Risk factors for severe low anterior resection syndrome in patients with rectal cancer undergoing sphincter-preserving resection: A systematic review and meta-analysis

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Abstract. The present study aimed to evaluate the incidence and risk factors of severe low anterior resection syndrome (LARS) in patients with rectal cancer undergoing sphincter-preserving resection, and to provide the clinical basis and reference for the treatment of rectal cancer and the prevention of LARS. Studies on the incidence and risk factors for severe LARS in patients with rectal cancer undergoing sphincter-preserving resection were searched using PubMed, Embase, Cochrane Library, Scopus and Web of Science, according to the inclusion and exclusion criteria. After evaluating the study quality and extracting relevant data, RevMan 5.2 and STATA software were used to conduct a meta-analysis. A total of 12 articles were considered eligible for the present meta-analysis. Within these articles, there were 3,877 cases of sphincter-preserving resection for rectal cancer and 1,589 cases of severe LARS; the incidence of severe LARS was 40.99%. The results of the meta-analysis revealed that sex [female; odds ratio (OR), 6.54; 95% CI, 3.63-11.76; Z, 6.27; P<0.00001], radiotherapy and chemotherapy (OR, 3.45; 95% CI, 2.29-5.21; Z, 5.91; P<0.00001), total mesorectal excision (TME; OR, 4.39; 95% CI, 3.32-5.79; Z, 10.41; P<0.00001), and distance between tumor and anal margin (OR, 2.74; 95% CI, 0.86-8.72; Z, 1.70; P<0.00001) may be the risk factors for severe LARS.

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Key words: rectal cancer, low anterior resection syndrome, sphincter-preserving resection, total mesorectal excision

Introduction

Rectal cancer is a type of malignant tumor of the digestive tract. Although the overall incidence of rectal cancer is slowly decreasing year by year, the incidence in adults <65 years old is still increasing (1). Most patients with rectal cancer have low rectal cancer (tumor distance from anus <5 cm) (2). Abdominoperineal resection (Miles operation) has been used to treat low rectal cancer; however, patients require permanent abdominal wall fistulation following the operation. Although this operation can achieve local radical resection of the tumor, a permanent stoma in the abdominal wall can affect the postoperative life of patients. Miles operation has a marked influence on some normal functions of patients after operation, such as defecation, voiding and sexual functions (3). With the development of surgical instruments and the improvement of surgical technology, clinicians have aimed to identify methods to cure tumors and preserve the anus (4). To protect the anus, total mesorectal excision (TME), intersphincteric resection and anterior resection have been widely used. With the progression of surgical approaches, it is now possible to perform sphincter-preserving resection (SPR) on patients with low rectal cancer. However, novel problems have also emerged, with 60-90% of patients with rectal cancer experiencing defecation disorders after SPR. These disorders are known as low anterior resection syndrome (LARS) (5). LARS may reduce the quality of life of patients after operation, and severe LARS will negatively affect the daily life of patients (6). Currently, there is no specific treatment for LARS, and most of the treatments are symptomatic; therefore, the prevention of LARS is necessary (7). Notably, accurate prediction of the influencing factors of LARS is of great significance in reducing the incidence of LARS. Numerous theories on the pathogenesis and influencing factors of LARS have been put forward; however, there are some problems, such as small sample size, incomplete research projects, inconsistent research results, lack of convincing research results and lack of in-depth research (8). Therefore, the present study performed a meta-analysis to systematically evaluate the studies on the influencing factors of LARS in rectal cancer, with the aim of identifying accurate and reliable influencing factors of LARS and providing a

theoretical basis and reference for clinical work, to reduce the incidence of LARS.

Materials and methods

Literature source. Studies on the efficacy of the risk factors for severe LARS in patients with rectal cancer undergoing sphincter-preserving surgery were searched using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (www.embase.com), Cochrane Library (https://www.cochranelibrary.com/), Scopus (https://www.scopus.com/) and Web of Science (https://www.webofscience.com/). The studies published in these databases between January 1, 2000 and December 31, 2022 on the influencing factors of LARS in patients with rectal cancer undergoing sphincter-preserving surgery were searched.

