation of Gynecology and Obstetrics (FIGO) stage, radiotherapy, chemotherapy, lymph node (LN) metastasis, LN dissection and the number of LNs dissected. In addition, the researchers evaluated the quality of all retrospective studies according to the NOS standards, and the quality of the 12 included studies was high.

Meta-analysis of main risk factors for lower extremity lymphedema after treatment of cervical cancer

A meta-analysis of the included studies was conducted. Of the risk factors, 8 reported BMI, 8 included age, 9 included FIGO stage, 8 included radiotherapy, 5 included chemotherapy, 2 included LN metastasis, 5 included

Table 2 Results of meta-analysis of risk factors for lower limb lymphedema after treatment of cervical cancer

Factor	No. of studies	No. of patients	OR (95% CI)	P value
BMI (≥25, <25 kg/m^2)	8	756/1,351	1.37 (1.10, 1.71)	0.005
Age (≥50/60, <50/60 years)	8	753/1,829	1.68 (1.07, 2.64)	0.02
FIGO stage (≥II, <II)	9	1,023/1,914	1.50 (1.24, 1.82)	<0.001
Radiotherapy (yes, no)	8	834/1,993	2.87 (1.71, 4.82)	<0.001
Chemotherapy (yes, no)	5	606/674	1.64 (0.78, 3.42)	0.19
Lymph node metastasis (yes, no)	2	154/597	1.40 (0.86, 2.26)	0.17
Lymph node dissection (yes, no)	5	1,287/1,268	3.24 (1.44, 7.31)	0.005
Lymph node clearance (≥20, <20)	4	588/678	2.34 (1.80, 3.05)	<0.001

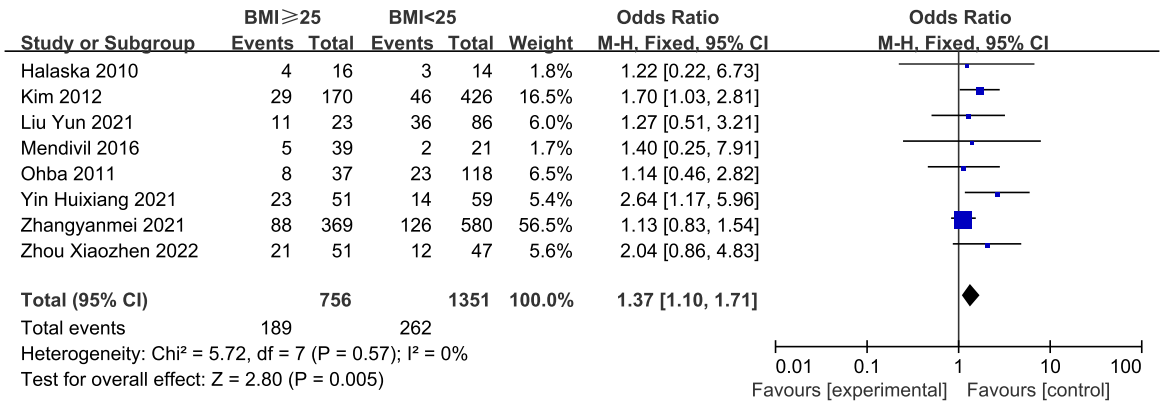

Figure 2 Forest diagram of BMI. BMI, body mass index.

LN dissection, and 4 included LN clearance. The heterogeneity test results showed that the I^2 of age, FIGO stage, radiotherapy, chemotherapy and LN dissection was 68%, 8%, 77%, 75% and 79%, respectively, which was heterogeneous, so the random-effects model was adopted. BMI, LN metastasis and the number of LNs dissected were not heterogeneous, so the fixed-effects model was adopted. The results of the meta-analysis results showed that BMI, age, FIGO stage, radiotherapy, LN dissection and number of LNs dissected were the main risk factors of lower extremity lymphedema after cervical cancer treatment (*Table 2*, *Figures 2-9*). Egger's test showed that there was no publication bias among the literatures (P>0.05).

