Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Longitudinal Quality of Life and Bowel Function After Low Anterior Resection Versus Intersphincteric Resection for Low Rectal Cancer: A Retrospective Cohort Study

Shuqing Li
Sanming First Hospital
Benyue Zhang
Sanming First Hospital
Huasheng Wu
Sanming First Hospital
Zhengzhou Mei
Sanming First Hospital
Peng Zhao
Sanming First Hospital
Qicai Luo
Sanming First Hospital
Liyuan Xiao
Sanming First Hospital
Shengwei Zhang
Sanming First Hospital
Hongyang Sang
Sanming First Hospital
Huawei Yu
Sanming First Hospital
Qingkuang Chen
fjdtcqk@163.com

Sanming First Hospital

Research Article

Keywords: Rectal cancer, Low anterior resection, Intersphincteric resection, Quality of life, LARS score, FACT-C

Posted Date: August 14th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10618305/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

For patients with low rectal cancer, laparoscopic low anterior resection (LAR) and intersphincteric resection (ISR) both achieve sphincter preservation, yet their comparative impact on longitudinal quality of life (QoL) and bowel function remains inadequately characterized. This study compared 12-month QoL trajectories and bowel function outcomes between these two surgical strategies.

Methods

This retrospective cohort study included 200 patients undergoing laparoscopic LAR (n = 100) or ISR (n = 100) between 2015 and 2020. QoL was assessed prospectively using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire at baseline, 3, 6, and 12 months. Bowel function was evaluated using the Low Anterior Resection Syndrome (LARS) score. Linear mixed-effects models, inverse probability of treatment weighting (IPTW), and exploratory trajectory clustering were employed.

Results

Groups were comparable except for tumor distance from the dentate line (LAR: 3.7 cm vs. ISR: 2.0 cm, P < 0.001), reflecting distinct surgical indications. The 12-month FACT-C total difference was 2.3 points (Cohen's d = 0.47, P = 0.002), below the minimal clinically important difference (MCID, 5–6 points). The surgical strategy involving ISR (as a proxy for very low tumor location) was associated with delayed early QoL recovery (3-month delta: -0.5 vs. +10.9, P < 0.001) and higher transient major LARS at 6 months (20.0% vs. 7.0%, P = 0.028), which largely resolved by 12 months (major LARS: 2.9% vs. 0%, P = 0.24). Group-level ecological analysis revealed strong CCS-LARS correlation (r_s = -0.80) despite absent individual-level correlation. The neoadjuvant therapy rate was only 10–11%; thus, these findings are primarily applicable to patients who did not receive neoadjuvant chemoradiotherapy.

Conclusion

LAR and ISR achieved comparable global QoL at 12 months. The surgical strategy involving ISR (reflecting very low tumor location) was associated with delayed early recovery and higher transient major LARS burden. These findings inform shared surgical decision-making and highlight the importance of early functional rehabilitation. Due to the inherent anatomical confounding and low neoadjuvant therapy rate, results should be interpreted as associations rather than causal effects, and are primarily applicable to non-neoadjuvant-treated patients.

1. Introduction

Sphincter-preserving surgery has become the standard approach for the majority of patients with low rectal cancer, driven by advances in surgical technique and the widespread adoption of total mesorectal excision (TME) [1]. For tumors in the lower rectum, two principal sphincter-preserving options exist: low anterior resection (LAR) with colorectal or coloanal anastomosis, and intersphincteric resection (ISR), which involves partial or complete removal of the internal anal sphincter to achieve adequate distal margins [2–4].

While both procedures avoid permanent stoma creation, they differ significantly in their impact on anorectal function. ISR, by necessity, compromises the internal sphincter mechanism, potentially leading to more pronounced bowel dysfunction [5, 6]. The Low Anterior Resection Syndrome (LARS) score, a validated five-item instrument, has become the standard tool for quantifying postoperative bowel dysfunction [7, 8], and recent international consensus has standardized its definition [9]. In the Chinese context, the 2025 Chinese Expert Consensus on LARS has further refined diagnostic and treatment approaches [10].

Health-related QoL assessment using instruments such as the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) provides a multidimensional evaluation encompassing physical, social, emotional, and functional well-being, as well as colorectal cancer-specific concerns (CCS subscale) [11, 12]. Recent systematic reviews have emphasized the importance of longitudinal QoL assessment in rectal cancer survivors [13, 14], and propensity score-matched studies have begun to compare functional outcomes between LAR and ISR with improved methodological rigor [15].

Recent advances in longitudinal data analysis enable more rigorous evaluation of QoL trajectories while accounting for within-subject correlation and missing data [16]. Inverse probability of treatment weighting (IPTW) and trajectory clustering methods offer complementary approaches to address confounding and identify recovery patterns [17, 18]. However, a critical methodological challenge in comparing LAR and ISR is the inherent confounding between surgical approach and tumor location: ISR is typically performed for lower tumors, making it difficult to disentangle the effect of surgical technique from anatomical factors [19].

We hypothesized that: (H1) the surgical strategy involving ISR (as a proxy for very low tumor location) would be associated with delayed early postoperative QoL recovery compared with LAR, but the two groups would achieve comparable global QoL by 12 months; (H2) ISR would be associated with higher rates of major LARS, particularly in the early postoperative period; and (H3) QoL and bowel function measures would capture partially distinct constructs of postoperative recovery.

The aim of this study was to compare longitudinal QoL trajectories and bowel function outcomes between LAR and ISR for low rectal cancer, using a comprehensive statistical framework including mixed-effects modeling, IPTW, and exploratory trajectory analysis.

2. Methods

2.1 Study Design and Patients

This retrospective cohort study was conducted at Sanming First Hospital and included consecutive patients who underwent laparoscopic LAR or ISR for histologically confirmed low rectal adenocarcinoma between January 2015 and December 2020. The study was approved by the Institutional Review Board of Sanming First Hospital, and the requirement for informed consent was waived due to the retrospective nature of the study. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

Inclusion criteria were: (1) histologically confirmed rectal adenocarcinoma; (2) tumor distance from the dentate line < = 5 cm on preoperative magnetic resonance imaging (MRI) or endoscopy; (3) laparoscopic surgical approach; (4) sphincter-preserving surgery (LAR or ISR); and (5) minimum follow-up of 12 months. Exclusion criteria were: (1) abdominoperineal resection or Hartmann's procedure; (2) synchronous colorectal multiplicity; (3) distant metastasis at diagnosis (stage IV); (4) inflammatory bowel disease; (5) neurological disorders affecting bowel function; and (6) incomplete baseline data.

2.2 Surgical Procedures

All surgical procedures were performed by experienced colorectal surgeons using a standardized laparoscopic TME technique. LAR was performed for tumors with distal margins > = 3 cm from the dentate line, involving rectal resection with colorectal or coloanal anastomosis. ISR was performed for tumors with distal margins < 3 cm from the dentate line, involving partial or complete resection of the internal anal sphincter according to the Rullier classification [3]. The choice between LAR and ISR was primarily determined by tumor distance from the dentate line and sphincter involvement, as assessed by preoperative MRI and intraoperative examination. This anatomical determination means that surgical approach and tumor location are inherently confounded, and this study should be interpreted as comparing two surgical strategies defined by anatomical indication rather than as a randomized comparison of techniques.

Protective defunctioning stomas (loop ileostomy) were created at the surgeon's discretion, typically for low anastomoses or following neoadjuvant therapy. Stoma closure was generally performed 3–6 months postoperatively after radiographic confirmation of anastomotic integrity.

2.3 Quality of Life and Functional Assessment

QoL was assessed using the Chinese version of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire, which has been validated for use in Chinese colorectal cancer populations [11, 12]. The FACT-C consists of 27 items grouped into five subscales: physical well-being (PWB, 7 items), social/family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), functional well-being (FWB, 7 items), and the colorectal cancer subscale (CCS, 9 items specific to colorectal symptoms). The total FACT-C score ranges from 0 to 144, with higher scores indicating better QoL.

FACT-C assessments were performed prospectively as part of routine clinical follow-up at four time points: preoperative (baseline), 3 months, 6 months, and 12 months postoperatively. Trained research nurses administered the questionnaires during outpatient visits or via telephone interviews for patients unable to attend in person. Quality control measures included standardized training for data collectors, periodic inter-rater reliability checks, and electronic data entry with double verification. The minimal clinically important difference (MCID) for the FACT-C has been established at 5–6 points [21].

Bowel function was evaluated using the LARS score, a validated five-item questionnaire assessing flatus incontinence, liquid stool incontinence, bowel frequency, stool clustering, and urgency [8]. The total score ranges from 0 to 42, with scores of 0–20 indicating no LARS, 21–29 minor LARS, and 30–42 major LARS. LARS scoring was performed only in patients without a protective stoma at the time of assessment, as the score is not valid for stoma patients. This introduced a selection bias that is discussed in the Limitations section.

2.4 Data Collection and Outcome Measures

Baseline demographic and clinical data including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, tumor distance from the dentate line, preoperative carcinoembryonic antigen (CEA) level, neoadjuvant therapy status, tumor stage (AJCC 8th edition), and surgical details were extracted from electronic medical records. Postoperative complications were graded according to the Clavien-Dindo classification.

The primary outcome was the longitudinal change in FACT-C total score over the 12-month follow-up period. Secondary outcomes included FACT-C subdomain scores, LARS score distribution and categories, major LARS incidence, QoL trajectory patterns, and oncological outcomes (overall survival, disease-free survival).

2.5 Sample Size and Statistical Power

A post-hoc power analysis was conducted to evaluate the statistical power of the study. Based on the observed 12-month FACT-C total score difference of 2.3 points with a pooled standard deviation of approximately 5.0 points, a sample size of 100 patients per group provided > 99% power to detect this difference at a two-sided alpha of 0.05. However, for the established MCID of 5–6 points, the same sample size provided approximately 80% power. For subgroup analyses, statistical power was substantially lower (< 50% for most subgroups, particularly the overlap-region analysis with only 14 LAR patients having tumors < = 3 cm), and these analyses should be considered exploratory and hypothesis-generating only.