Search strategy. A systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (9). The search strategy was carried out in the databases based on the search string: [(Rectal Neoplasms (Medical Subject Headings, MeSH Terms)) OR (Rectal Tumor (MeSH Terms)) OR ((MeSH Tumor, Rectal Terms)) OR (Neoplasms (MeSH Terms)) OR (Cancer of Rectum (MeSH Terms))] AND [(Anterior resection syndrome) OR (Fecal incontinence) OR (Postoperative complication) OR (LARS) OR (Low Anterior Resection Syndrome)] AND [Radiofrequency ablation] AND [(Influencing factors) OR (Interfering factors)]. All detected studies were assessed for eligibility.

Literature inclusion criteria. The inclusion criteria were as follows: i) Published literature on the related influencing factors of severe LARS for patients with rectal cancer; ii) all articles used the LARS score (6) to evaluate severe LARS (LARS score >29) and its risk factors; iii) all subjects were patients with rectal cancer diagnosed by colonoscopy and pathology before operation; iv) there was no defecation dysfunction or pelvic surgery history before the operation; v) the research results described odds ratio (OR) and 95% CI values, or OR and 95% CI could be calculated using the literature data; and vi) Newcastle Ottawa scale (NOS) (10) score ≥6 points.

Literature exclusion criteria. The exclusion criteria were as follows: i) Reviews, animal studies, preliminary reports of research, case reports, letters to editors, meeting minutes, commentaries and studies published in languages other than English; ii) published in repeated publications in different databases; iii) the purpose of the study was not defined, and/or the data were not detailed or inconsistent; and iv) the diagnosis of the patient was not clear, and the LARS score was not used for LARS diagnosis in the article.

Literature screening and data extraction. According to the unified retrieval strategy, two independent researchers retrieved and imported the studies into EndNote 21 software (https://endnote.com/). Literature screening, data extraction and risk of bias assessment were all carried out by two reviewers independently. Conflicts were resolved by a third independent reviewer. The EndNote software automatically deleted reviews, animal experiments, repetitive literature, case reports and literature published prior to 2000. All studies were read and the literature was excluded if it contained inconsistent research content, incorrect research methods (diagnosis of the case was not clear and LARS was not diagnosed using the LARS score) or no extractable data that met the inclusion criteria. The sample size, the source of patients, the research methods, and the factors affecting the incidence and occurrence of LARS were extracted from the studies.

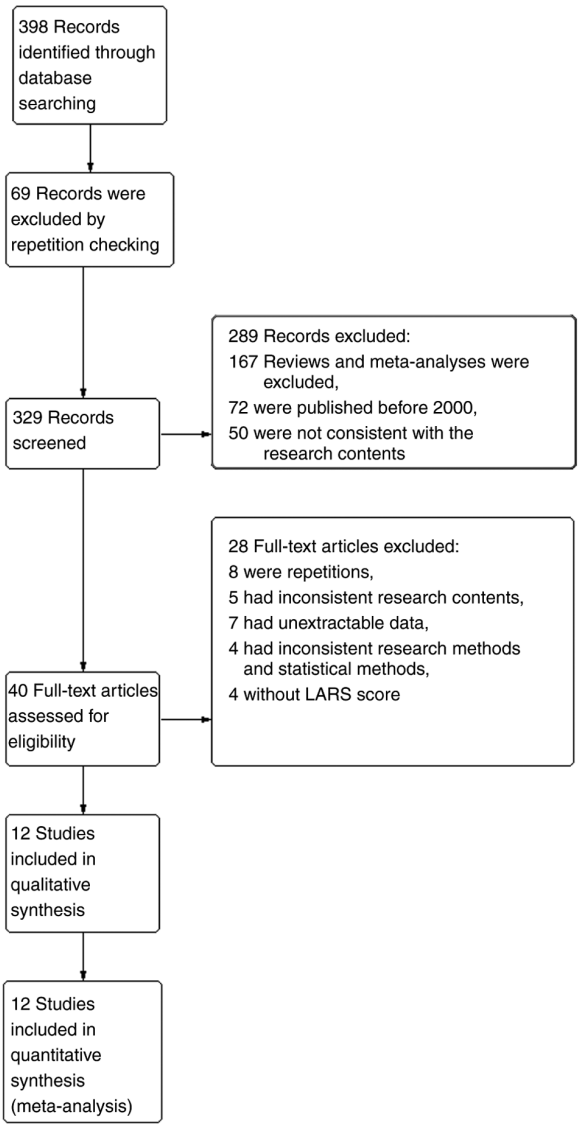

Figure 1. Literature screening process and results. LARS, low anterior resection syndrome.

