


# BMJ Open Preventive strategies for low anterior resection syndrome: a protocol for systematic review and evidence mapping

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## ABSTRACT

**Introduction** Rectal cancer is one of the top 10 cancers worldwide. Up to 80% of patients with rectal tumours have had sphincter-saving surgery, mainly due to the large expectation of anal preservation. However, patients tend to experience low anterior resection syndrome (LARS) after rectal resection, which is disordered bowel function that includes faecal incontinence, urgency, frequent defecation, constipation and evacuation difficulties. LARS, with an estimated prevalence of 41%, has been reported to substantially decrease the quality of life of patients. However, no comprehensive preventive strategies are currently available for LARS. This systematic review aims to synthesise evidence on the current LARS preventive strategies.

**Methods and analysis** This protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist. Literature in PubMed (via Medline), Embase and the Cochrane Library from inception to July 2023 will be searched to identify articles relevant to preventive effectiveness against LARS. The Cochrane Collaboration's risk of bias tool for randomised controlled trials and the Newcastle-Ottawa Scale for clinical controlled trials, cohort studies and case-control studies will be used to assess the risk of bias. We will group the included studies by the type of LARS prevention strategy and present an overview of the main findings in the form of evidence mapping. A meta-analysis is planned if there is no substantial clinical heterogeneity between the included studies. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) will be used to evaluate the quality of the evidence.

**Ethics and dissemination** Ethical approval is not needed for systematic review of published data. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences.

**PROSPERO registration number** CRD42023402886.

## INTRODUCTION

Rectal cancer is one of the top 10 cancers worldwide, with an estimated 732 210 new cases (3.8% of the total cases) and 339 022 new deaths (3.4% of the total deaths due to cancer) in 2020.<sup>1</sup> Radical rectectomy has remained the cardinal treatment for rectal tumours. Due to advancements in surgical

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will comprehensively identify and summarise evidence relevant to low anterior resection syndrome (LARS) prevention strategies for perioperative management.
- ⇒ The review will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, and the protocol was registered in PROSPERO, indicating the transparent process.
- ⇒ Evidence mapping, with an overall and clear understanding of the current diagnosis and treatment of LARS, will be performed to contribute to clinical awareness and practical management.
- ⇒ Large heterogeneity might exist among the included studies due to the usage of different scoring systems for evaluating bowel dysfunction.
- ⇒ Our findings may be affected by potential publication bias because of the restriction to the English language.

techniques and patients' expectations for anal preservation, more and more patients prefer to avoid a permanent colostomy, and sphincter-saving surgery is performed in up to 80% of patients with rectal cancer.<sup>2</sup> However, the structural preservation of the anus does not assure the complete functional preservation of the anal sphincter complex. Up to 90% of such patients were reported to experience major changes in bowel habits, including faecal incontinence, urgency, frequent defecation, diarrhoea, constipation and evacuation difficulties occurring alone or in combination.<sup>3</sup> This wide spectrum of disturbed bowel movements occurring after rectal resection is termed low anterior resection syndrome (LARS).<sup>4</sup>

LARS was pragmatically defined as 'disordered bowel function after rectal resection, leading to a detriment in quality of life' in 2012.<sup>3</sup> A meta-analysis found that the estimated prevalence of major LARS (regarded to have a significant impact on quality of life) was 41% (95% CI: 34% to 48%).<sup>5</sup> The

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rectum plays a role as the reservoir of stool.<sup>3</sup> Thus, resection of the rectum results in a partial loss of this function. In addition, radiotherapy, with accompanying surgical damage to the anal sphincter and anastomotic leakage, could also contribute to the deterioration of defecatory function.<sup>2–6</sup> Of more than 30 symptoms associated with LARS reported in 128 studies, the most frequently mentioned symptom was faecal incontinence (97% of the studies), followed by stool frequency (80%), flatus incontinence (70%), urgency (67%) and pad-wearing (66%).<sup>4</sup> Toileting dependence caused by such daily episodes of troublesome defecation has a strong impact not only on patients' social and daily activities but also on their mental and emotional well-being.<sup>7</sup> Furthermore, LARS tends to persist for a prolonged period, even up to 15 years.<sup>2,3</sup> And worse, a proportion of patients undergoing sphincter-saving surgery require a colostomy again to eliminate LARS.<sup>8,9</sup>

No current comprehensive preventive strategies are presently available for LARS. LARS is a series of multifactorial postoperative complications, and the causative factors have been identified to include radiotherapy, tumour height, anastomotic technique and diverting stoma.<sup>5,6</sup> Trials have been conducted to explore the modifiable variables for preventing LARS, such as preoperative consult,<sup>10</sup> colonic J-pouch or side-to-end anastomosis,<sup>11</sup> pelvic floor rehabilitation<sup>12</sup> and dietary modifications.<sup>13</sup> However, data were scattered and not systematic, and little evidence on preventive interventions for LARS has been reported in guidelines and expert consensus. One management guideline for LARS covers its prevention and supportive care. However, most recommendations were based on expert opinions.<sup>14</sup> Therefore, this study aims to conduct a systematic review to synthesise evidence on current preventive strategies concerning LARS, which could contribute to clinical awareness and practical management. We also aim to demonstrate available evidence in the form of evidence mapping to depict a clear understanding of LARS for medical staff and patients.