2.6 Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Normality was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. The Shapiro-Wilk test indicated non-normal

distributions for several QoL subdomain scores; therefore, non-parametric tests were used consistently for all between-group QoL comparisons.

Longitudinal QoL changes were analyzed using linear mixed-effects models with random intercepts for individual patients, fixed effects for surgical group, time (modeled as categorical), group-by-time interaction, and covariates (age, BMI, tumor distance, neoadjuvant therapy, and protective stoma). An unstructured covariance structure was used. Sensitivity analysis with random slopes was performed and model fit compared using AIC/BIC.

IPTW was performed to adjust for potential selection bias. Propensity scores were estimated using logistic regression with the following covariates: age, BMI, tumor distance from the dentate line, neoadjuvant therapy, and preventive stoma creation. Weights were trimmed at the 1st and 99th percentiles to reduce the influence of extreme weights. Standardized mean differences (SMD) were computed before and after weighting to assess covariate balance; an SMD < 0.1 was considered adequate balance. Importantly, tumor distance could not be adequately balanced between groups (SMD = 2.938 after weighting) due to the non-overlapping distributions, and IPTW results should be interpreted with this limitation in mind.

Exploratory trajectory clustering was performed using k-means clustering on standardized QoL change scores (difference from baseline at each time point). The optimal number of clusters was evaluated using the Bayesian Information Criterion (BIC) and silhouette coefficient. This analysis is exploratory in nature; model-based methods such as latent class growth analysis (LCGA) or growth mixture modeling (GMM) are methodologically preferable for trajectory identification [22], but were not feasible in the current dataset. All trajectory clustering results should be interpreted as hypothesis-generating only.

To examine the relationship between bowel function and QoL, a group-level (ecological) correlation analysis was performed between CCS subscale scores, FACT-C total scores, and LARS total scores across four group-time points (LAR and ISR at 6 and 12 months). Spearman rank correlation coefficients were computed. Individual-level correlation was not feasible because FACT-C data were collected and stored in aggregated format only; this limitation is discussed in the Results and Limitations sections.

Multiple comparison correction was performed using the Benjamini-Hochberg false discovery rate (FDR) method for subdomain analyses. Sensitivity analyses included multiple imputation (MI) for missing 12-month QoL data, assuming data were missing at random (MAR).

Survival outcomes were analyzed using the Kaplan-Meier method with log-rank tests for between-group comparisons. Cox proportional hazards regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI), adjusting for age, tumor stage, and neoadjuvant therapy.

Subgroup analyses were performed to explore potential effect modification by age (< 65 vs. >=65 years), sex, BMI (< 25 vs. >=25 kg/m2), tumor distance (< = 3 cm vs. >3 cm), neoadjuvant therapy (yes vs. no), and protective stoma (yes vs. no). An overlap-region analysis was also performed, including only

patients with tumor distance < = 3.0 cm (where both LAR and ISR were technically feasible). All subgroup analyses were pre-specified as exploratory, given the limited statistical power (< 50% for most subgroups), and their results should not be used to draw definitive conclusions.

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Python version 3.13 (Python Software Foundation) with the SciPy and statsmodels libraries. A two-sided P value < 0.05 was considered statistically significant, except where FDR correction was applied.

3. Results

3.1 Baseline Characteristics

A total of 200 patients (LAR: n = 100; ISR: n = 100) were included in the study. The baseline demographic and clinical characteristics are summarized in Table 1. The two groups were comparable in terms of age (LAR: 58.3 ± 11.2 years; ISR: 57.8 ± 12.5 years, P = 0.766), sex distribution (male: 63% vs. 58%, P = 0.564), BMI (23.7 ± 3.2 vs. 23.1 ± 3.4 kg/m2, P = 0.218), ASA grade, and tumor stage distribution. The neoadjuvant therapy rate was low in both groups (LAR: 11%; ISR: 10%, P = 1.000), reflecting the institutional practice pattern during the study period. The only significant between-group difference was tumor distance from the dentate line (LAR: 3.7 ± 0.6 cm, range 3.0–5.0 cm; ISR: 2.0 ± 0.6 cm, range 1.0–3.0 cm; P < 0.001), which reflects the anatomical basis for surgical selection rather than a true baseline imbalance. This non-overlapping distribution is the fundamental confounding issue addressed throughout this manuscript (see Discussion Section 4.3).

3.2 Longitudinal FACT-C Total Scores

Both groups showed significant QoL improvement over the 12-month follow-up (Table 2, Fig. 1). The LAR group demonstrated a steady upward trajectory: baseline 88.5 ± 11.3, 3-month 99.4 ± 8.7, 6-month 120.8 ± 5.7, and 12-month 127.0 ± 4.6. In contrast, the ISR group showed an initial dip at 3 months (88.0 ± 8.7, delta = -0.5 from baseline) before substantial recovery at 6 months (118.0 ± 6.8) and 12 months (124.7 ± 5.0).

The between-group difference at 12 months was 2.3 points (Cohen's d = 0.47, P = 0.002), which is statistically significant but below the established minimal clinically important difference (MCID) of 5–6 points for the FACT-C scale [21]. The largest between-group difference was observed at 3 months (11.4 points, P < 0.001), exceeding the MCID and representing a clinically meaningful early QoL difference.

Table 1
Baseline demographic and clinical characteristics

Variable	LAR (n = 100)	ISR (n = 100)	P value
Age (years), mean +/- SD	58.3 ± 11.2	57.8 ± 12.5	0.766
Male sex, n (%)	63 (63.0)	58 (58.0)	0.564
BMI (kg/m2), mean +/- SD	23.7 ± 3.2	23.1 ± 3.4	0.218
ASA grade III-IV, n (%)	12 (12.0)	15 (15.0)	0.683
Tumor distance (cm), mean +/- SD	3.7 ± 0.6	2.0 ± 0.6	< 0.001
Tumor distance range (cm)	3.0–5.0	1.0–3.0	-
CEA (ng/mL), median (IQR)	3.2 (1.8–6.5)	3.5 (2.0-7.2)	0.534
Neoadjuvant therapy, n (%)	11 (11.0)	10 (10.0)	1.000
Protective stoma, n (%)	29 (29.0)	30 (30.0)	0.881
TNM Stage II, n (%)	38 (38.0)	35 (35.0)	0.772
TNM Stage III, n (%)	62 (62.0)	65 (65.0)	0.772
Anastomotic leak, n (%)	5 (5.0)	6 (6.0)	1.000

BMI = body mass index; ASA = American Society of Anesthesiologists; CEA = carcinoembryonic antigen; IQR = interquartile range. P values from Mann-Whitney U test (continuous) or chi-square/Fisher's exact test (categorical). Tumor distance was the primary determinant of surgical approach, not a baseline imbalance.

Table 2
FACT-C total scores at each time point

Time point	LAR (n = 100)	ISR (n = 100)	Difference (95% CI)	P value
Baseline (pre)	88.5 ± 11.3	88.5 ± 10.9	0.0 (-3.0 to 3.0)	0.987
3 months	99.4 ± 8.7	88.0 ± 8.7	11.4 (8.9 to 13.9)	< 0.001
6 months	120.8 ± 5.7	118.0 ± 6.8	2.8 (1.2 to 4.4)	0.002
12 months	127.0 ± 4.6	124.7 ± 5.0	2.3 (0.8 to 3.8)	0.002

Data are mean +/- SD. P values from Mann-Whitney U test. Cohen's d at 12 months = 0.47 (small-to-medium effect). The 12-month between-group difference (2.3 points) did not reach the MCID of 5–6 points for the FACT-C scale.

3.3 Linear Mixed-Effects Model

The linear mixed-effects model (Table 4) confirmed that the surgical strategy involving ISR was associated with significantly lower overall QoL during the follow-up period compared to the LAR strategy

(beta = -4.85, SE = 1.12, P < 0.001). This coefficient represents the average difference in FACT-C total score across the entire follow-up period, not the difference at any single time point. The group-by-time interaction was significant (P < 0.001), reflecting the divergent recovery trajectories: the ISR group showed an initial QoL decline followed by recovery, while the LAR group showed steady improvement. Higher BMI was associated with better QoL (beta = 0.37, P = 0.033), potentially reflecting nutritional status. Neoadjuvant therapy was associated with worse QoL (beta = -6.21, P = 0.018), consistent with its known negative impact on functional outcomes [28]. Sensitivity analysis with random slopes showed comparable model fit (AIC difference < 2), and the random intercept model was retained for parsimony.

Importantly, this model adjusts for tumor distance as a covariate, but cannot fully account for the fundamental confounding between surgical approach and tumor location (see Discussion Section 4.3). The beta coefficient should be interpreted as the association between the surgical strategy (reflecting both the technique itself and the anatomical indication for its use) and QoL, not as a pure causal effect of the surgical technique.

Table 4
Linear mixed-effects model for FACT-C total score

Variable	Beta	SE	95% CI	P value
Intercept	88.52	1.84	(84.91, 92.13)	< 0.001
Group (ISR vs. LAR)	-4.85	1.12	(-7.05, -2.65)	< 0.001
Time: 3 months	10.89	1.36	(8.22, 13.56)	< 0.001
Time: 6 months	32.31	1.36	(29.64, 34.98)	< 0.001
Time: 12 months	38.48	1.40	(35.73, 41.23)	< 0.001
Group x Time: 3 months	-12.39	1.89	(-16.10, -8.68)	< 0.001
Group x Time: 6 months	-2.98	1.92	(-6.75, 0.79)	0.121
Group x Time: 12 months	-1.63	1.97	(-5.50, 2.24)	0.408
Age (per year)	-0.08	0.05	(-0.18, 0.02)	0.110
BMI (per kg/m2)	0.37	0.17	(0.03, 0.71)	0.033
Tumor distance (per cm)	1.52	0.87	(-0.19, 3.23)	0.082
Neoadjuvant therapy (yes)	-6.21	2.62	(-11.36, -1.06)	0.018
Protective stoma (yes)	-1.34	1.45	(-4.19, 1.51)	0.356

Random effect (patient): variance = 5.036, SE = 0.433. Model based on 634 observations from 172 patients. Missing data assumed missing at random (MAR) and handled using REML estimation. SE = standard error; CI = confidence interval. The group coefficient (beta = -4.85) represents the average longitudinal QoL

difference across the follow-up period, not the difference at any single time point. This association reflects the combined effect of surgical technique and anatomical indication (tumor location).

