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REVIEW

Therapeutic strategies for low anterior resection syndrome: an umbrella review of systematic reviews

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Abstract

Purpose The purpose of this umbrella review was to systematically evaluate the effectiveness of therapeutic strategies for managing low anterior resection syndrome following sphincter-preserving surgery for rectal cancer and to provide evidence-based recommendations for clinical practice.

Methods A systematic literature search was performed across five electronic databases. Two independent reviewers screened titles/abstracts, assessed full-text studies, and extracted data, with discrepancies resolved by consensus. The study adhered to AMSTAR-2 and GRADE frameworks for methodological quality and evidence certainty assessments.

Results Sixteen systematic reviews (including nine meta-analyses) published between 2018 and 2025 were analyzed, covering therapeutic strategies such as transanal irrigation, pelvic floor rehabilitation, sacral nerve stimulation, percutaneous tibial nerve stimulation, pelvic floor muscle training, and biofeedback therapy. For quality assessment, two studies were evaluated as moderate quality, five as low, and nine as critically low.

Conclusion TAI and PFR are recommended as first-line therapies for LARS, while SNS or PTNS may be considered for refractory cases, especially those with predominant fecal incontinence. Future research should focus on standardizing protocols, improving patient compliance, and conducting high-quality randomized controlled trials to strengthen the evidence base.

Keywords Low anterior resection syndrome · Sphincter-preserving surgery · Therapeutic strategy · Umbrella review

Introduction

According to updated estimates from the International Agency for Research on Cancer (IARC) [1], colorectal cancer ranks third in incidence but second in mortality, with incidence rates steadily rising. Of particular clinical significance, rectal cancer constitutes over one-third of all colorectal cancer diagnoses, and about 65% of rectal cancer is in the mid-to-low position [2, 3]. Surgery remains the mainstay of rectal cancer treatment, with sphincter-preserving low anterior resection (LAR) constituting the gold standard for mid-to-low rectal cancer [4]. Although sphincter-preserving surgery avoids permanent stoma by retaining the anal sphincter, 70–90% of patients develop varying degrees of bowel dysfunction after LAR, a condition termed low anterior resection syndrome (LARS) [5]. LARS is defined as a condition occurring in patients who have undergone low anterior resection and experience at least one symptom (e.g., fecal incontinence, urgency, altered stool consistency, emptying difficulties, increased frequency, unpredictable bowel function, repeated painful stools or soiling), resulting in at

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least one consequential impact (including but not limited to toilet dependency, preoccupation with bowel function, or dissatisfaction with bowels) [6]. Such symptoms profoundly compromise quality of life by disrupting basic daily activities and social interactions, while generating considerable psychological burden [7].

The etiology of LARS is multifactorial, involving anal sphincter dysfunction, neural injury, a reduction in neorectal storage capacity, diminished rectal compliance, and altered peristaltic activity in the reconstructed rectum [8]. Currently, the Low Anterior Resection Syndrome Score (LARS score) serves as the primary tool for assessing symptom severity in affected patients. This validated instrument evaluates five key domains: incontinence to flatus or liquid stool, stool frequency, clustering, and urgency. Scores are categorized as follows: 0–20 ("no LARS"), 21–29 ("minor LARS"), and 30–42 ("major LARS") [9]. Current studies have proposed several non-pharmacological interventions for LARS, including transanal irrigation, pelvic floor rehabilitation, and sacral neuromodulation, and have demonstrated their efficacy in alleviating LARS symptoms [10].

Although systematic reviews and meta-analyses on therapeutic strategies for LARS have proliferated in recent years, their conclusions remain inconsistent. Consequently, the most effective and optimal therapeutic strategy for LARS remains undetermined in current clinical practice. Umbrella reviews systematically identify, critically appraise, and synthesize evidence from published systematic reviews and meta-analyses. By comparing multiple interventions, they provide a comprehensive summary of the accumulated evidence, while also identifying critical knowledge gaps to inform clinical decision-making [11]. Through comprehensive umbrella review methodology, this study aims to (1) systematically evaluate therapeutic strategies for LARS and (2) generate evidence-based recommendations to guide clinical decision-making.