Discussion

Although the factors related to the occurrence of lower extremity lymphedema in patients after treatment of cervical cancer have been discussed, a consistent conclusion has not been reached. Searching the published systematic reviews at home and abroad, Bona *et al.* (21) included 23 relevant studies. However, due to lack of data and heterogeneity, only a descriptive systematic literature review was conducted in this study. The results of the descriptive analysis of this study showed that the main factors causing lymphedema after cervical cancer treatment were the number of lymph nodes dissected, adjuvant radiation therapy, cellulitis, lymphocyst formation, increasing age, invasive lymph node staging, higher body mass index and insufficient physical activity (21). The meta-analysis results of 8 relevant studies reported by Deng (22) showed that radiotherapy, LN dissection, LN metastasis and FIGO stage were the main risk factors for lower limb lymphedema after cervical cancer treatment.

Our study included the latest research and combined the results for a meta-analysis. There were great differences in

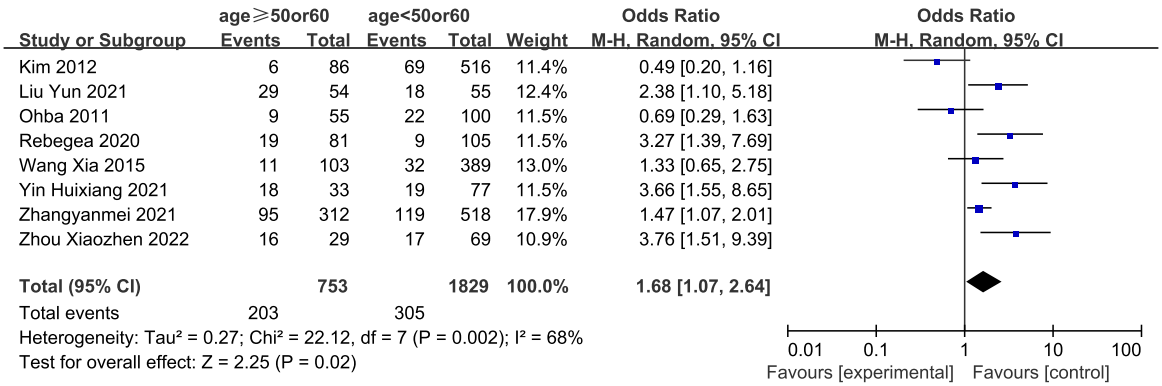

Figure 3 Forest diagram of age.

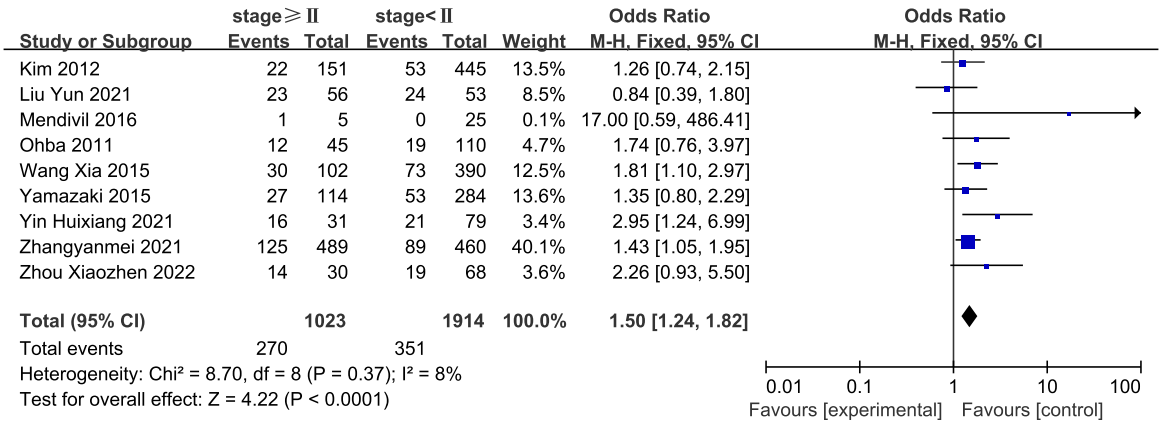

Figure 4 Forest diagram of FIGO stage. FIGO, International Federation of Gynecology and Obstetrics.