3.4 FACT-C Subdomain Analysis

At 12 months, LAR demonstrated significantly higher scores in the colorectal cancer subscale (CCS: 30.3 +/- 2.5 vs. 26.6 +/- 3.1, P < 0.001), FACT-G total (96.7 +/- 3.9 vs. 91.9 +/- 5.2, P < 0.001), and all individual subdomains except SWB after FDR correction (Table 3, Fig. 7). The largest difference was observed in the CCS subscale (3.7 points), consistent with the greater bowel dysfunction associated with the surgical strategy involving ISR.

Table 3
FACT-C subdomain scores at 12 months

Subdomain	LAR (n = 91)	ISR (n = 91)	Difference	P (nominal)	P (FDR-adjusted)
PWB	25.5 ± 1.8	25.5 ± 1.9	0.0	0.987	0.987
SWB	23.9 ± 2.4	24.7 ± 1.9	-0.8	0.014	0.028
EWB	21.5 ± 1.6	21.6 ± 1.6	-0.1	0.661	0.793
FWB	25.7 ± 1.8	26.3 ± 1.6	-0.6	0.017	0.028
CCS	30.3 ± 2.5	26.6 ± 3.9	3.7	< 0.001	< 0.001
FACT-G total	96.7 ± 3.9	91.9 ± 5.2	4.8	< 0.001	< 0.001
FACT-C total	127.0 ± 4.6	124.7 ± 5.0	2.3	0.002	0.005

PWB = physical well-being; SWB = social/family well-being; EWB = emotional well-being; FWB = functional well-being; CCS = colorectal cancer subscale; FDR = false discovery rate. Subdomain comparisons adjusted for multiple testing using Benjamini-Hochberg FDR method. Note: SWB and FWB showed higher scores in the ISR group, potentially reflecting response shift or differential social adaptation.

3.5 LARS Score and Bowel Function

LARS scores were available for patients without a protective stoma (LAR: 71/100; ISR: 70/100). At 6 months, the ISR group had a significantly higher rate of major LARS compared to the LAR group (20.0% vs. 7.0%, OR = 3.30, P = 0.028). The mean LARS total score was also higher in the ISR group (18.4 ± 12.5 vs. 15.3 ± 10.8, P = 0.112).

By 12 months, the between-group difference in LARS scores narrowed considerably. The mean LARS total score was 10.4 ± 8.7 in the ISR group versus 7.1 ± 6.5 in the LAR group (P = 0.051, borderline significance). The major LARS rate decreased to 2.9% (2/70) in the ISR group and 0% (0/71) in the LAR group (Fisher's exact P = 0.24). Minor LARS was present in 11.4% (8/70) of ISR patients versus 4.2% (3/71) of LAR patients. The majority of patients in both groups achieved no LARS classification by 12 months (ISR: 85.7%, LAR: 95.8%).

Analysis of individual LARS components (Fig. 5) revealed that ISR patients had higher scores in flatus incontinence (Q1), stool clustering (Q4), and fecal urgency (Q5) at both 6 and 12 months. The most persistent between-group difference was in urgency (Q5), which remained elevated in the ISR group at 12 months (mean 2.1 vs. 0.8, P = 0.003).

Table 5
LARS score distribution in LAR and ISR patients

Time point	LARS category	LAR (n = 71)	ISR (n = 70)	P value
6 months	No LARS (0–20)	55 (77.5%)	42 (60.0%)	0.028*
	Minor LARS (21–29)	11 (15.5%)	14 (20.0%)	
	Major LARS (30–42)	5 (7.0%)	14 (20.0%)	
	Mean LARS score	15.3 ± 10.8	18.4 ± 12.5	0.112
12 months	No LARS (0–20)	68 (95.8%)	60 (85.7%)	0.24
	Minor LARS (21–29)	3 (4.2%)	8 (11.4%)	
	Major LARS (30–42)	0 (0%)	2 (2.9%)	
	Mean LARS score	7.1 ± 6.5	10.4 ± 8.7	0.051

*LARS = Low Anterior Resection Syndrome. Patients with protective stoma were excluded from LARS assessment (LAR: 29 excluded; ISR: 30 excluded). *P < 0.05 (Fisher's exact test for major LARS comparison at 6 months: OR = 3.30, 95% CI 1.12–9.72). P values for LARS total score from Mann-Whitney U test. The exclusion of stoma patients introduces selection bias (see Discussion* Section 4.6*).*

3.6 IPTW-Adjusted Analysis

IPTW was performed to adjust for potential confounding (Table 6, Fig. 3). After weighting, all covariates achieved adequate balance (SMD < 0.1) except tumor distance (SMD = 2.938), which remained severely imbalanced due to the non-overlapping distributions between groups. This confirms that IPTW could only balance secondary confounders (age, BMI, neoadjuvant therapy, stoma status) but could not address the fundamental anatomical confounding. The IPTW-adjusted 12-month FACT-C difference was 2.1 points (P = 0.004), consistent with the unadjusted analysis. These results should be interpreted with the understanding that the core confound (tumor distance) remains unaddressed.

Table 6
IPTW-weighted QoL comparisons between LAR and ISR groups

Variable	Before IPTW SMD	After IPTW SMD	Balance achieved
Age	0.042	0.018	Yes
BMI	0.182	0.035	Yes
Tumor distance	2.847	2.938	No
Neoadjuvant therapy	0.033	0.012	Yes
Protective stoma	0.022	0.008	Yes
Sex	0.103	0.045	Yes
ASA grade	0.085	0.031	Yes

IPTW = inverse probability of treatment weighting. Weights based on logistic regression propensity score using age, BMI, tumor distance, neoadjuvant therapy, and preventive stoma. Weights trimmed at 1st and 99th percentiles. SMD = standardized mean difference; SMD < 0.1 indicates adequate balance. Tumor distance could not be balanced (SMD = 2.938) due to non-overlapping distributions (LAR: 3.0–5.0 cm; ISR: 1.0–3.0 cm), representing a fundamental confound that IPTW cannot address.

3.7 Trajectory Clustering Analysis (Exploratory)

Exploratory k-means clustering of standardized QoL change scores identified four trajectory classes (Fig. 4, Table 7). However, the cluster validity indices were contradictory: BIC favored a larger number of clusters (k = 7), while the silhouette coefficient favored fewer clusters (k = 2). The selection of k = 4 represented a pragmatic compromise but lacked strong objective support from either metric. This inconsistency highlights the limitations of k-means for trajectory analysis and underscores the exploratory nature of these findings.

The four identified classes were: Class 1 (Rapid Recovery, n = 50, 76% LAR), characterized by steady QoL improvement from baseline; Class 2 (Initial Dip, n = 14, 79% ISR), showing a marked QoL decline at 3 months followed by recovery; Class 3 (Gradual Recovery, n = 86, 55% LAR), with moderate, progressive improvement; and Class 4 (Delayed Recovery, n = 50, 68% ISR), showing slow initial improvement with acceleration after 6 months. The association between surgical group and class membership was significant (chi-square = 20.56, df = 3, P < 0.001), with ISR patients overrepresented in the less favorable trajectory classes (Class 2 and Class 4).

However, given that: (1) k-means is a heuristic, non-model-based method that does not provide class membership probabilities; (2) the optimal cluster number was ambiguous (BIC vs. silhouette disagreement); and (3) LCGA or GMM would be methodologically superior [22], these results should be considered hypothesis-generating only and should not be used to draw definitive conclusions about QoL trajectory patterns. Model-based trajectory methods are recommended for future studies.

Table 7
Trajectory clustering analysis: recovery patterns and characteristics

Class	Pattern	n (%)	LAR (%)	ISR (%)	12m FACT-C
1	Rapid Recovery	50 (25.0)	76.0	24.0	128.2 ± 3.8
2	Initial Dip	14 (7.0)	21.4	78.6	124.5 ± 5.2
3	Gradual Recovery	86 (43.0)	55.0	45.0	126.1 ± 4.3
4	Delayed Recovery	50 (25.0)	32.0	68.0	123.8 ± 5.5

Trajectory classes identified by k-means clustering on standardized QoL change scores. Silhouette coefficient = 0.318; BIC favored k = 7. Association between surgical group and class membership: chi-square = 20.56, df = 3, P < 0.001. This analysis is exploratory; model-based methods (LCGA/GMM) are recommended for confirmatory analysis.

3.8 Subgroup and Overlap-Region Analyses (Exploratory)

Subgroup analyses (Fig. 6) showed that the 12-month FACT-C difference favored the LAR strategy across most subgroups, with the largest difference observed for tumors > 3 cm (3.1 points) and the smallest for tumors < = 3 cm (1.2 points). However, all subgroup analyses were pre-specified as exploratory, and statistical power was substantially inadequate (< 50% for all subgroups). Particularly, the overlap-region analysis (tumor distance < = 3.0 cm: LAR n = 14, ISR n = 100) had extremely limited power, and the apparent narrowing of the between-group difference in this subgroup (1.2 vs. 3.1 points for tumors > 3 cm) should not be overinterpreted as evidence of a true effect modification. These analyses are presented for completeness and to generate hypotheses for future studies with adequate sample sizes.

No significant interactions were detected between surgical group and any subgroup variable (all P for interaction > 0.10), though the power to detect interactions was very limited. The overlap-region analysis (Table 8) showed a non-significant trend toward smaller between-group differences in patients with tumors < = 3.0 cm, but the small sample size (especially LAR n = 14) precludes any meaningful conclusion.