Methods

As several systematic reviews/meta-analyses have been published previously with inconsistent findings, this study conducted an umbrella review to synthesize the evidence. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD420251017057.

Selection criteria

Inclusion criteria

1) Population (P): patients diagnosed with LARS following sphincter-preserving surgery for rectal cancer.
2) Intervention (I): therapeutic strategies including, but not limited to pelvic floor rehabilitation (pelvic floor muscle training, biofeedback therapy, rectal balloon training), transanal irrigation, sacral nerve stimulation, or percutaneous tibial nerve stimulation.
3) Comparison (C): routine nursing care (including dietary guidance, medication management, pelvic floor muscle training), sham therapy, or other active treatments.
4) Outcome (O) [12]: primary outcomes: LARS score, severity of fecal incontinence(e.g., Wexner Fecal Incontinence Score, St. Marks' Fecal Incontinence Grading Score), and other bowel symptom evaluations (e.g., Memorial Sloan Kettering Cancer Centre Bowel Function Instrument, bowel frequency); and secondary outcomes: quality of life scores (e.g., EORTC QLQ-C30, EORTC QLQ-C29, FIQL, SF-36).
5) Study design (S): systematic reviews with or without meta-analyses.

Exclusion criteria

1) Studies involving patients with diverting stoma or focusing on LARS prevention
2) Conference abstracts, trial registry records, research protocols, or other unpublished data
3) Non-English publications
4) Duplicate publications

Search strategy

We systematically searched five databases (PubMed, Cochrane Library, Embase, Web of Science, and CINAHL) from their inception to March 2025. The search strategies employed a combination of Medical Subject Headings (MeSH) terms and free-text words, initially constructed using the following key concepts: "low anterior resection syndrome" AND ("treatment" OR "therapy" OR "intervention") AND ("Systematic Review" OR "Meta-Analysis"). A preliminary search in PubMed revealed that relevant target publications were missed with this strategy. Therefore, we expanded the final search strategy to include LARS AND ("treatment" OR "therapy" OR "intervention") AND ("Systematic Review" OR "Meta-Analysis" OR "review" OR "meta-analysis"). The detailed search strategies are provided in the Supplementary Material.

Date collection and extraction

The retrieved records were imported into EndNote X9 (Clarivate Analytics) for reference management. Two independent reviewers (both trained in evidence-based medicine and specializing in colorectal oncology) performed literature screening and data extraction, with cross-verification of results. The process consisted of duplicate removal using EndNote's automated deduplication function with manual verification, initial screening based on title/abstract using predefined eligibility criteria, and full-text assessment of potentially relevant articles. Any disagreements were resolved through discussion with an experienced colorectal surgeon (≥ 10 years in both clinical practice and academic research) until consensus was reached.

Data extraction included

1) Study characteristics (first author, publication year)
2) Methodology (study design, types and number of included primary studies, quality assessment tool)
3) Population details (total sample size, interventions and control measures)
4) Outcome measures (primary/secondary outcomes, key results)

Methodological quality assessment

The methodological quality of included systematic reviews was independently evaluated by two trained reviewers using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) tool [13], with cross-verification of results. There are 16 items in AMSTAR 2, with seven of them being critical domains: (item 2) protocol registration, (item 4) literature search, (item 7) justification for study exclusion, (item 9) risk of bias in included studies, (item 11) appropriate meta-analytical methods, (item 13) consideration of risk of bias when interpreting results, and (item 15) assessment of publication bias and its likely impact. Discrepancies were resolved through consultation with a third senior researcher.

In compliance with AMSTAR-2 criteria, reviews were classified into four categories:

1) High (≤ 1 non-critical weakness): The review provides an accurate and comprehensive outcome synthesis.
2) Moderate (> 1 non-critical weakness): The review offers a reasonably accurate synthesis.
3) Low (1 critical flaw with or without non-critical weaknesses): The review's outcome synthesis is incomplete.
4) Critically low (> 1 critical flaw with or without non-critical weaknesses): The review fails to provide reliable conclusions.