## METHODS

The protocol was designed in line with the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P).<sup>15,16</sup>

### Patient and public involvement

No patients will be involved in this study.

### Research questions

In directing the systematic review, research questions were identified consistent with our research objectives, as follows:

1. What is the current evidence on preventive strategies for LARS before, during or after sphincter-preserving surgery?

2. Would these interventions be effective in reducing the incidence or severity of LARS?

### Eligibility criteria

Studies will be included if (1) the study participants diagnosed with rectal cancer had or will have sphincter-preserving surgery; (2) the interventions of interest could avoid LARS or minimise the incidence and severity of LARS, such as faecal incontinence, urgency, frequent defecation, diarrhoea, constipation and evacuation difficulties, before, during or after surgery; (3) the outcomes of interest include at least one type of bowel dysfunction evaluated by validated scoring systems (eg, LARS scale, Jorge-Wexner scale, International Prostate Syndrome Score or Cleveland Clinic Incontinence Score) or objective measurements (eg, bowel squeeze pressure, resting pressure, tolerated volume or the incidence of bowel dysfunction) and (4) the study type is a randomised controlled trial (RCT), clinical controlled trial, cohort study or case-control study, in which the baseline characteristics of the participants were comparable in all groups.

We will exclude (1) conference abstracts, (2) animal studies and (3) cross-sectional studies lacking comparisons.

### Search strategy

We will develop search strategies combining LARS-related terms used in systematic reviews and guidelines in this area.<sup>4,6,14</sup> A comprehensive literature search will be conducted in PubMed (via Medline), Embase and the Cochrane Library from inception until July 2023. A manual search will also be performed by screening the references of the included studies and similar reviews to identify relevant reports missed in the search strategies. Only articles in English will be included, without restrictions on publication time. The search strategy to be used in Pubmed (via Medline) is presented in [table 1](#). Similar strategies will be performed in Embase and the Cochrane Library (online supplemental file 1).

### Study selection

Two reviewers (X-YZ and K-LY) will independently screen the titles and abstracts of the articles identified from the databases based on the eligibility criteria using Endnote and Rayyan software and review the full text of potentially eligible studies. Any discrepancies in the selection process will be resolved through discussion with the third reviewer (QW). After exclusion, we will report the literature selection and final totals in a PRISMA flow diagram.

### Data extraction

Two reviewers (YL (Air Force Military Medical University) and RSL) will independently extract data from the included studies using a standardised data collection form designed for our study. The data charted will include but not be limited to the following items: first author, year of publication, country of origin, study design, purpose, sample size, diagnosis, tumour height, surgery, radiotherapy, anastomosis, diverting stoma,

**Table 1** Search strategy in PubMed (via Medline) database

No.	Search term
#1	'Low Anterior Resection Syndrome' [MeSH] OR 'Low Anterior Resection Syndrome' [Title/Abstract] OR 'Anterior Resection Syndrome' [Title/Abstract]
#2	'Transanal Endoscopic Surgery' [MeSH] OR 'Transanal Endoscopic Microsurgery' [MeSH] OR 'Sphincter-Preserving Surgery' [Title/Abstract] OR 'Sphincter Saving Surgery' [Title/Abstract] OR 'Low Anterior Resection' [Title/Abstract] OR 'Intersphincteric Resection' [Title/Abstract] OR 'Transanal Local Resection' [Title/Abstract] OR 'Transanal Excision' [Title/Abstract] OR 'Transanal Endoscopic Microsurgery' [Title/Abstract] OR 'Transanal Minimally Invasive Surgery' [Title/Abstract] OR 'Natural Orifice Transluminal Endoscopic Surgery' [Title/Abstract] OR 'Anterior Perineal Plane for Ultra-Low Anterior Resection of the Rectum' [Title/Abstract] OR 'Transanal Total Mesorectal Excision' [Title/Abstract] OR 'Coloanal Anastomosis' [Title/Abstract]
#3	'Diarrhea' [MeSH] OR 'Fecal Incontinence' [MeSH] OR 'Constipation' [MeSH] OR Diarrhea*[Title/Abstract] OR Diarrhoea [Title/Abstract] OR 'Bowel Incontinence' [Title/Abstract] OR 'Fecal Incontinence' [Title/Abstract] OR 'Faecal Incontinence' [Title/Abstract] OR 'Faeces Incontinence' [Title/Abstract] OR 'Rectal Incontinence' [Title/Abstract] OR Constipation [Title/Abstract] OR Obstipation [Title/Abstract] OR Dyschezia [Title/Abstract] OR 'Faecal Urgency' [Title/Abstract]
#4	#2 AND #3
#5	#1 OR #4