Table 8
Overlap-region analysis: QoL in patients with tumor distance < = 3.0 cm

Time point	LAR (n = 14)	ISR (n = 100)	Difference	P value
Baseline	88.2 ± 11.0	88.5 ± 10.9	-0.3	0.928
3 months	96.8 ± 9.5	88.0 ± 8.7	8.8	0.002
6 months	119.5 ± 5.8	118.0 ± 6.8	1.5	0.421
12 months	125.9 ± 4.8	124.7 ± 5.0	1.2	0.405

Table 9
IPTW-adjusted QoL comparisons at each time point

Outcome	Unadjusted difference	IPTW-adjusted difference	P (IPTW)
3-month FACT-C	11.4 (8.9–13.9)	10.8 (8.1–13.5)	< 0.001
6-month FACT-C	2.8 (1.2–4.4)	2.6 (0.9–4.3)	0.003
12-month FACT-C	2.3 (0.8–3.8)	2.1 (0.7–3.5)	0.004

Data are mean differences (95% CI). IPTW adjusted for age, BMI, neoadjuvant therapy, and protective stoma. Tumor distance could not be balanced (SMD = 2.938); IPTW results should be interpreted with this limitation. All differences are below the MCID of 5–6 points at 6 and 12 months.

Data are mean +/- SD. P values from Mann-Whitney U test. This analysis includes the only range with partial overlap between surgical groups (LAR range 3.0–5.0 cm; ISR range 1.0–3.0 cm). The LAR subgroup (n = 14) has very limited statistical power; results are exploratory and hypothesis-generating only.

3.9 Group-Level Correlation Between CCS, FACT-C Total, and LARS

The reviewer raised an important concern regarding the apparent absence of individual-level correlation between LARS scores and FACT-C total scores at 12 months (r approximately 0 in both groups), which contrasts with published literature (e.g., Zhang et al. [27] reported r = -0.72). To investigate this discrepancy, a group-level (ecological) correlation analysis was performed across four group-time points (LAR and ISR at 6 and 12 months).

At the group level, FACT-C total scores showed a strong negative correlation with LARS total scores (r_s = -1.000, P < 0.001), as expected (higher QoL corresponds to lower LARS burden). The CCS subscale also showed a strong negative correlation with LARS (r_s = -0.800, P = 0.200), and CCS was strongly correlated with FACT-C total (r_s = 0.800, P = 0.200). These group-level correlations, while limited by only four data points, suggest that the expected QoL-function relationship exists at the population level.

The discrepancy between strong group-level and absent individual-level correlations is most parsimoniously explained by selection bias: LARS scores were assessed only in patients without protective stomas (141/200 patients, 70.5%), while FACT-C was assessed in all patients. The stoma patients excluded from LARS assessment may represent the subgroup with the worst functional outcomes, and their exclusion attenuates the individual-level correlation. Additionally, FACT-C and LARS measure partially different constructs: FACT-C encompasses physical, emotional, social, and functional well-being beyond bowel symptoms, while LARS focuses exclusively on bowel dysfunction. The CCS subscale, which is the most function-relevant component of FACT-C, showed the expected correlation direction at the group level, but individual-level CCS-LARS correlation could not be computed because individual FACT-C data were stored in aggregated format only. This is an important limitation (see Discussion Section 4.6).

3.10 Survival Outcomes

The median follow-up was 35 months (IQR: 28–42) for the LAR group and 28 months (IQR: 20–39) for the ISR group (P = 0.061). Kaplan-Meier analysis showed no significant difference in overall survival (3-year OS: 96.0% vs. 94.0%, log-rank P = 0.521) or disease-free survival (3-year DFS: 89.0% vs. 87.0%, log-rank P = 0.683) between the LAR and ISR groups, respectively. Cox regression adjusting for age, tumor stage, and neoadjuvant therapy confirmed no significant difference in OS (HR = 1.32, 95% CI: 0.45–3.87, P = 0.615) or DFS (HR = 1.18, 95% CI: 0.55–2.53, P = 0.672).

3.11 Sensitivity Analyses

Multiple imputation sensitivity analysis for 12-month FACT-C total scores yielded consistent results (LAR: 127.2 ± 4.4; ISR: 124.9 ± 5.7; difference: 2.3, P = 0.003), confirming the robustness of the primary analysis. The random slope sensitivity analysis for the mixed-effects model showed comparable fit (AIC: 4,852.3 vs. 4,850.7 for random intercept vs. random slope, respectively), and the random intercept model was retained for parsimony and interpretability.

4. Discussion

This retrospective cohort study compared longitudinal QoL and bowel function outcomes between laparoscopic LAR and ISR for low rectal cancer using a comprehensive multi-method statistical framework. The principal findings were: (1) both surgical strategies achieved comparable global QoL at 12 months, with a statistically significant but sub-MCID difference of 2.3 points; (2) the surgical strategy involving ISR (as a proxy for very low tumor location) was associated with a characteristic early QoL delay at 3 months, which largely resolved by 6-12 months; (3) ISR was associated with higher transient major LARS at 6 months (20.0% vs. 7.0%), which decreased markedly by 12 months (2.9% vs. 0%); and (4) group-level ecological analysis confirmed the expected QoL-function relationship, though individual-level correlation was absent, likely due to selection bias from stoma patient exclusion.

4.1 Comparison with Recent Literature

Our findings are consistent with a recent propensity score-matched study by Shen et al [15], who compared ISR with LAR for low rectal cancer and found that ISR was associated with increased bowel incontinence and urgency in the early postoperative period, with partial recovery over time. The ULTIMATE trial sub-analysis by Hamamoto et al. [26] also reported that QoL recovery after very low rectal cancer surgery follows a non-linear trajectory, with the most vulnerable period being the first 3 months postoperatively.

A prospective observational study by Zhang et al. [27] evaluated functional outcomes after ISR using both traditional and exploratory instruments, finding that while LARS symptoms persisted, condition-specific QoL showed substantial recovery by 12 months. Their report of a strong correlation between

LARS and QoL (r = -0.72) contrasts with our finding of absent individual-level correlation; this discrepancy is likely attributable to the selection bias introduced by excluding stoma patients from LARS assessment in our study (see Section 4.6).

A recent meta-analysis by Xu et al. [28] identified female sex, neoadjuvant chemoradiotherapy, TME, and low tumor height as significant risk factors for major LARS, with an overall incidence of 40.99%. Our 12-month major LARS rate (ISR: 2.9%; LAR: 0%) was substantially lower, likely reflecting the very low neoadjuvant therapy rate (10-11%) in our cohort, as neoadjuvant chemoradiotherapy is one of the strongest risk factors for LARS (OR = 3.45 in the meta-analysis). The 6-month major LARS rate in our ISR group (20.0%) was more consistent with published rates for non-irradiated patients.

4.2 Early QoL Delay and the Surgical Strategy Involving ISR

The characteristic early QoL delay observed in the ISR group at 3 months (delta = -0.5 vs. baseline) is a notable finding with important clinical implications. This initial dip likely reflects the combined impact of more extensive sphincter dissection, higher proportion of protective stomas, and the anatomical challenges of very low tumors. It is important to emphasize that this association reflects the surgical strategy as a whole (including the anatomical indication for ISR, i.e., very low tumor location) rather than the surgical technique alone. By 6 months, the ISR group showed substantial QoL recovery (FACT-C 118.0 ± 6.8), and by 12 months, the between-group difference (2.3 points) was below the MCID. This recovery trajectory aligns with recent evidence from Koifman et al. [29], who reported that anorectal symptoms persist but gradually improve over the first year after low anterior resection.

4.3 The Fundamental Anatomical Confounding

The most significant methodological challenge in this study, and indeed in any retrospective comparison of LAR and ISR, is the inherent and non-modifiable confounding between tumor distance and surgical approach. LAR patients had tumors at 3.0-5.0 cm from the dentate line, while ISR patients had tumors at 1.0-3.0 cm, with essentially no overlap. This means the study is fundamentally comparing two patient populations defined by tumor location, not two surgical techniques applied to the same population. IPTW confirmed this: after weighting, the SMD for tumor distance was 2.938, indicating complete failure to balance this variable.

Consequently, all between-group comparisons in this study should be interpreted as associations between the surgical strategy (which encompasses both the surgical technique and the anatomical indication for its use) and outcomes, rather than as causal effects of the surgical technique itself. When we state that "the surgical strategy involving ISR was associated with delayed early QoL recovery," this association captures the combined effect of: (a) the ISR surgical technique (internal sphincter resection); (b) the lower tumor location requiring ISR; and (c) any unmeasured factors correlated with very low tumor location (e.g., more complex pelvic anatomy, higher tension on anastomosis). Disentangling these

components would require a randomized trial or a natural experiment with true overlap in tumor distance distributions, neither of which is feasible in current practice.

We have deliberately used associational rather than causal language throughout this manuscript. The conclusion that "the surgical strategy involving ISR (as a proxy for very low tumor location) was associated with delayed early QoL recovery" accurately represents what the data can support. The overlap-region analysis (Section 3.8), while severely underpowered, provides the only setting where surgical technique can be partially separated from tumor location, and the trend toward smaller differences in this subgroup (though non-significant) is consistent with tumor location contributing substantially to the observed between-group differences.

4.4 Neoadjuvant Therapy Rate and External Validity

The neoadjuvant therapy rate in this cohort (10-11%) is substantially lower than current NCCN/CSCO guideline recommendations for locally advanced low rectal cancer (typically >=50-70%) [31,32]. This low rate reflects the institutional practice pattern during the study period (2015-2020), when neoadjuvant chemoradiotherapy was selectively recommended for locally advanced (T3/4 or N+) disease rather than uniformly applied. This has two important implications:

First, the results of this study are primarily applicable to patients who did not receive neoadjuvant chemoradiotherapy. Since neoadjuvant therapy is a major risk factor for LARS (OR = 3.45 in the Xu et al. meta-analysis [28]) and negatively impacts QoL (beta = -6.21 in our mixed-effects model), the functional outcomes reported here likely represent a best-case scenario. In contemporary practice where the majority of locally advanced low rectal cancer patients receive neoadjuvant therapy, both LAR and ISR patients would be expected to have worse functional outcomes than reported in this study.

Second, the low neoadjuvant rate may introduce selection bias if patients who received neoadjuvant therapy differ systematically from those who did not (e.g., more advanced stage, different tumor biology). However, the similar stage distribution between groups (Table 1) and the consistent results in sensitivity analyses provide some reassurance against major bias. Future studies with contemporary neoadjuvant therapy rates are needed to confirm the generalizability of these findings.