Certainty of evidence assessment

The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [14]. Following the GRADE approach, evidence is rated as high, moderate, low, or very low. For systematic reviews incorporating randomized controlled trials (RCTs), the baseline evidence quality starts as "high," while those including observational studies begin as "low." The final rating is determined by evaluating five factors that may downgrade evidence—risk of bias, inconsistency (I^2 heterogeneity), indirectness of evidence, imprecision (wide confidence intervals), publication bias—and three factors that may upgrade evidence—large magnitude of effect (e.g., RR > 2 or < 0.5), dose–response gradient, and plausible confounding increasing certainty.

Results

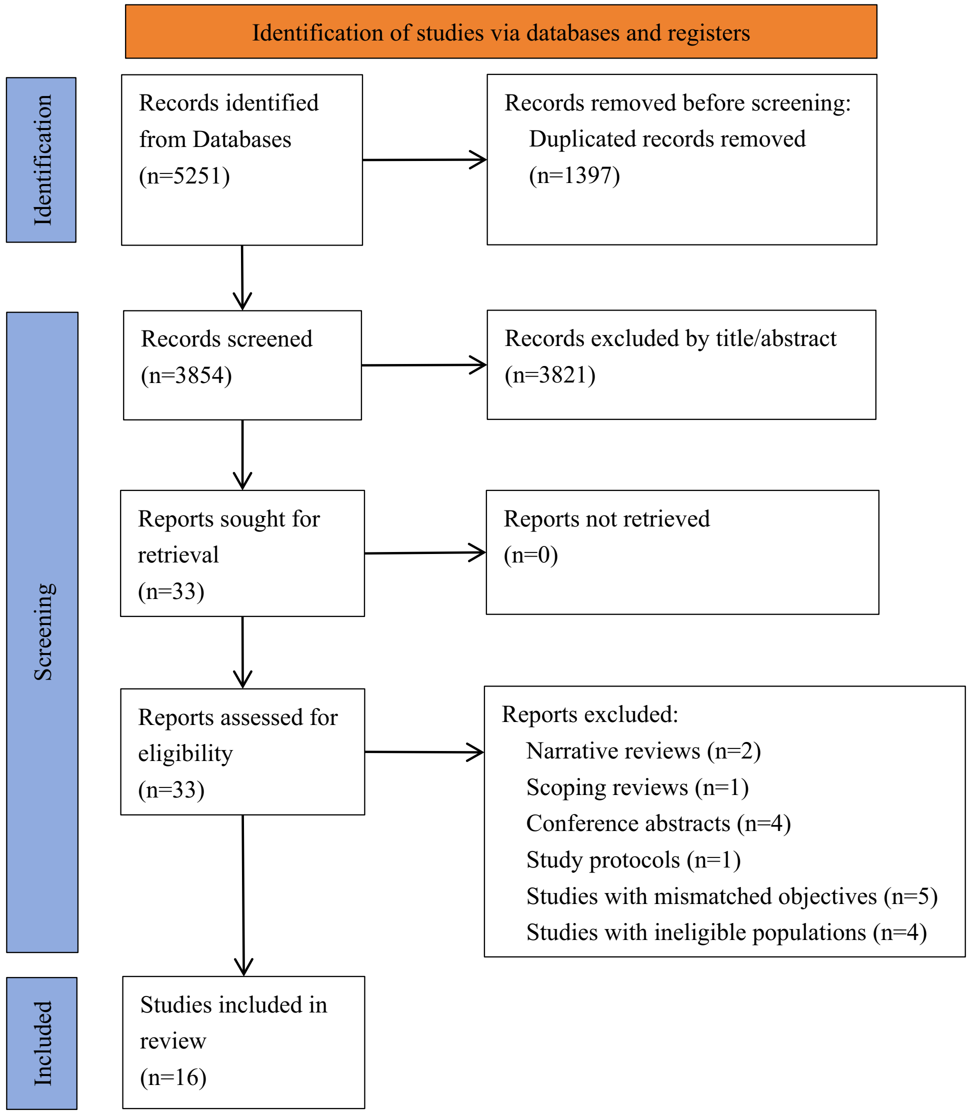
We identified 5251 studies using our search strategy (PubMed, 1292; Web of Science, 815; Cochrane Library, 1177; CINAHL, 37; Embase, 1930). Initially, 1397 duplicate studies were excluded using EndNote X9. After screening titles and examining abstracts, we excluded 3309 irrelevant studies, 43 non-English publications, 27 conference proceedings, and 442 trial registry records. Of the remaining 33 articles that underwent full-text assessment, 17 were excluded because they did not meet the inclusion criteria. Among these, two were narrative reviews, one was a scoping review, four were conference abstracts, one was a study protocol, five included populations not matching our criteria, and four studied interventions outside our defined scope. Finally, 16 studies met all inclusion criteria and were included in our analysis. The complete selection process is shown in Fig. 1.