Quality evaluation. The quality of the literature was evaluated according to the NOS scale (10). The case-control NOS scale was scored based on three aspects: Case group and control group selection, comparability and exposure. There were eight scoring conditions, with a total score of 9. Literature with a score of ≥7 was considered high-quality, whereas that with a score of ≤4 was considered low-quality literature.

Statistical analysis. Data for meta-analysis were entered into MS Excel 2019 (Microsoft Corporation). Meta-analysis was carried out using RevMan 5.2 (The Cochrane Collaboration)

Table I. Basic information of the included literature.

First author/s, year	Country	Study design	Sample size	Severe LARS cases	NOS score	Influencing factors	(Refs.)
Bondeven *et al*, 2015	Denmark	Retrospective	125	47	8	1	(12)
Bregendahl *et al*, 2013	Denmark	Retrospective	938	383	8	1,2,3,4	(13)
Cheong *et al*, 2019	South Korea	Prospective	203	106	7	1,2	(14)
Ekkarat *et al*, 2016	Thailand	Retrospective	129	23	6	1	(15)
Emmertsen *et al*, 2013	Denmark	Retrospective	193	84	9	1,4	(16)
Jimenez-Gomez *et al*, 2017	Spain	Cross sectional	184	104	9	1,4	(17)
Lynes and Thaha, 2016	UK	Retrospective	1,093	447	8	1,2	(18)
Qin *et al*, 2017	China	Cross sectional	142	63	8	1,5	(19)
Sun *et al*, 2019	China	Retrospective	129	60	8	2	(20)
Hughes *et al*, 2017	UK	Retrospective	68	38	6	1	(21)
van Heinsbergen, 2018	Netherlands	Retrospective	412	141	7	2,5	(22)
Kupsch *et al*, 2018	Germany	Retrospective	261	93	6	5	(23)

1, Radiotherapy and chemotherapy; 2, sex; 3, anastomotic leakage; 4, total mesorectal excision/partial mesorectal excision; 5, distance between tumor and anal margin. LARS, low anterior resection syndrome; NOS, Newcastle Ottawa scale.

and STATA (version 14.0; StataCorp LLC) software. Forest plots were drawn using RevMan 5.2 software. $P<0.05$ was considered to indicate a statistically significant difference. Q test and I^2 test were used to determine the heterogeneity of the results. The random-effects models were used to pool the effect estimates in this meta-analysis. The publication bias was assessed using a Begg's funnel chart using STATA (11). The source of heterogeneity was identified by sensitivity analysis or subgroup analysis. The sensitivity analysis was carried out using a random-effects model. Heterogeneity was evaluated by the Cochran's Q test and I^2 statistic. $I^2 \geq 50\%$ indicated greater heterogeneity. Subgroup analysis was created to explore the source of heterogeneity. Subgroup analysis was based on the study population, measurement method, number of adjusted variables and study quality.

Results

Literature retrieval results. A total of 398 original pieces of literature were obtained, all of which were imported into the EndNote 21 software; 69 records were excluded by repetition checking, 167 studies were excluded as they were reviews or meta-analyses, and 72 articles published before 2000 were excluded. The abstracts of the remaining literature were preliminarily screened, 50 articles that were not consistent with the research contents were excluded, and the remaining 40 articles were left after preliminary screening. After reading the complete text, eight repetitive studies, five articles with inconsistent research contents, seven articles with unextractable data, four articles with inconsistent research methods and statistical methods, and four articles without LARS scores were excluded. A total of 12 articles were included for quality evaluation (Fig. 1).

Essential characteristics of the included literature. A total of 12 articles were included in the present meta-analysis. The cases were from eight countries: China, Denmark, South Korea, Thailand, Spain, UK, Netherlands and Germany (12-23). A total of 3,877 patients were included in the study, of which 1,589 patients had severe LARS (Table I). The factors that could affect the incidence of LARS were numbered and outlined. The basic information of the included studies is shown in Table I.

Quality evaluation of the included literature. The quality of the 12 articles that met the criteria for inclusion in the present meta-analysis was evaluated. After quality evaluation, nine high-quality articles with a NOS score of ≥7 and three articles with a NOS score of 6 were obtained (Table I).