intervention characteristics, follow-up duration and incidence or severity of LARS. All extracted information will be cross-checked in Microsoft Excel by two reviewers for validation.

### Risk of bias assessment

Two reviewers (YL (Capital Medical University) and S-QW) will independently assess the risk of bias in the included studies. We will use the risk of bias tool recommended by the Cochrane Collaboration to assess RCTs.<sup>17</sup> The tool contains six domains, including selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias, which can be assessed as low, unclear or high risk of bias. We will use the Newcastle-Ottawa Scale (NOS) to assess non-randomised studies (NRS, including CCTs, cohort studies and case-control studies). The NOS contains eight items, with a total scale score of 9.<sup>18</sup> Higher scores suggest a lower risk of bias. Any disagreements regarding quality ratings will be resolved by consulting the third reviewer (QW).

### Data synthesis and analysis

We will group the included studies by the type of LARS prevention strategies and summarise the population characteristics, intervention details and LARS measurements in each group, along with other main findings. We will calculate the relative risk with 95% CI for dichotomous data and mean differences with 95% CIs for continuous data. We will synthesise and present the results concerning the effectiveness of LARS prevention in the included studies in the form of forest plots using Review Manager (RevMan V.5.3) if there is no significant clinical heterogeneity. The results of each prevention strategy will be subtotaled and totaled simultaneously based on the different study types. However, we will not pool the data if there is significant clinical heterogeneity. The Chi-squared ( $I^2$ ) test will be used to evaluate the statistical heterogeneity of results between the included studies. We will use the random-effects model to synthesise the data regardless of statistical heterogeneity, as there are likely to be many sources

of heterogeneity. We will also demonstrate the overview of our main findings in the form of evidence mapping, such as graphs and tables, for clear understanding.

We plan to conduct a subgroup analysis according to risk factors, such as radiotherapy, tumour height, anastomotic technique and diverting stoma if the relevant data are available. Tests of interaction terms will be performed to determine statistical differences in the effect estimates in different subgroups.

If more than 10 studies are included in the meta-analysis, we will assess publication bias using funnel plots.

### Quality of evidence

Two reviewers (X-YZ and K-LY) will independently assess the quality of evidence produced in this systematic review using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.<sup>19</sup> Evidence in different study types will be assessed and graded separately using the corresponding evaluation criteria. The quality of evidence will be graded as high, moderate, low or very low. Five factors will be used to rate the quality of the evidence for risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Any divergence will be resolved by discussion between two other reviewers (QW and X-NL).

Study selection is being performed and is anticipated to be completed in December 2023.

### DISCUSSION

In this review, we will systematically appraise and summarise LARS prevention strategies in the perioperative period of sphincter-preserving surgery. Sphincter-saving surgery was originally developed to preserve normal anal defecation and avoid impairing body image. However, its surgical outcomes have been disputed as a result of the extremely low life quality.<sup>20</sup> An international consensus definition of



LARS identified eight symptoms and eight consequences, including physiology, psychology, emotion, social activities, relationships and responsibility, which covered almost all essential aspects.<sup>7</sup> Two scoping reviews reported intervention options for managing bowel symptoms after sphincter-saving rectal cancer surgery. However, they both only focused on postoperative interventions.<sup>21 22</sup> Prevention strategies presurgery and during surgery are lacking. Therefore, comprehensive prevention strategies for avoiding or minimising the incidence or severity of LARS with evidence mapping will be reported on the completion of this systematic review. According to our findings, future research recommendations will be suggested, and an evidence-based preventive strategy for preventing LARS may be conducted.

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**Contributors** QW, X-NL and YL (Capital Medical University) conceived the idea and designed the study protocol. X-YZ and K-LY developed the search strategy. YL (Air Force Military Medical University), R-SL, YL (Capital Medical University) and S-QW extracted data and assessed the risk of bias of included studies. X-YZ and QW drafted the manuscript. All authors read and approved the final version.

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**Competing interests** None declared.

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