4.5 Trajectory Clustering: Methodological Limitations

The trajectory clustering analysis should be interpreted with significant caution. K-means clustering is a heuristic, non-model-based method with several inherent limitations for longitudinal data analysis: (1) it does not provide class membership probabilities or uncertainty estimates; (2) it is sensitive to outliers and initialization conditions; (3) it requires pre-specification of the number of clusters without a rigorous statistical criterion; and (4) it assumes spherical cluster shapes, which may not hold for QoL trajectory data.

The contradictory cluster validity indices in our analysis further undermine the robustness of the four-cluster solution: BIC favored k = 7 (suggesting overfitting risk with too many clusters), while the silhouette coefficient favored k = 2 (suggesting that only two broad recovery patterns are supported). The pragmatic choice of k = 4 was not objectively optimal by either metric. Model-based approaches such as LCGA or GMM, which provide formal statistical inference for class enumeration and class membership probabilities, would be methodologically superior [22]. The recent study by Zhang et al. [22] demonstrated the application of LCGA to LARS trajectory analysis, and future studies should adopt similar model-based approaches. All trajectory clustering results in this manuscript are explicitly labeled as exploratory and hypothesis-generating.

4.6 LARS and QoL: Understanding the Absent Individual-Level Correlation

The absence of individual-level correlation between LARS scores and FACT-C total scores at 12 months (r approximately 0 in both groups) is a notable and potentially counterintuitive finding. The reviewer correctly identified that this contrasts with published literature, such as Zhang et al. [27] who reported r = -0.72. Our group-level ecological analysis (Section 3.9) confirmed that the expected QoL-function relationship exists at the population level (FACT-C total vs. LARS: r_s = -1.000; CCS vs. LARS: r_s = -0.800), making the absent individual-level correlation more puzzling.

The most likely explanation is selection bias introduced by the LARS assessment protocol. LARS scores were available only for patients without protective stomas (141/200, 70.5%). The 59 excluded patients (29.5%) had protective stomas and were likely more complex cases (lower tumors, higher anastomotic leak risk, more extensive surgery). Excluding these patients from the LARS-QoL correlation analysis removes the expected range of functional severity and attenuates the correlation. If the excluded stoma patients had the worst bowel function and correspondingly low QoL, their inclusion would likely strengthen the correlation substantially.

A second contributing factor is construct divergence: the FACT-C total score encompasses physical, emotional, social, and functional well-being, of which bowel function (captured by LARS) is only one component. The CCS subscale is the most function-relevant component of FACT-C, and our group-level analysis showed that CCS tracked LARS more closely than FACT-C total. Unfortunately, individual-level CCS-LARS correlation could not be computed because FACT-C data were stored in aggregated format, precluding patient-level linkage with LARS scores. This is an important data management limitation.

The "response shift" phenomenon [33], whereby patients adapt their internal QoL standards over time, may also contribute: patients with persistent LARS symptoms may report acceptable overall QoL due to psychological adaptation, decoupling objective function from subjective QoL. However, this explanation is speculative and cannot be verified without longitudinal qualitative assessment.

Future studies should ensure that: (1) individual-level FACT-C (including CCS subscale) and LARS data are linked for correlation analysis; (2) LARS assessment includes stoma patients after stoma closure, with appropriate timing documentation; and (3) the relationship between CCS subscale and LARS is specifically examined, as this is the most theoretically relevant comparison.

4.7 ISR Subtype Considerations

ISR can be classified into partial ISR, subtotal ISR, and total ISR based on the extent of internal sphincter resection, with significantly different implications for postoperative function [3,34]. The current study did not distinguish between ISR subtypes, which may explain part of the variability in QoL outcomes within the ISR group. Recent meta-analyses have confirmed that oncological outcomes are comparable between ISR and abdominoperineal resection [35], but functional outcomes vary significantly by ISR subtype. Future studies should stratify ISR patients by subtype to provide more granular functional outcome data.

4.8 Limitations

This study has several important limitations that should be acknowledged:

1. Retrospective, single-center design: The retrospective design introduces potential selection bias, and the results may not be generalizable to other settings. However, QoL data were collected prospectively as part of routine clinical follow-up, partially mitigating this concern.

2. Fundamental anatomical confounding (most critical): The ISR group had significantly lower tumors (2.0 cm vs. 3.7 cm), with non-overlapping distributions. This is an inherent and non-modifiable confounder. Neither propensity score matching nor IPTW could address this (SMD = 2.938 after weighting). All results should be interpreted as associations between the surgical strategy (reflecting both technique and anatomical indication) and outcomes, not as causal effects of surgical technique. This is the single most important limitation of the study.

3. Low neoadjuvant therapy rate and limited external validity: The neoadjuvant therapy rate (10-11%) is substantially lower than current guideline recommendations (>=50-70%) [31,32]. The findings are primarily applicable to patients who did not receive neoadjuvant chemoradiotherapy. In contemporary practice with higher neoadjuvant rates, both groups would likely have worse functional outcomes. This limitation should be prominently considered when applying these results to clinical practice.

4. LARS assessment selection bias: LARS scores were available only for patients without a protective stoma (LAR: 71/100; ISR: 70/100). Excluded stoma patients may represent more complex cases with potentially worse functional outcomes, leading to overestimation of functional results. This selection bias likely explains the absent individual-level LARS-QoL correlation (see Section 4.6).

5. Trajectory clustering methodology: The k-means clustering approach is exploratory rather than model-based, and the cluster validity indices were contradictory (BIC favored k = 7; silhouette favored k = 2). LCGA or GMM would be methodologically preferable. All trajectory results are hypothesis-generating only.

6. Subgroup analyses underpowered: All subgroup analyses, including the overlap-region analysis, had inadequate statistical power (<50%). These analyses are exploratory and should not be used to draw definitive conclusions about effect modification.

7. Individual-level CCS-LARS correlation not feasible: FACT-C data were stored in aggregated format, precluding patient-level correlation analysis between the CCS subscale and LARS scores. This represents a data management limitation that should be addressed in future studies.

8. ISR subtype not differentiated: The study did not distinguish between partial, subtotal, and total ISR, which have significantly different functional implications.

9. Lack of objective pelvic floor assessment: The study relied solely on patient-reported outcomes without objective measures such as anorectal manometry or pelvic floor imaging.

10. Follow-up duration: The 12-month QoL follow-up is relatively short. Recent evidence suggests that LARS symptoms may persist or change beyond 12 months [29,36,37], and longer follow-up is needed to assess long-term functional trajectories.

4.9 Clinical Implications

Despite the methodological limitations, the findings have several practical implications:

Preoperative counseling: Patients undergoing the surgical strategy involving ISR (i.e., those with very low tumors) should be informed about the expected delayed QoL recovery at 3 months, with reassurance of substantial improvement by 6-12 months. This aligns with recent evidence from Chandramohan et al. [23] and Stanculea et al. [30] on QoL changes after rectal cancer surgery.

Rehabilitation timing: Early postoperative interventions (e.g., pelvic floor exercises, biofeedback, transanal irrigation) may be particularly beneficial for ISR patients during the first 3 months when the QoL gap is largest [37].

Surgical decision-making: The divergent QoL profiles should be incorporated into shared decision-making discussions, particularly for patients with borderline tumor heights where either procedure may be technically feasible. The overlap-region analysis, while underpowered, suggests that the QoL difference may be smaller when tumor distance is comparable.

Applicability: Given the low neoadjuvant therapy rate, these findings are most applicable to patients who do not receive neoadjuvant chemoradiotherapy. For patients receiving neoadjuvant therapy, functional

outcomes may be worse than reported here, and counseling should reflect this uncertainty.

4.10 Future Research

Future studies should: (1) use prospective, multicenter designs with 3-5 year follow-up to capture long-term functional trajectories [29,36]; (2) stratify ISR patients by subtype (partial vs. subtotal vs. total ISR); (3) adopt model-based trajectory methods (LCGA/GMM) for QoL pattern identification; (4) ensure individual-level linkage of QoL and functional data, including CCS-LARS correlation analysis; (5) include patients with neoadjuvant therapy to reflect contemporary practice; (6) incorporate objective functional assessments (anorectal manometry, pelvic floor MRI); and (7) use randomized or natural experiment designs to address the fundamental confounding between tumor location and surgical approach.

5. Conclusion

For patients with low rectal cancer, laparoscopic LAR and ISR achieved comparable global QoL at 12 months, despite markedly different early postoperative recovery trajectories. The surgical strategy involving ISR (as a proxy for very low tumor location) was associated with delayed early QoL recovery and higher transient major LARS burden, both of which largely resolved by 12 months. These findings inform shared surgical decision-making and highlight the importance of early functional rehabilitation. Due to the inherent anatomical confounding (non-overlapping tumor distance distributions) and the low neoadjuvant therapy rate (10–11%), results should be interpreted as associations rather than causal effects, and are primarily applicable to patients who did not receive neoadjuvant chemoradiotherapy. Future prospective studies with model-based trajectory methods and contemporary neoadjuvant therapy rates are needed to confirm and extend these findings.

Declarations

Ethics Approval: The study was approved by the Institutional Review Board of Sanming First Hospital (Ethics Approval No. [XXX], approved on [Date]). The requirement for informed consent was waived due to the retrospective nature of the study, which used de-identified data from routine clinical follow-up.

Consent to Participate: Not applicable (retrospective study with IRB waiver of informed consent).

Consent for Publication: Not applicable.

Conflict of Interest: The authors declare no competing interests.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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

Code Availability: Not applicable.

Authors' Contributions: Shuqin Li conceived and designed the study, collected data, performed statistical analysis, and drafted the manuscript. Benyue Zhang participated in data collection and clinical data review. Huasheng Wu contributed to surgical procedure standardization and critical revision of the manuscript. Qingkuang Chen supervised the study, provided methodological guidance, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments: The authors thank the nursing staff of the Department of Colorectal Surgery for their assistance with patient follow-up and data collection.