The 16 included systematic reviews were published between 2018 and 2025, of which nine reviews were meta-analyses. The number of original studies included ranged from 5 to 38, but only three meta-analyses included only RCTs. The details of the 16 studies and AMSTAR-2 assessment results of the included systematic reviews are summarized in the supplementary material.

Transanal irrigation (TAI)

A total of six studies evaluated the therapeutic effects of TAI, with one study focusing primarily on TAI and five studies including TAI as part of their evaluations. Among these six studies, three exclusively included randomized controlled trials (RCTs) and conducted meta-analyses. Emile et al. [15] found significant improvement in LARS after TAI (moderate-quality evidence). A systematic review identified short-term improvements in bowel function and quality of life, particularly for incomplete evacuation cases. However, their study found that these benefits were not sustained long-term due to high dropout rates caused by discomfort and practicality issues (very low-quality evidence) [4]. Similarly, Yu et al. [16] demonstrated through meta-analysis that TAI was the most effective intervention for improving LARS

Fig. 1 PRISMA flow diagram



scores (MD = − 14.13, 95% CI − 20.11, − 7.83) and fecal incontinence severity (SMD = − 1.34, 95% CI − 1.97, − 0.71) in the short term (< 6 months). However, no significant differences were observed between TAI and standard care in the long term (> 6 months), although TAI showed the highest surface under the cumulative ranking curve (SUCRA) values among all therapeutic strategies (moderate-quality evidence). On the contrary, another meta-analysis reported that TAI remained the most effective intervention for reducing LARS scores during 3–12 months follow-up (low-quality evidence) [17]. Dulskas et al. [18] concluded that TAI represents a simple-to-learn, cost-effective intervention that significantly reduces bowel frequency and incontinence symptoms while enhancing quality of life. Moreover, the authors emphasized this therapy requires long-term patient adherence (very low-quality evidence). Another systematic review also demonstrated that TAI significantly reduces LARS scores and improves quality of life, but its success depends on patient compliance and standardized implementation (very low-quality evidence) [19].

Pelvic floor rehabilitation (PFR)

Six studies (all systematic reviews, two with meta-analyses) evaluated the therapeutic effects of PFR on LARS. One meta-analysis ranked PFR as the second most effective short-term intervention for alleviating LARS (low-quality evidence) [16]. Separately, another meta-analysis found modest efficacy in reducing bowel frequency and LARS scores, particularly in early-stage LARS, but benefits diminished over time (low-quality evidence) [17]. Two systematic reviews [18, 20] consistently demonstrated PFR significantly improved bowel frequency and fecal incontinence in LARS patients, though Dulskas [18] noted substantial protocol heterogeneity and both provided very low-quality evidence (GRADE). Sharp et al. [4] also highlighted that PFR is beneficial for fecal incontinence, although long-term outcomes are inconsistent. It requires patient commitment and specialized therapists (very low-quality evidence). Another systematic review identified PFR as a potential therapeutic and preventive option for LARS (very low-quality evidence) [21].