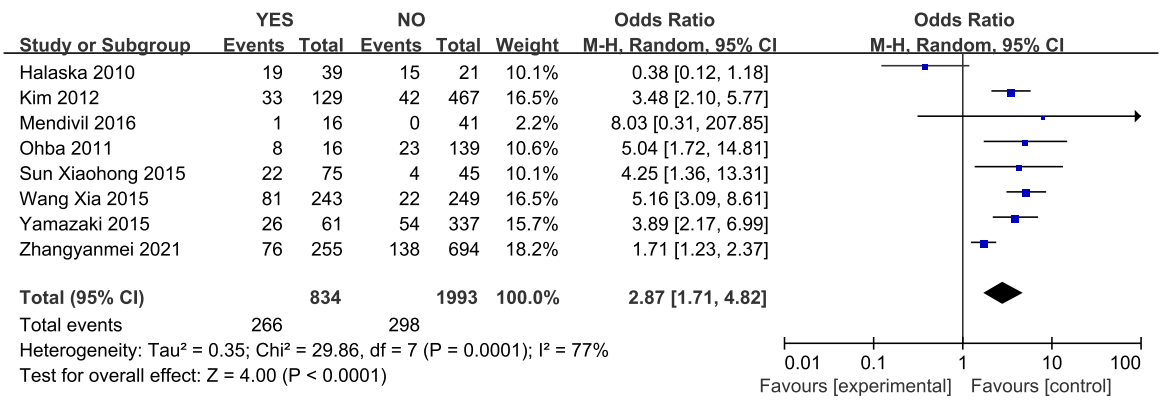

Figure 5 Forest diagram of radiotherapy.

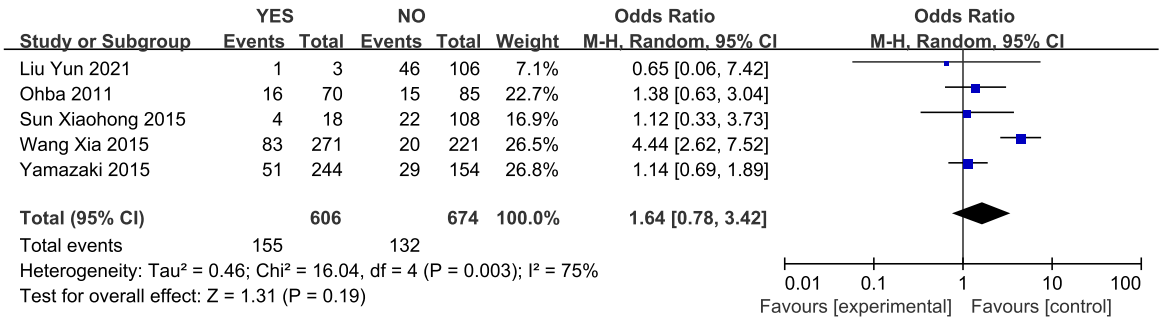

Figure 6 Forest diagram of chemotherapy.

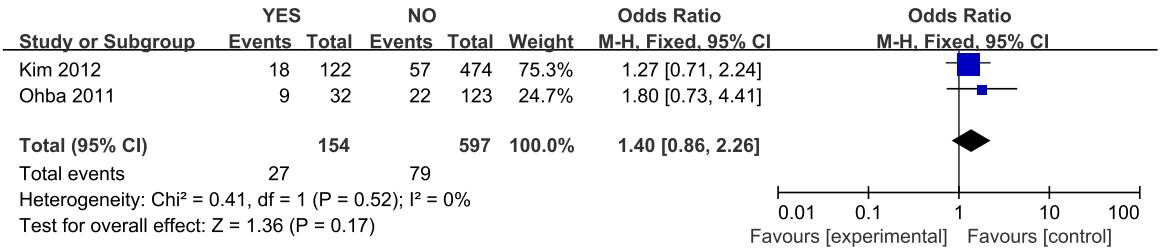

Figure 7 Forest map of LN metastasis. LN, lymph node.

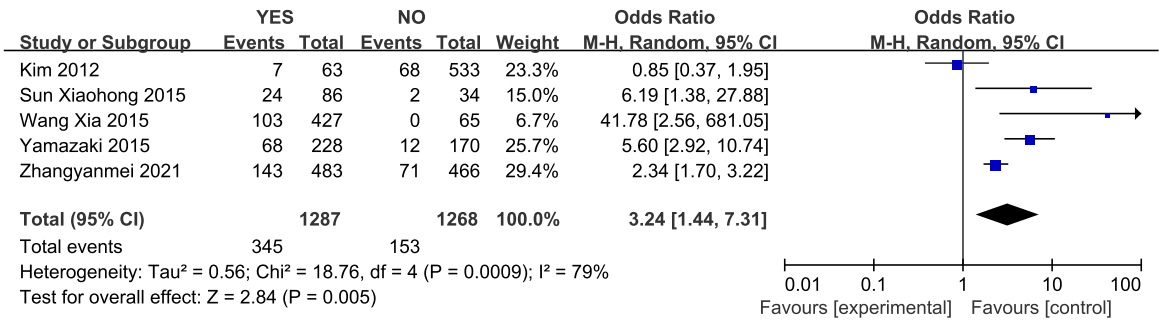

Figure 8 Forest map of LN dissection. LN, lymph node.