Effect of radiotherapy and chemotherapy on severe LARS in rectal cancer. A total of 10 studies reported on the association between radiotherapy and chemotherapy and severe LARS (Table II). The forest plot of the random-effects meta-analysis of the effect of radiotherapy and chemotherapy on severe LARS in rectal cancer is shown in Fig. 2 (OR, 3.45; 95% CI, 2.29-5.21; Z, 5.91; $P<0.00001$). Sensitivity analysis was carried out to assess the stability of the results. No significant variations were observed when eliminating any one article. According to whether only radiotherapy was used as the standard, the eligible articles were divided into only radiotherapy and non-only radiotherapy subgroups. The results of the subgroup analysis are shown in Fig. 3. The heterogeneity of only radiotherapy articles was $I^2=83\%$, $P=0.003$. The heterogeneity of non-only radiotherapy articles was $I^2=89\%$, $P<0.00001$. These findings indicated that radiotherapy and chemotherapy were risk factors for severe LARS, and the radiotherapy alone group had a higher risk of LARS than the non-only radiotherapy group. A Begg's funnel map was used to perform publication bias analysis for radiotherapy and chemotherapy (Fig. 4). The results indicated that there was a particular publication bias, but the bias was slight.

Table II. Radiotherapy and chemotherapy as risk factors for severe LARS.

First author/s, year	Risk factors	OR	OR_LL	OR_UL	(Refs.)
Bondeven *et al*, 2015	Neoadjuvant therapy (yes/no)	3.50	1.15	9.40	(12)
Bregendahl *et al*, 2013	Neoadjuvant therapy (yes/no)	2.48	1.73	3.55	(13)
Cheong *et al*, 2019	Chemoradiation (yes/no)	3.89	2.98	16.60	(14)
Ekkarat *et al*, 2015	Radiation therapy (yes/no)	6.50	2.37	3.55	(15)
Emmertsen *et al*, 2013	Neoadjuvant therapy (yes/no)	2.41	1.00	5.83	(16)
Hughes *et al*, 2017	Neoadjuvant treatment (radiotherapy) (yes/no)	19.90	3.50	113.10	(21)
Jimenez-Gomez *et al*, 2017	Postoperative radiotherapy (yes/no)	9.52	1.74	3.00	(17)
Lynes and Thaha, 2016	Neoadjuvant chemoradiotherapy (yes/no)	3.89	2.49	6.07	(18)
Qin *et al*, 2017	Neoadjuvant therapy (NCRT/NCT)	5.13	2.29	11.49	(19)
Sun *et al*, 2019	Neoadjuvant therapy (NCRT/NCT)	2.20	1.24	3.91	(20)

The OR data were calculated in the previous studies. NCRT, neoadjuvant radiochemotherapy; NCT, neoadjuvant chemotherapy; OR, odds ratio; LL, long long; UL, unsigned long.

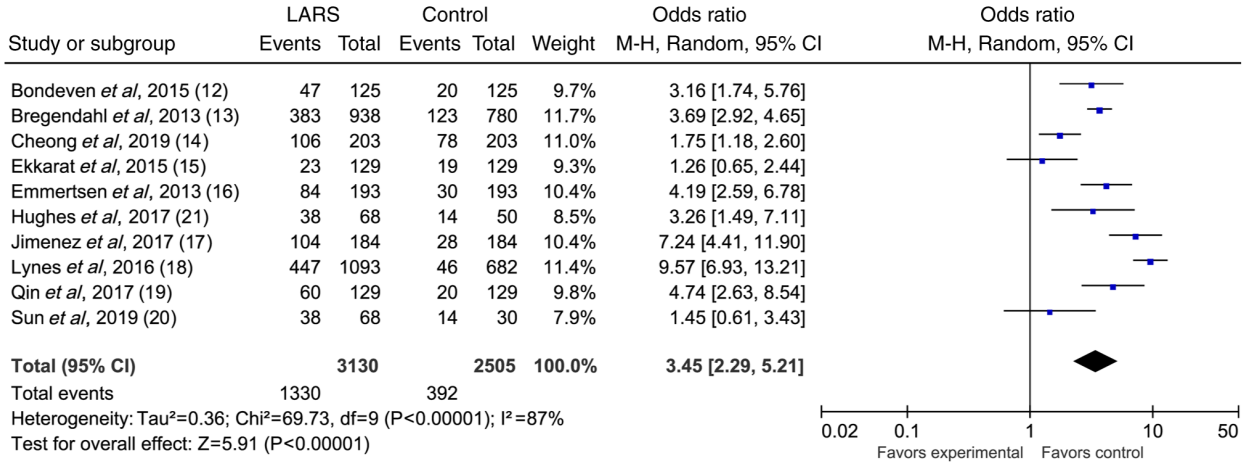

Figure 2. Forest plot of the random-effects meta-analysis of the effect of radiotherapy and chemotherapy on severe LARS in rectal cancer. df, degrees of freedom; LARS, low anterior resection syndrome; M-H, Mantel-Haenszel; experimental, LARS group; control, Control group.