Pelvic floor muscle training (PFMT)

Three studies evaluated the therapeutic effects of PFMT on LARS. A meta-analysis identified PFMT as an effective intervention for improving both bowel function and health-related quality of life (HRQOL) in low anterior resection patients (very low-quality evidence) [22]. Another meta-analysis demonstrated superior efficacy of PFMT compared to standard care at 6-month follow-up (47.8% vs. 21.3% improvement rates, respectively), though this significant difference was not maintained at 12 months (40.0% vs. 34.9%) (moderate-quality evidence) [15]. A systematic review advocated for early implementation of PFMT as a therapeutic approach to accelerate LARS recovery (low-quality evidence) [23].

Biofeedback therapy (BFT)

Limited studies have evaluated BFT, with only one systematic review and meta-analysis assessing its effectiveness in patients with bowel dysfunction after rectal cancer surgery identified, conducted by Li et al. [24]. The results demonstrated bowel function and health-related quality of life significantly improved after BFT (very low-quality evidence).

Sacral nerve stimulation (SNS)

The therapeutic effects of SNS were observed in seven studies (all systematic reviews, three of which included meta-analyses). According to the GRADE framework, the overall certainty of evidence for these outcomes was assessed as very low. A systematic review found that compared to percutaneous tibial nerve stimulation (PTNS), SNS provided greater symptom improvement, though its high cost must be weighed [25]. Another systematic review suggested that SNS may be suitable for LARS patients with predominant fecal incontinence, but it is costly, requires surgical implantation, and lacks high-quality randomized controlled trials for support [18]. Additionally, Ansar et al. [23] indicated that SNS was most effective for incontinent patients but less beneficial for those with evacuation difficulties, necessitating careful patient selection. A meta-analysis reported that SNS significantly improved fecal incontinence and bowel function in LARS patients, potentially offering symptomatic benefits for those refractory to medical therapy [26]. Two additional meta-analyses [27, 28] demonstrated that SNS significantly improved fecal incontinence symptoms and quality of life in LARS patients. The consistent findings across these studies reinforce SNS's clinical value. Sharp et al. [4] concluded that SNS primarily targeted fecal incontinence, showing significant improvements in LARS scores and quality of life. However, a high dropout rate (due to infection, pain, or treatment failure) remained a limitation.

Percutaneous tibial nerve stimulation (PTNS)

This outcome was evaluated in seven systematic reviews (four with included meta-analyses). Liapis et al. [29] reported that PTNS significantly improved bowel function and quality of life in LARS patients (very low-quality evidence). One meta-analysis highlighted the clinically meaningful role of PTNS, demonstrating superior reduction in LARS scores compared to conventional care during the 3 to 6 months follow-up periods (low-quality evidence) [17]. On the contrary, another meta-analysis of three randomized controlled trials (RCTs) found that PTNS showed improvements in both LARS scores and fecal incontinence scales compared to standard care or sham stimulation; these differences did not reach statistical significance (very low-quality evidence) [15]. Finally, a recent meta-analysis identified that PTNS shows promise for long-term LARS management, though further research is required to confirm its efficacy and enhance patient compliance (low-quality evidence) [16]. Two systematic reviews [4, 18] demonstrated that the potential efficacy of PTNS for LARS management (both very low-quality evidence). While Sharp et al. [4] reported benefits restricted to specific patient subgroups, Dulskas et al. [18] emphasized the need for larger sample sizes to validate these findings. Another systematic review demonstrated moderate therapeutic effects, proposing PTNS as an alternative option for patients with mild symptoms or those unsuitable for SNS (very low-quality evidence) [25].

Discussion

The main purpose of this umbrella review was to assess the effectiveness of diverse therapeutic strategies on low anterior resection syndrome. This study identified 16 systematic reviews with/without meta-analyses between 2018 and 2025, including a total of 192 distinct primary studies. Among these reviews, the effects of transanal irrigation (TAI), pelvic floor rehabilitation (PFR), sacral nerve stimulation (SNS), percutaneous tibial nerve stimulation (PTNS), pelvic floor muscle training (PFMT), and biofeedback therapy (BFT) on bowel function, fecal incontinence, bowel frequency, and quality of life were reported. However, although these therapeutic strategies have shown potential for LARS improvement to varying degrees, the overall quality of evidence is generally low and has many limitations.