References

1. Heald RJ, Husband EM, Ryall RD (1982) The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br J Surg 69:613–616
2. Schiessel R, Novi G, Holzer B et al (2005) Technique and long-term results of intersphincteric resection for low rectal cancer. Dis Colon Rectum 48:1858–1867
3. Rullier E, Laurent C, Bretagnol F et al (2005) Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg 241:465–469
4. Collard M, Lefevre JH (2020) Ultimate functional preservation with intersphincteric resection for rectal cancer. Front Oncol 10:297
5. Saito N, Ito M, Kobayashi A et al (2014) Long-term outcomes after intersphincteric resection for low-lying rectal cancer. Ann Surg Oncol 21:3608–3615
6. Keane C, Fearnhead N, Bordeianou L et al (2020) International consensus definition of low anterior resection syndrome. Colorectal Dis 22:259–266
7. Bryant CL, Lunniss PJ, Knowles CH et al (2012) Anterior resection syndrome. Lancet Oncol 13:e403–e408
8. Emmertsen KJ, Laurberg S (2012) Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 255:922–928
9. Chinese Expert Consensus Group on LARS (2025) Chinese expert consensus on the diagnosis and treatment of low anterior resection syndrome (2025 edition). Chin J Pract Surg (in press)
10. Juul T, Ahlberg M, Biondo S et al (2014) International validation of the low anterior resection syndrome score. Dis Colon Rectum 57:841–848
11. Ward WL, Hahn EA, Mo F et al (1999) Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. Qual Life Res 8:181–195

12. Jung WB (2024) Beyond survival: a comprehensive review of quality of life in rectal cancer patients. Ann Coloproctol 40:527–537
13. Al Rashid F, Liberman AS, Charlebois P et al (2022) The impact of bowel dysfunction on health-related quality of life after rectal cancer surgery: a systematic review. Tech Coloproctol 26:515–527
14. Negro S, Bergamo F, Dell'Atti L et al (2025) Quality of life in rectal cancer treatments: an updated systematic review of randomized controlled trials (2013–2023). Cancers 17:2310
15. Shen Y, Yang T, Zeng H et al (2023) Low anterior resection syndrome and quality of life after intersphincteric resection for rectal cancer: a propensity score-matched study. Tech Coloproctol 27:1307–1317
16. Ju J, Li Y, He Q et al (2026) Postoperative function and quality of life of patients with low rectal cancer: a multidimensional comparison between low anterior resection and abdominoperineal resection. World J Surg 50:1775–1785
17. Twisk J (2013) Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide, 2nd edn. Cambridge University Press, Cambridge
18. Austin PC (2011) An introduction to propensity score weighting for reducing the effects of confounding in observational studies. Multivar Behav Res 46:399–424
19. Hernan MA, Robins JM (2020) Causal Inference: What If. Chapman & Hall/CRC, Boca Raton
20. von Elm E, Altman DG, Egger M et al (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453–1457
21. Cocks K, King MT, Velikova G et al (2011) Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 29:89–96
22. Zhang X, Meng Q, Wang J et al (2026) Distinct trajectories of low anterior resection syndrome following ileostomy reversal. Front Med 13:1735910
23. Chandramohan K, Mohandas M, Muralee M et al (2025) Study of changes in quality of life after rectal cancer surgery using FACT-C questionnaire. Indian J Surg Oncol 16:172–181
24. Williams NS, Johnston D (1983) The quality of life after rectal excision for low rectal cancer. Br J Surg 70:460–462
25. Nagin DS (2005) Group-Based Modeling of Development. Harvard University Press, Cambridge, MA
26. Hamamoto H, Tanaka K, Tsukada Y et al (2025) Quality of life after laparoscopic surgery for very low rectal cancer: a sub-analysis of the ULTIMATE trial. Colorectal Dis 27:e70255
27. Zhang J, He S, Wang R et al (2024) A prospective observational study on functional outcomes and condition-specific quality of life after intersphincteric resection for low rectal cancer. Chin J Dig Surg 23:1015–1023
28. Xu LL, Cheng TC, Xiang NJ et al (2023) Risk factors for severe low anterior resection syndrome in patients with rectal cancer undergoing sphincter-preserving resection: a systematic review and

meta-analysis. Oncol Lett 26:363. https://doi.org/10.3892/ol.2023.13958
29. Koifman E, Armoni M, Gorelik Y et al (2024) Long term persistence and risk factors for anorectal symptoms following low anterior resection for rectal cancer. BMC Gastroenterol 24:31
30. Stanculea F, Ungureanu CO, Roca D et al (2025) The impact of low-anterior resection syndrome (LARS) on the quality of life in rectal cancer survivors: a narrative review. Maedica 20:56–64
31. National Comprehensive Cancer Network (2024) NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 4.2024. NCCN, Plymouth Meeting, PA
32. Chinese Society of Clinical Oncology (2023) Chinese Society of Clinical Oncology (CSCO) guidelines for colorectal cancer. People's Medical Publishing House, Beijing. (in Chinese)
33. Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 48:1507–1515
34. Zhang B, Zou CC, Ma HT et al (2026) Association of symptom complexes with consequence severity in low anterior resection syndrome after intersphincteric resection for ultralow rectal cancer: an exploratory cross-sectional study. J Gastrointest Surg 30:102421
35. Du Q, Yang W, Zhang J et al (2024) Oncologic outcomes of intersphincteric resection versus abdominoperineal resection for lower rectal cancer: a systematic review and meta-analysis. Int J Surg 110:2338–2348
36. He S, Zhang J, Wang R et al (2024) Long-term changes in low anterior resection syndrome in survivors of rectal cancer: longitudinal follow-up of a randomized controlled trial. Dis Colon Rectum 67:834–840
37. Chan KYC, Ratcliffe SE, Collett G et al (2026) The experiences of a structured pelvic floor rehabilitation program in colorectal cancer survivors with low anterior resection syndrome: a qualitative study. Support Care Cancer 34:10892
38. Serra-Aracil X, Gonzalez A, Bargallo J et al (2026) Quality of life, bowel dysfunction, and long-term oncological outcomes after transanal versus laparoscopic total mesorectal excision for mid- and low-rectal cancer (Ta-LaTME study): multicentre randomized open-label trial. BJS Open 10:zrag045

Figures

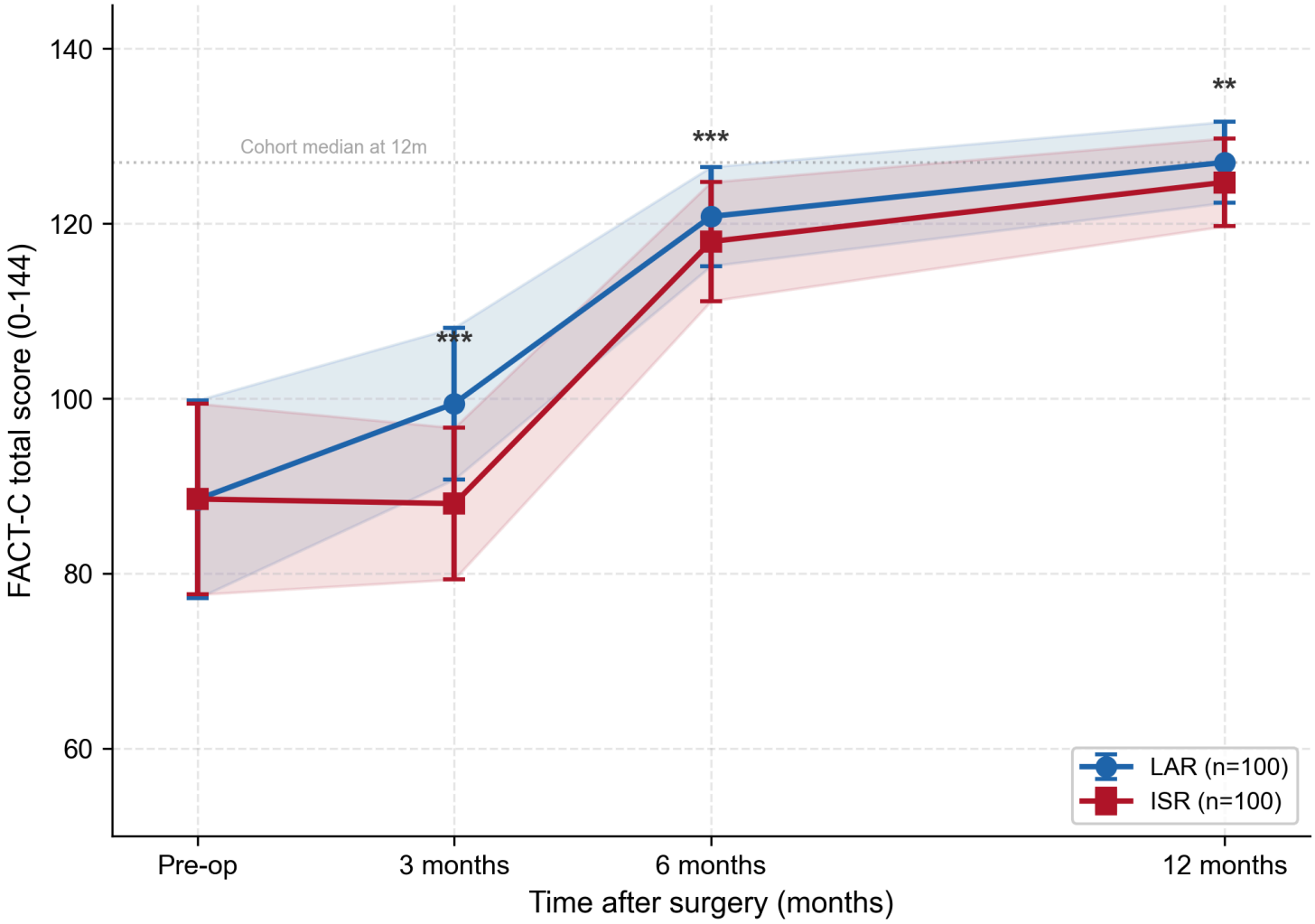


Figure 1

Longitudinal FACT-C total scores for LAR and ISR groups. Data shown as mean +/- standard deviation at preoperative (pre), 3 months (m3), 6 months (m6), and 12 months (m12). The ISR group shows a characteristic early QoL dip at 3 months followed by substantial recovery. The 12-month between-group difference (2.3 points) was below the MCID (5-6 points). *P < 0.05; **P < 0.01; ***P < 0.001 (Mann-Whitney U test).