Effect of sex on severe LARS in rectal cancer. A total of four studies reported on the association between sex and the incidence of severe LARS, and the random-effects model was used to examine the effects of sex on severe LARS. As shown in Fig. 5, the heterogeneity was apparent: I^2=94%, P<0.00001. Through sensitivity analysis, it was revealed that Cheong *et al* (14) was the source of heterogeneity, and the forest plot of the random-effects meta-analysis after elimination is shown in Fig. 6. The results revealed that the risk of severe LARS in female patients was slightly higher (OR, 6.54; 95% CI, 3.63-11.76; Z, 6.27; P<0.00001).

Effect of TME on severe LARS in rectal cancer. A total of four articles reported the relationship between TME and severe LARS. The forest plot of the random-effects meta-analysis showed a significant association between TME and the incidence of severe LARS (OR, 4.39; 95% CI, 3.32-5.79; Z, 10.41; P<0.00001; Fig. 7). These findings indicated that TME was an influencing factor of severe LARS in rectal cancer.

Effect of distance between tumor and anal margin on severe LARS in rectal cancer. Two articles reported on the relationship between the distance between the tumor and anal margin and severe LARS. The forest plot of the random-effects meta-analysis showed that there was a significant association between the distance between the tumor and anal margin and severe LARS (OR, 2.74; 95% CI, 0.86-8.72; Z, 1.70; P<0.00001; Fig. 8). These findings suggested that the distance between the tumor and anal margin was an influencing factor of severe LARS in rectal cancer.

Discussion

Numerous studies have reported on the influencing factors of postoperative LARS in rectal cancer; however, the results vary (24,25). The present study collected literature on the influencing factors of severe LARS in rectal cancer between January 1, 2000 and December 31, 2020, and systematically analyzed the association between the influencing factors and