This umbrella review found that TAI effectively improved bowel function and quality of life, suggesting it may be the most effective short-term (≤ 6 months) intervention for LARS. However, these conclusions have been derived from low-certainty evidence, and long-term benefits have not yet been firmly established. The principle of TAI is to evacuate retained stool from the rectum and colon, thereby reducing fecal accumulation, decreasing bowel frequency, and mitigating fecal incontinence risk [10]. This principle substantiates TAI's efficacy in alleviating core LARS symptoms including unpredictable bowel function, increased stool frequency, emptying difficulties, incontinence, and urgency [6]. However, the umbrella review revealed no statistically significant differences in long-term TAI outcomes (> 6 months), attributable to poor patient compliance. Thus, it is necessary to enhance patient compliance with this treatment.

TAI has been well-established as an effective therapeutic approach for LARS [30]. Moreover, recent investigations have extended its application as a prophylactic treatment for LARS, exploring whether early post-stoma-reversal TAI could reduce LARS incidence [31]. However, current evidence is insufficient to determine the optimal initiation timing and intervention duration of preventive TAI, requiring further investigation through large-scale, long-term follow-up studies [32]. Several challenges persist in TAI's clinical application: (1) the absence of standardized protocols for irrigation volume and frequency and (2) limitations of current irrigation devices (balloon or cone types), which compromise both patient comfort and treatment efficacy [33]. These limitations highlight the urgent need for improved irrigation devices and standardized protocols to ensure safety and user-friendliness. In summary, TAI provides patients with controlled defecation, improves bowel symptoms, and alleviates anxiety related to unpredictable bowel function, thereby enhancing the overall quality of life.

In our study, PFR represented the second most effective intervention following TAI, particularly for LARS patients with predominant fecal incontinence and increased bowel frequency. PFR refers to a collection of rehabilitative techniques that includes pelvic floor muscle training (PFMT), biofeedback therapy (BFT), and rectal balloon training (RBT). The primary objective of PFMT is to augment muscular strength and optimize contraction coordination of the pelvic floor, thereby improving fecal continence [34]. BFT helps patients achieve clear perception and voluntary control of anal sphincter contraction and relaxation, significantly reducing fecal incontinence frequency [35]. RBT promotes the recovery of neural regulation in bowel function through simulating the defecation process, thereby normalizing bowel movement patterns [36].

The umbrella review further confirmed that both PFMT and BFT demonstrate independent therapeutic efficacy. As the most widely utilized components of PFR, both PFMT and BFT provide short-term symptomatic relief, though their long-term efficacy and sustained quality-of-life impacts require further investigation. Current evidence supports early initiation of PFMT to optimize bowel function recovery. In contrast, the therapeutic role of BFT remains poorly characterized owing to insufficient high-quality evidence, underscoring the need for well-designed trials to establish its efficacy and optimal implementation. Notably, the included studies did not evaluate RBT as a standalone therapy; future studies should explore its efficacy in specific LARS subtypes to clarify its potential role in clinical practice.

Studies demonstrate that neurostimulation can offer significant benefits to patients with fecal incontinence [37]. SNS is a minimally invasive approach that connects an implantable pulse generator to electrodes placed near the S3 nerve root—the most common target for treating pelvic floor disorders [38]. Although SNS has demonstrated well-established efficacy, its clinical adoption remains limited by substantial costs and technical complexity. PTNS, which shares similar mechanisms with SNS, is a cost-effective, user-friendly procedure associated with fewer adverse effects, positioning it as an SNS therapeutic substitute [39]. However, a systematic review and meta-analysis suggested that SNS results in significantly improved functional outcomes and quality of life compared to PTNS, consistent with the findings of our study [40]. In summary, for LARS patients manifesting primarily as fecal incontinence, SNS or PTNS could be a therapeutic option when other conservative interventions prove ineffective.