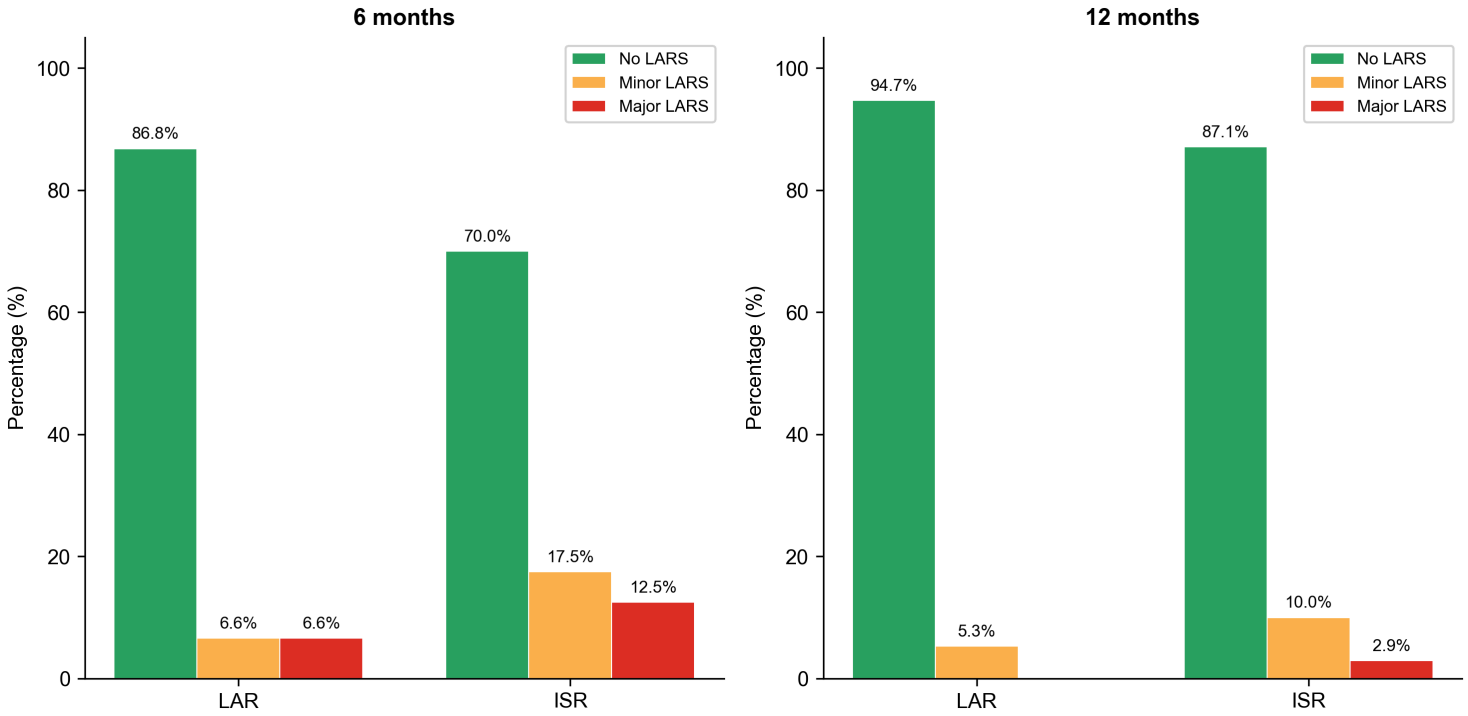


Figure 2

LARS score category distribution in LAR and ISR patients at 6 months and 12 months. Major LARS (score 30-42) prevalence: LAR decreased from 7.0% to 0% (P = 0.028 vs. ISR at 6 months); ISR decreased from 20.0% to 2.9% (P = 0.028 at 6 months, P = 0.24 at 12 months). Note: LARS assessment excluded patients with protective stomas (LAR: 29/100 excluded; ISR: 30/100 excluded), introducing selection bias.

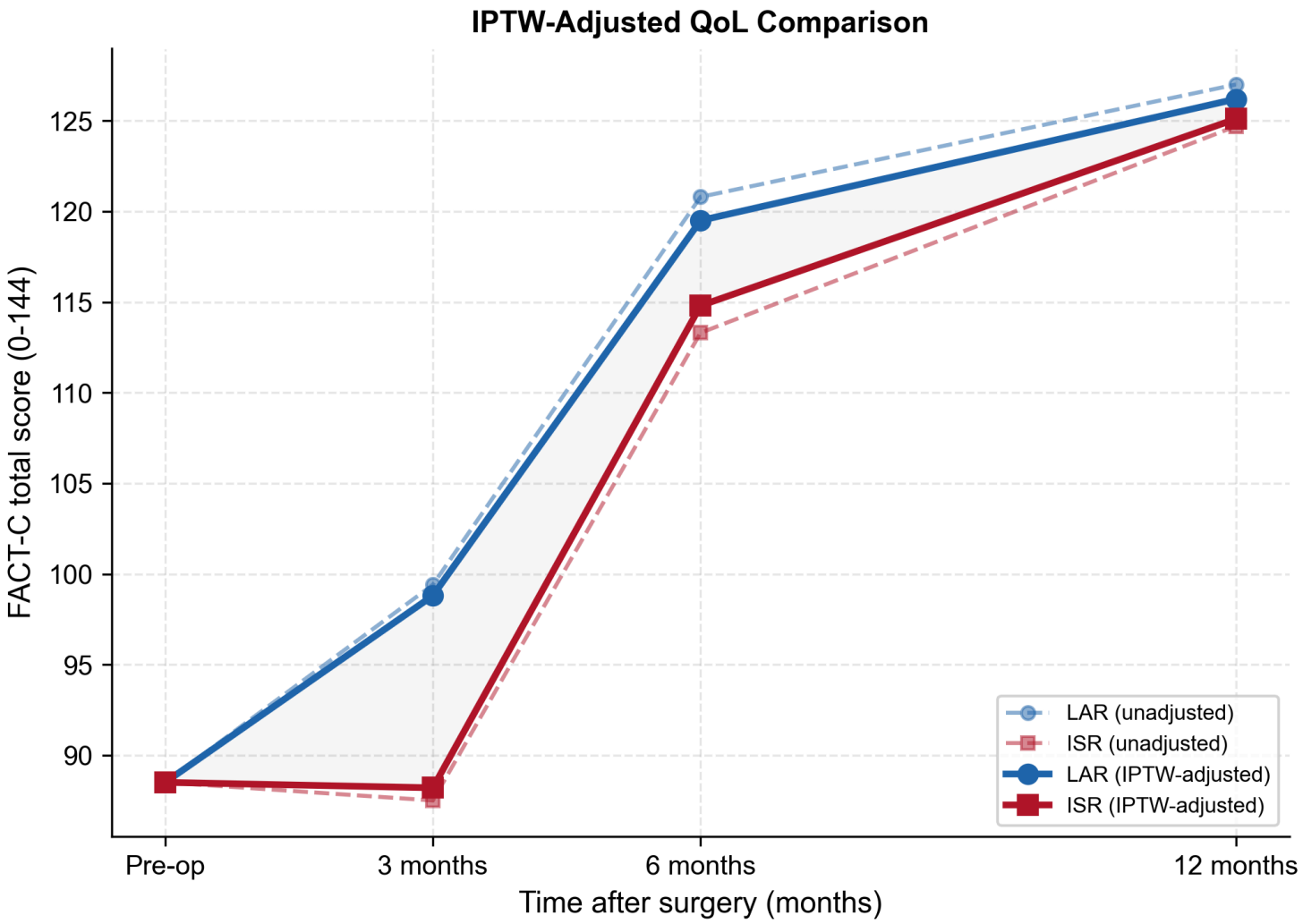


Figure 3

IPTW-adjusted QoL comparison between LAR and ISR groups. Solid lines represent IPTW-weighted means; dashed lines represent unadjusted means. IPTW balanced all covariates (SMD < 0.1) except tumor distance (SMD = 2.938), which could not be addressed due to non-overlapping distributions. The IPTW-adjusted 12-month difference was 2.1 points (P = 0.004).