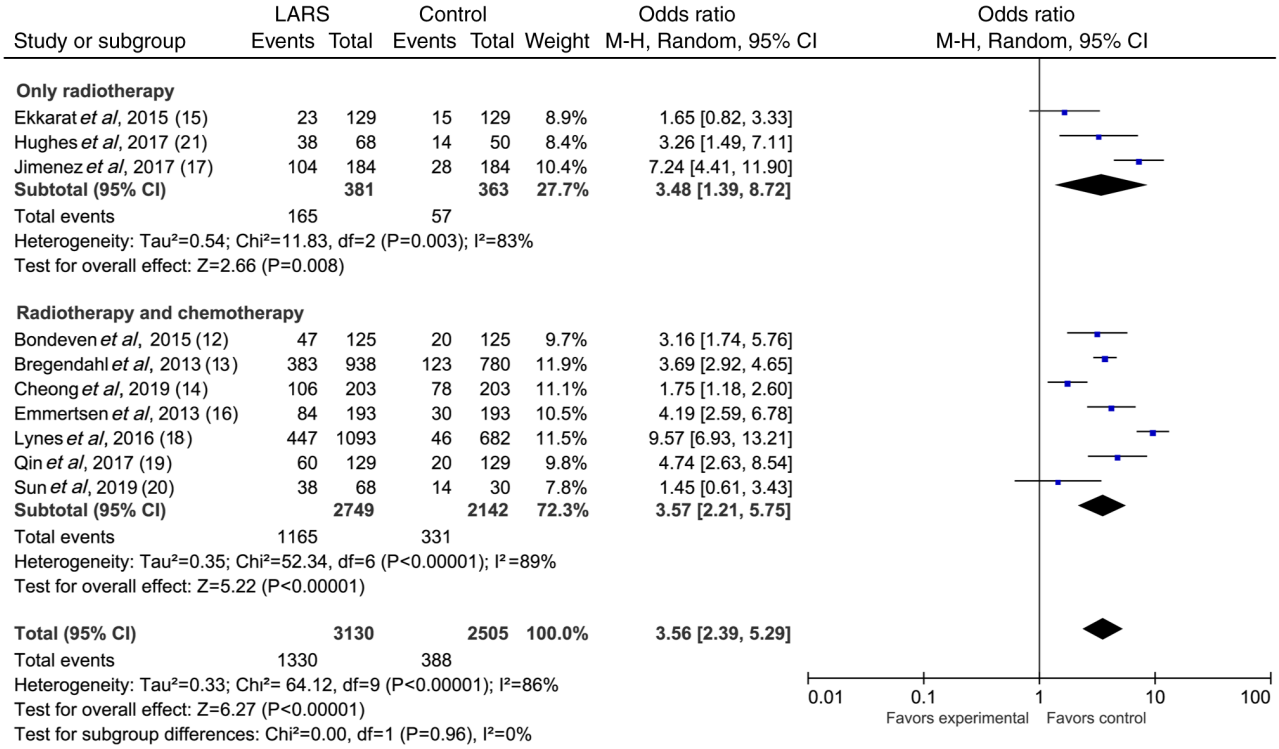

Figure 3. Subgroup analysis of the effect of radiotherapy and chemotherapy on severe LARS in rectal cancer. df, degrees of freedom; LARS, low anterior resection syndrome; M-H, Mantel-Haenszel; experimental, LARS group; control, Control group.

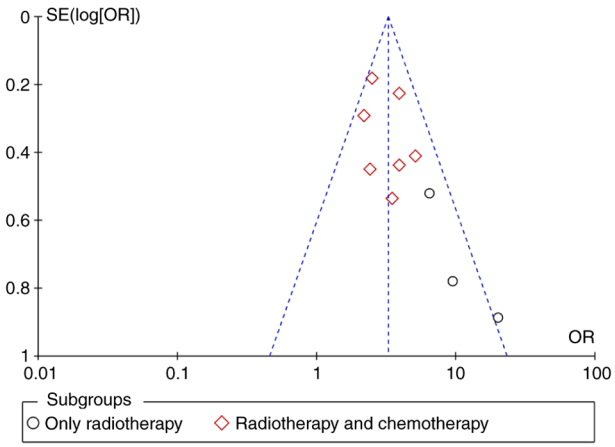

Figure 4. Begg's funnel map showing the publication bias analysis for radiotherapy and chemotherapy. A previous study has found that among the factors that affect the incidence of severe low anterior resection syndrome, radiotherapy and chemotherapy is an important factor (39). Therefore, the bias analysis was performed for the radiotherapy and chemotherapy factor. OR, odds ratio; SE, standard error.

the incidence of LARS. The meta-analysis results demonstrated that female sex, radiotherapy and chemotherapy, distance between the tumor and anal margin, and TME were the influencing factors of severe LARS in rectal cancer.

Tanaka *et al* (26) conducted a 5-year follow-up study on 506 patients with rectal cancer following anus-preserving surgery. The results revealed that female patients had a higher risk of developing LARS than male patients. The present results showed that the risk of LARS in women was higher than that in men, which was consistent with the results of this previous study. This may be because the anal sphincter of women is congenitally thinner than that in men, and most patients with rectal cancer are elderly patients. Most female elderly patients have a reproductive history; natural delivery through the birth canal can relax the pelvic floor muscles, which may be why the risk of LARS in female patients is higher than that in men (27). Furthermore, there are intrauterine organs in the female pelvis, which reduces the functional space during the operation to a certain extent (28). If the surgical technique is unsuccessful, it can increase the injury of the pelvic autonomic nerve and anal sphincter (29).

With the development of radiotherapy and chemotherapy, patients with colorectal cancer have a higher resection rate, sphincter preservation success rate, survival rate and clinical cure rate (30). However, the present meta-analysis found that radiotherapy and chemotherapy could increase the incidence of severe LARS. After subgroup analysis, it was observed that the radiotherapy alone group (OR=3.48) had a higher risk of LARS than the radiotherapy and chemotherapy group (OR=3.57). Emerging evidence has suggested that the incidence of severe LARS after neoadjuvant radiotherapy and chemotherapy is higher than that of severe LARS after neoadjuvant chemotherapy (30,31). In addition, a recent study has demonstrated that compared with those receiving relatively simple chemotherapy, patients receiving radiotherapy and chemotherapy have a higher incidence of postoperative complications (32,33). A recent study concluded that even patients who received radiotherapy without surgery developed severe LARS, possibly because radiotherapy was more toxic than sphincter-preserving resection (31). However, radiotherapy and chemotherapy can reduce the intestinal function of patients with colorectal cancer, which may be caused by