The evidence synthesized in this umbrella review suggests the following clinical recommendations for precision management of LARS. Primarily, a personalized therapeutic strategy should be implemented based on individual patient profiles. Recent studies [3] have established that minor LARS is primarily managed with conservative therapies, including dietary modifications and pharmacotherapy. In contrast, major LARS has been shown to require specialized therapy combining transanal irrigation, pelvic floor rehabilitation, and sacral neuromodulation. For cases that have failed neuromodulation and rehabilitation, end colostomy formation should be considered as a salvage intervention. However, current systematic reviews fail to classify patients according to LARS severity or stratify interventions based on core symptom profiles. We therefore recommend clinicians adopt a tailored, multimodal management approach, guided by both symptom characteristics and individual preferences. Based on these findings, Fig. 2 provides a clinically applicable decision pathway stratified by LARS severity and symptom subtype.

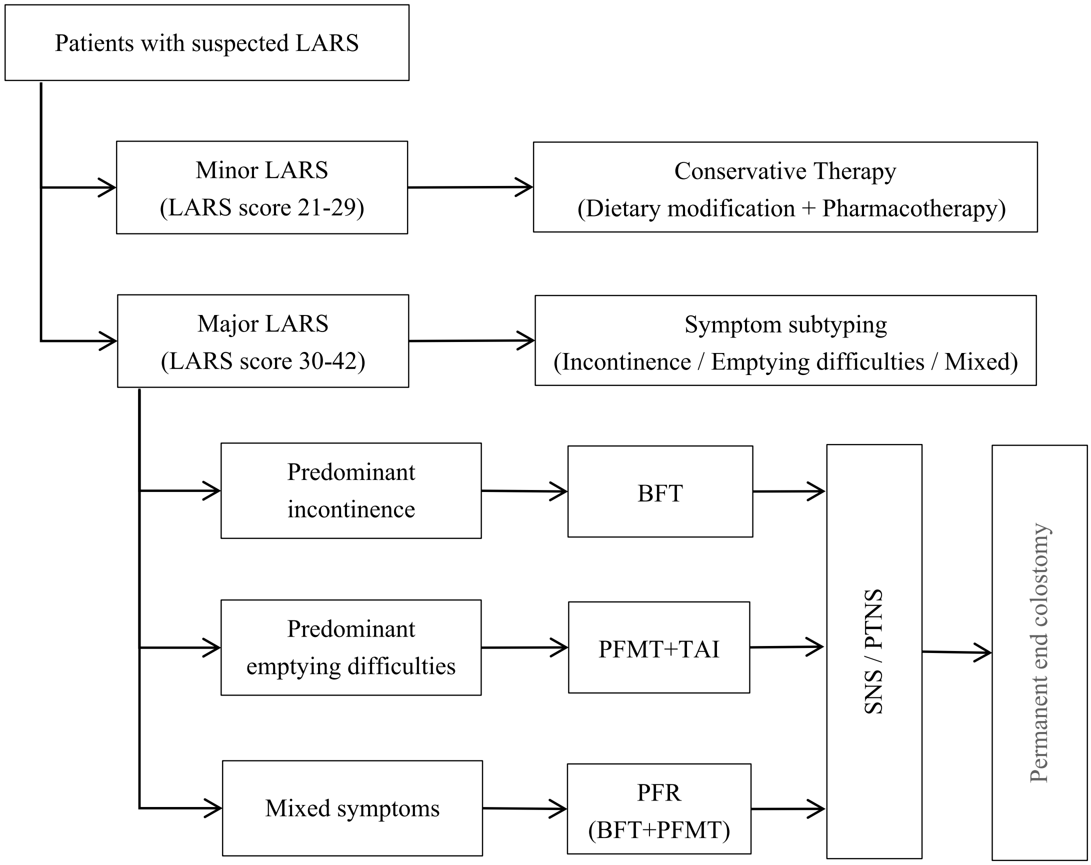


Fig. 2 Decision pathway stratified by LARS severity and symptom subtype

Secondly, this umbrella review identifies significant heterogeneity in included systematic reviews (e.g., divergent conclusions regarding TAI efficacy between Yu et al. [16] and Zhou et al. [17]). Potential explanations for this heterogeneity include the following:

(1) Study quality and sample size disparities: Yu et al. [16] analyzed 11 RCTs ($n=614$) with rigorous quality control (81.8% low-risk bias), likely capturing robust short-term effects, whereas Zhou et al. [17] included fewer RCTs ($n=450$, 22.2% high-risk bias), potentially compromising long-term validity despite high SUCRA values.