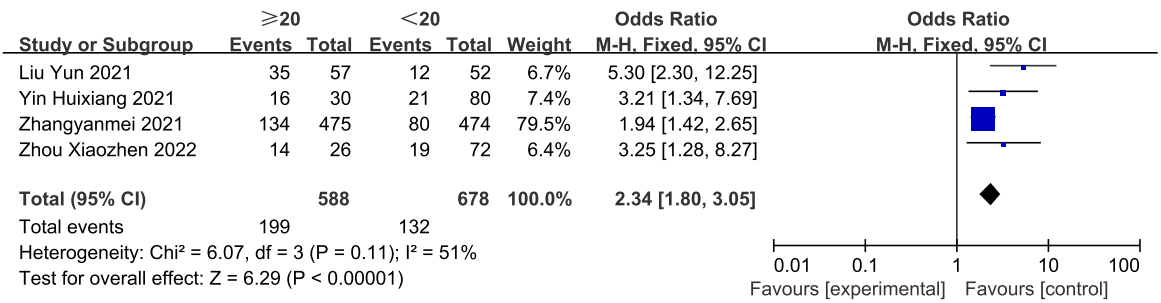

Figure 9 Number of LNs dissected. LN, lymph node.

the incidence of lower limb lymphedema in patients after treatment of cervical cancer. The incidence abroad was between 12.6% and 25.8%, while in China it was between 19.3% and 43.1%, which was relatively high and might be related to inconsistency of detection methods, diagnostic criteria and follow-up of lower limb lymphedema. The risk factors in the meta-analysis included cervical-related factors such as FIGO stage and LN metastasis. FIGO stage was a risk factor for lymphedema (OR =1.50, 95% CI: 1.24–1.82, P<0.001), but LN metastasis was not. Patient-related factors included BMI and age, which were risk factors (OR =1.37, 95% CI: 1.10–1.71, P=0.005; OR =1.68, 95% CI: 1.07–2.64, P=0.02). Treatment-related factors included radiotherapy, chemotherapy, LN dissection and the number of LNs dissected, all of which, except chemotherapy, were risk factors of lower limb lymphedema. The risk of lower limb lymphedema among cervical cancer patients in the radiotherapy group was 2.87-fold higher than that in the non-chemotherapy group, which may be due to the obstruction of lymphatic drainage caused by vein occlusion and lymphatic damage caused by radiotherapy. In addition, the risk of lower extremity lymphedema in patients with LN dissection was 2.24-fold higher than that in patients without LN dissection. The more LNs that were dissected, the greater the risk of lymphedema. Taking 20 LNs as the boundary value, the risk of >20 LNs dissected was 2.34-fold that of <20 LNs. Therefore, strict evaluation should be carried out to determine the appropriate LN dissection.

This study has some limitations. First of all, the number of Chinese and English studies included was equal, representing combined results of domestic and foreign studies to a certain extent. However, the included studies were all retrospective, and uneven in methodology and quality, which might lead to some bias in the results. Second, the literature included in our analysis was heterogeneous in some of the results. We have not been able to elucidate the source of heterogeneity. The generation of heterogeneity in our analysis may be related to the inconsistency of the criteria for lower extremity edema among studies. The existence of heterogeneity may have some influence on the results.

Conclusions

In conclusion, lower extremity lymphedema is a common complication after treatment of cervical cancer and has a high incidence, which merits greater attention from medical staff. This study showed that the main risk factors were BMI, age, FIGO stage, radiotherapy, LN dissection and the number of LNs. When treating patients with cervical cancer, we should aim to control these variables as much as possible and seek effective intervention measures to reduce the risk of lower limb edema and thus improve patients' health-related quality of life after treatment.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1256/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1256/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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