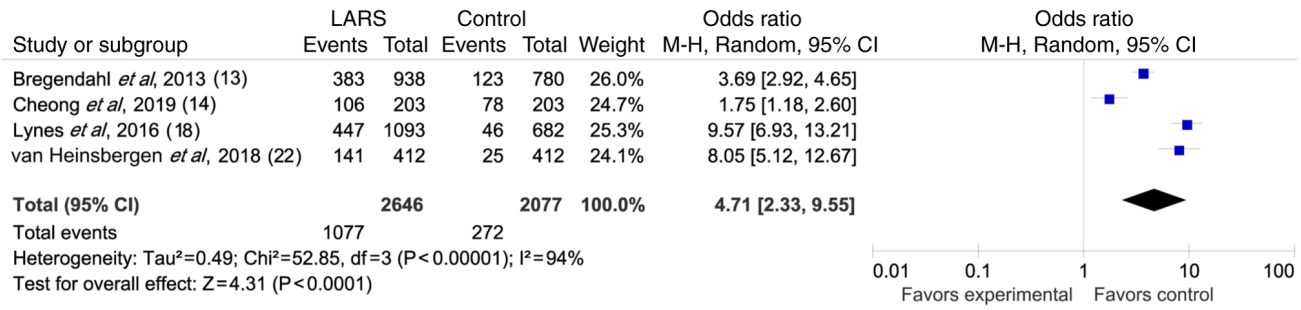

Figure 5. Forest plot of the random-effects meta-analysis of the effect of sex on severe LARS in rectal cancer. df, degrees of freedom; LARS, low anterior resection syndrome; M-H, Mantel-Haenszel; experimental, LARS group; control, Control group.

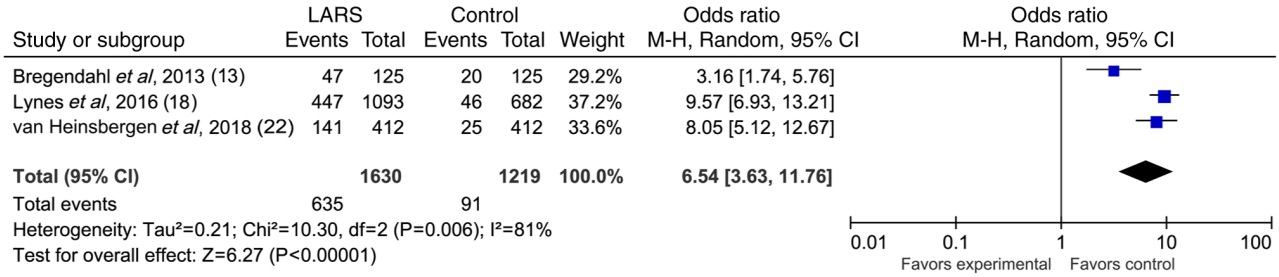

Figure 6. Forest plot of the random-effects meta-analysis of the effect of sex on severe LARS in rectal cancer after excluding Cheong *et al* (14). df, degrees of freedom; LARS, low anterior resection syndrome; M-H, Mantel-Haenszel; experimental, LARS group; control, Control group.

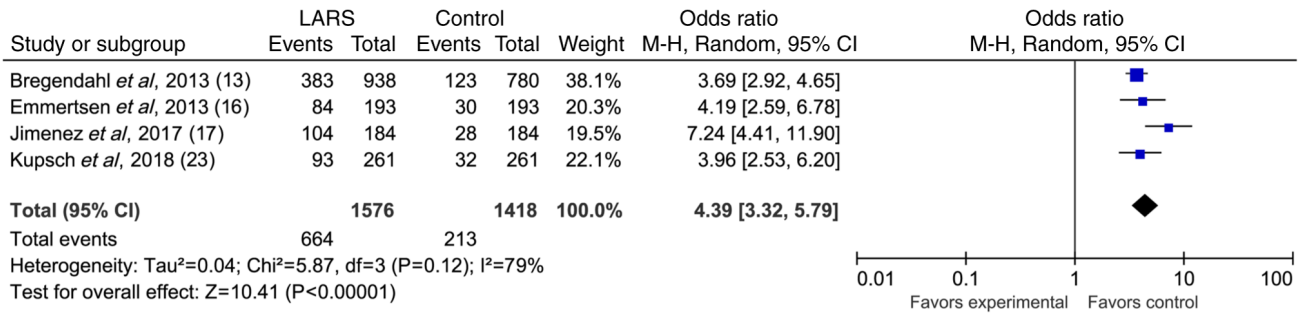

Figure 7. Forest plot of the random-effects meta-analysis of the effect of total mesorectal excision on severe LARS in rectal cancer. df, degrees of freedom; LARS, low anterior resection syndrome; M-H, Mantel-Haenszel; experimental, LARS group; control, Control group.