(2) Follow-up duration and dropout: Yu et al. [16] categorized outcomes into short- and long-term using a 6-month cutoff, finding no significant differences in long-term effects—a result potentially attributable to high patient dropout rates (approximately 30%) or declining adherence. In contrast, Zhou et al. [17] employed more granular follow-up intervals (3/6/12 months), demonstrating sustained efficacy of TAI throughout the 3- to 12-month period. However, their failure to analyze dropout rates may have obscured adherence declines.

(3) Intervention protocol variability: Yu et al. [16] implemented standardized TAI protocols (including irrigation volume and frequency), whereas Zhou et al. [17] did not provide detailed descriptions of TAI administration, potentially introducing performance bias in efficacy assessments.

(4) Control group differences: While Zhou et al. [17] primarily used routine care controls (e.g., dietary advice), Yu et al. [16] included active comparators (e.g., PTNS, PFR), potentially attenuating the relative long-term efficacy estimates of TAI.

(5) Population heterogeneity: Yu et al. [16] focused on patients with Major LARS, where short-term benefits may not sustain long-term. In contrast, Zhou et al. [17] did not stratify participants by baseline severity, potentially including Minor LARS that could lead to overestimation of TAI's long-term effectiveness.

(6) Outcome measurement inconsistency: Yu et al. [16] assessed multidimensional outcomes (LARS symptoms/incontinence severity), while Zhou et al. [17] prioritized LARS scores alone, neglecting quality-of-life impacts.

Therefore, the observed heterogeneity may stem from methodological variations, clinical diversity, and measurement inconsistencies. Key priorities for future studies include (1) uniform follow-up periods (3/6/12 months) with standardized efficacy definitions, (2) therapeutic strategies standardization with adherence monitoring, (3) stratified analysis by baseline severity to control for confounding, and (4) ensuring measurement tool consistency while integrating patient-reported outcomes (PROs) for comprehensive efficacy assessment.

Finally, current research predominantly focuses on the therapeutic effects of interventions while neglecting patients' real experiences during implementation. We therefore recommend qualitative or mixed-methods studies to capture patient perspectives. Identifying patient-reported discomforts and needs will guide therapeutic strategy refinement.

This umbrella review is subject to several limitations. Firstly, the methodological quality of most included systematic reviews was rated as low or critically low according to the AMSTAR-2 criteria, primarily due to unregistered protocols and inadequate risk-of-bias assessments, necessitating cautious interpretation of the synthesized evidence. Secondly, due to the generally low-quality evidence across available treatment options, only weak recommendations can be made for these therapeutic strategies. Thirdly, the restriction to English-language publications may have introduced potential language bias.

Conclusions

This umbrella review identified 16 systematic reviews exploring the effects of different therapeutic strategies for LARS. Based on our findings, we recommend TAI and PFR as first-line therapies for LARS patients. For cases with suboptimal response to these therapeutic strategies or predominant fecal incontinence, SNS or PTNS may be considered.

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Author contribution All authors contributed to the study conception and design. Tingting Liu and Congli Hu: literature search, data extraction, and analysis. Tingting Liu and Rui Su: methodological quality assessment. Tingting Liu and Jiangfeng Dong: evidence certainty assessment. Tingting Liu, Xueping Jiao and Qiaohong Niu: manuscript writing and revision. All authors read and approved the final manuscript.

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Data availability Data is provided within the manuscript or supplementary materials.

Declarations

Conflict of interest The authors declare no competing interests.

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