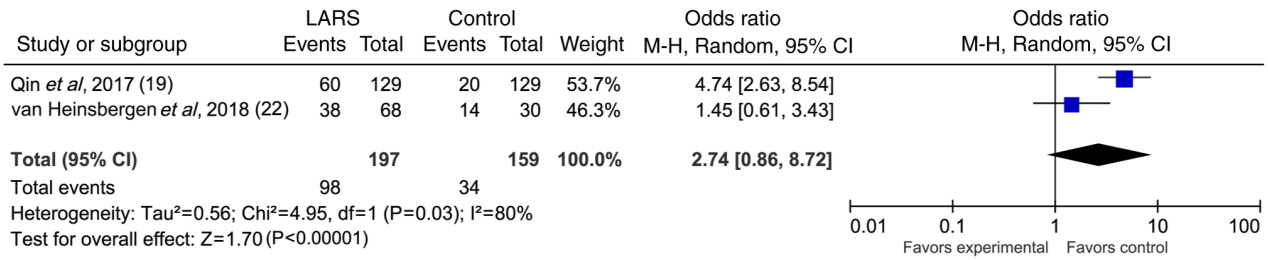

Figure 8. Forest plot of the random-effects meta-analysis of the effect of distance between tumor and anal margin on severe LARS in rectal cancer. df, degrees of freedom; LARS, low anterior resection syndrome; M-H, Mantel-Haenszel; experimental, LARS group; control, Control group.

damage to the anal sphincter, nerves in the pelvic cavity and intestinal microecology (34).

The present study demonstrated that the distance between the tumor and the anal margin, and TME were risk factors for severe LARS. A previous study reported that when the distance from the tumor to the anal margin decreases by 1 cm, the incidence of severe LARS increases by 1.29, and patients with relatively high positions of ultra-low rectal cancer have worse intestinal function (35). It has also been reported that a residual rectal length of ≤4 cm can lead to severe intestinal

dysfunction (36). The reason may be that the lower tumor leads to a shorter residual rectal length, and the shorter rectal residue affects the rectal compliance of the patient, thus increasing the sense of urgency of defecation. Compared with traditional surgery, TME surgery reduces the local recurrence rate and the incidence of postoperative complications (37). However, TME surgery for the inferior mesenteric artery and its branches can lead to changes in residual intestinal blood supply, which may lead to intestinal dysfunction (38).

Based on the existing research, the results of the present meta-analysis were reliable but still had some limitations. First, the studies were conducted in various Asian and European countries, on patients with different ethnicities who used different languages, which may lead to differences in measurement tools, treatment options and some definitions. Second, the included literature did not mention specific radiotherapy and chemotherapy regimens, and surgical anastomoses were not introduced. There was a slight heterogeneity among the included studies, which may affect the results. Finally, more literature on other factors, such as age and anastomotic leakage, should be included; therefore, larger samples and multicenter studies are needed to clarify these factors.

In conclusion, radiotherapy and chemotherapy, TME, the distance between the tumor and anal margin, and female sex were revealed to be risk factors for severe LARS, which can seriously affect the intestinal function of patients with rectal cancer post-operation. Notably, clinicians should pay more attention to the differences in female pelvic organs during surgery and strengthen multidisciplinary cooperation to formulate more personalized radiotherapy and chemotherapy programs and surgical methods so that patients with rectal cancer have an improved intestinal function and a higher survival rate.

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Availability of data and materials

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

Authors' contributions

LLX and TCC were involved in study methodology, investigation and data curation, and wrote the original draft. PC was responsible for research design and conducted the experiments. NJX and ZWJ were responsible for data analysis, and reviewed and edited the manuscript. XXL was involved in the concepts and supervision, and reviewed and edited the manuscript. LLX and TCC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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