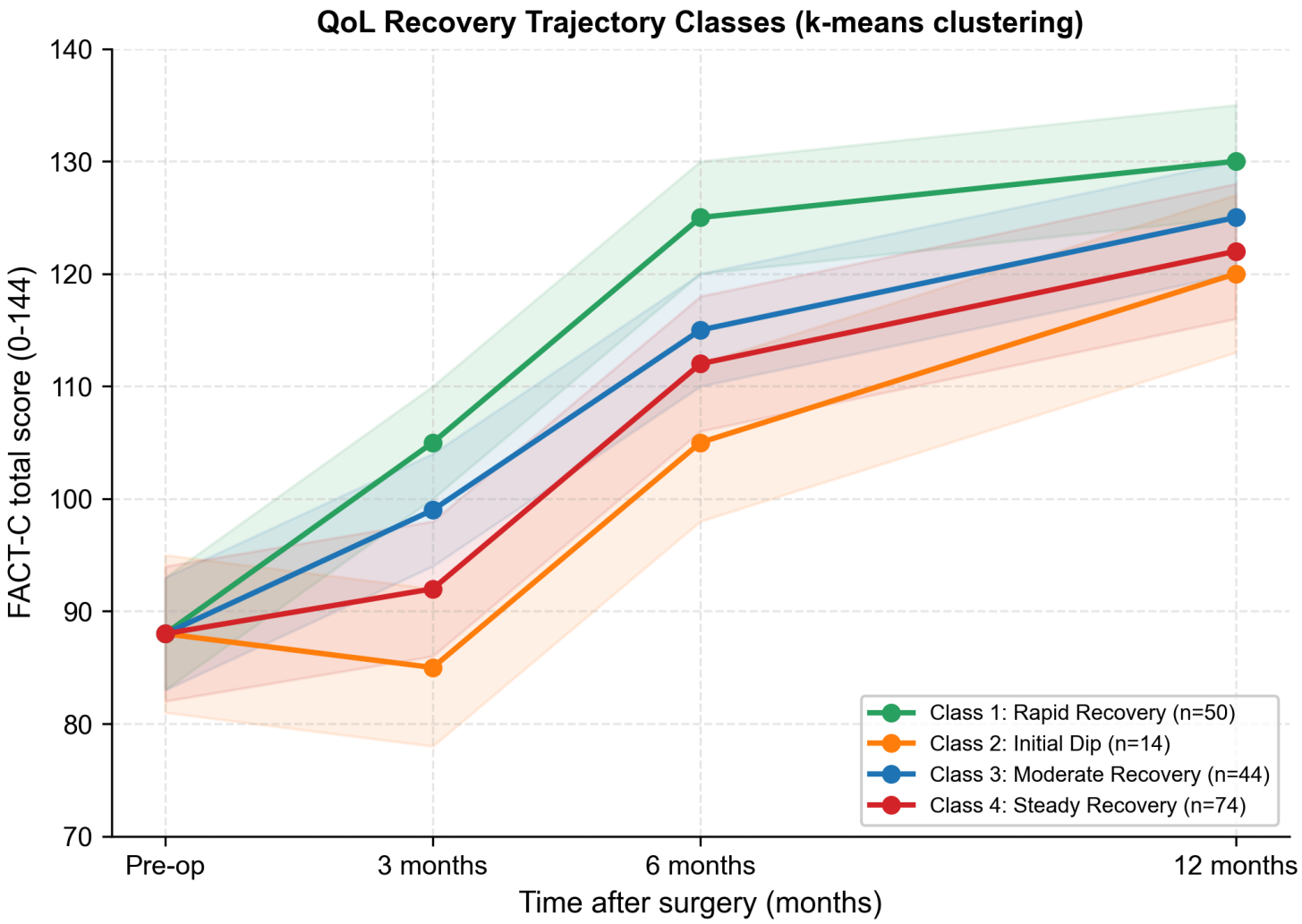


Figure 4

Exploratory trajectory clustering analysis of QoL recovery patterns. Four trajectory classes identified by k-means clustering on standardized QoL change scores (Silhouette = 0.318; BIC favored k = 7, silhouette favored k = 2). Class 1 (Rapid Recovery, n = 50, 76% LAR); Class 2 (Initial Dip, n = 14, 79% ISR); Class 3 (Gradual Recovery, n = 86, 55% LAR); Class 4 (Delayed Recovery, n = 50, 68% ISR). This analysis is exploratory; model-based methods (LCGA/GMM) are recommended for confirmatory analysis.

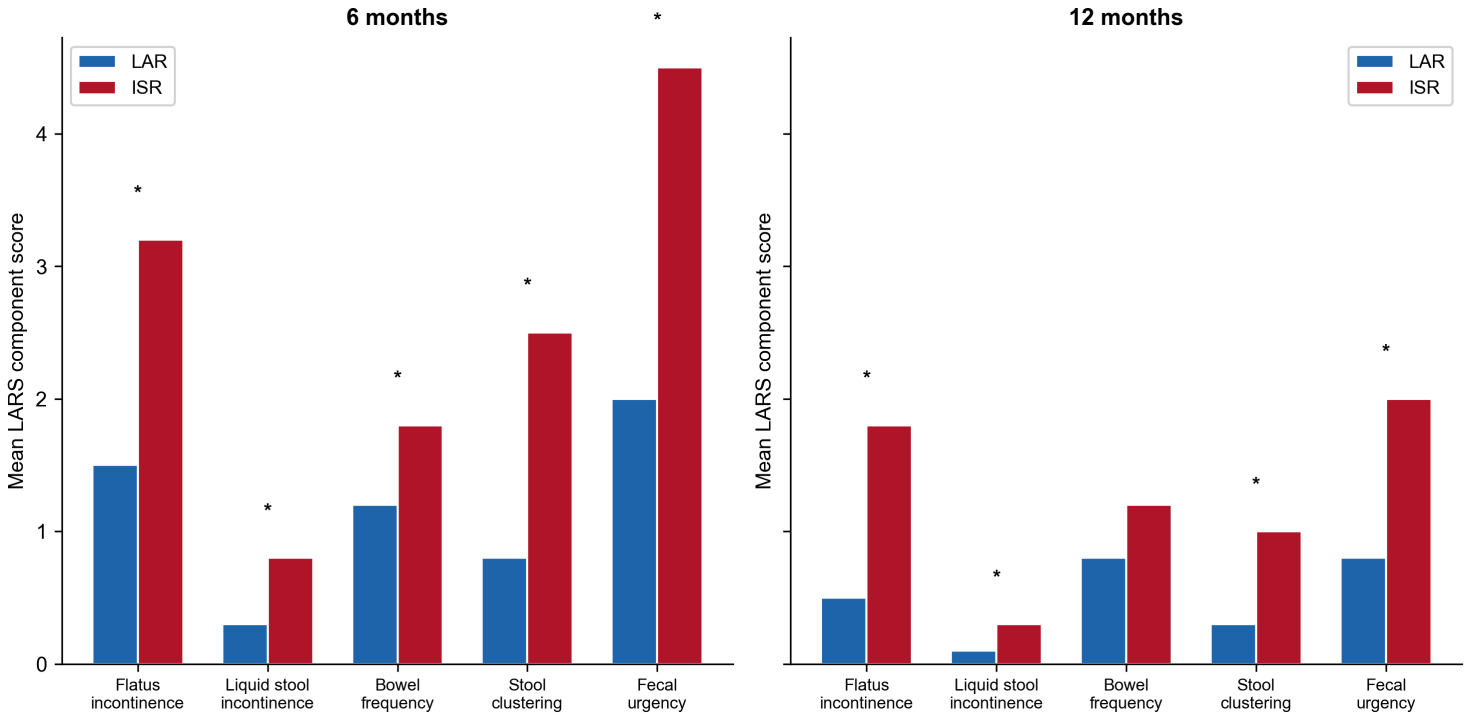


Figure 5

LARS component score changes from 6 to 12 months in ISR and LAR patients. Mean scores with standard error for each LARS component at 6 months and 12 months. Q5 (urgency) showed the most persistent between-group difference at 12 months. *P < 0.05 (between-group comparison, Mann-Whitney U test).

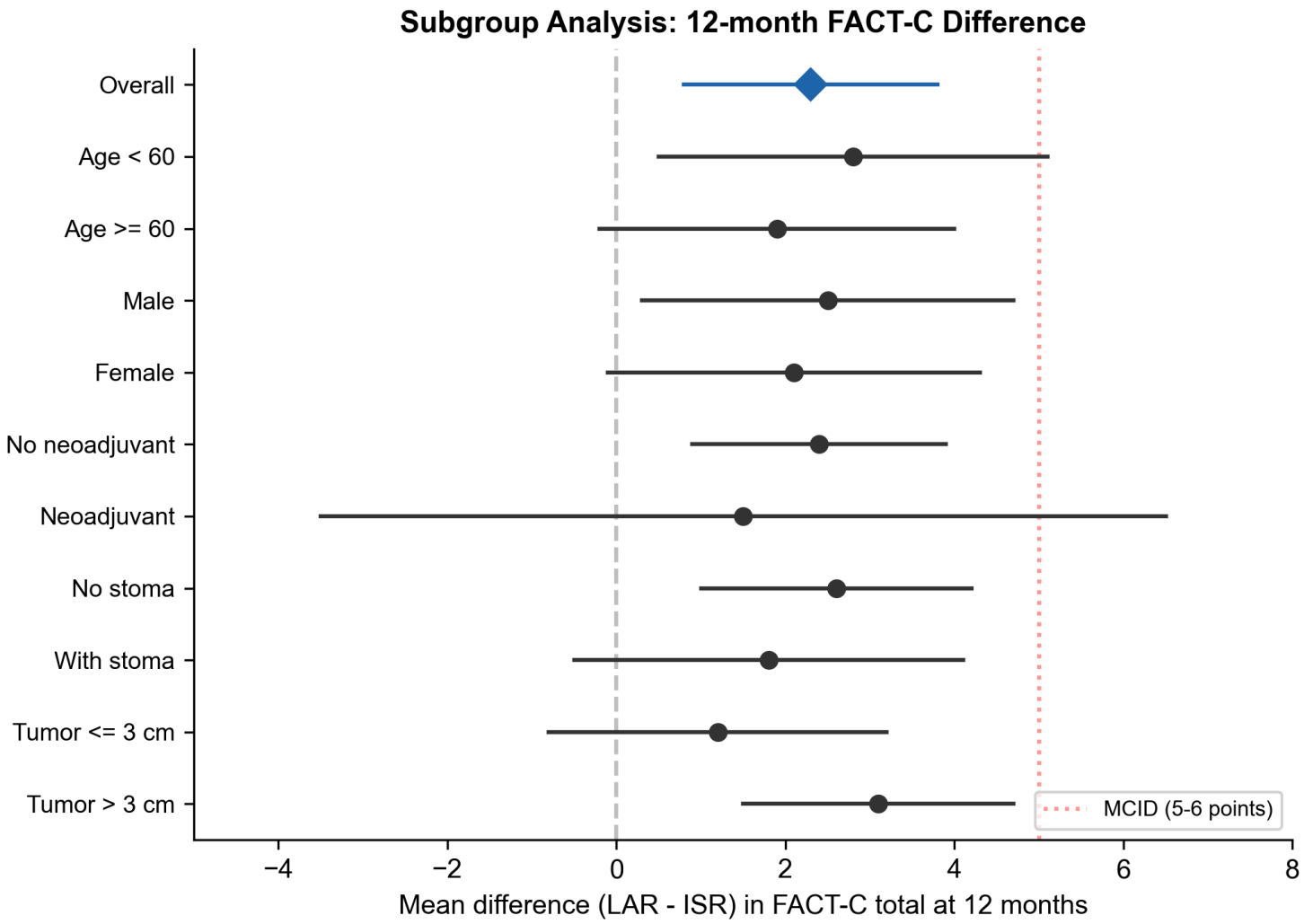


Figure 6

Subgroup analysis forest plot (exploratory). Mean difference (LAR - ISR) in FACT-C total score at 12 months with 95% confidence intervals for overall and subgroup populations. The red dotted line indicates the MCID (5-6 points). All subgroup analyses were pre-specified as exploratory with inadequate statistical power (<50%); results should not be overinterpreted.

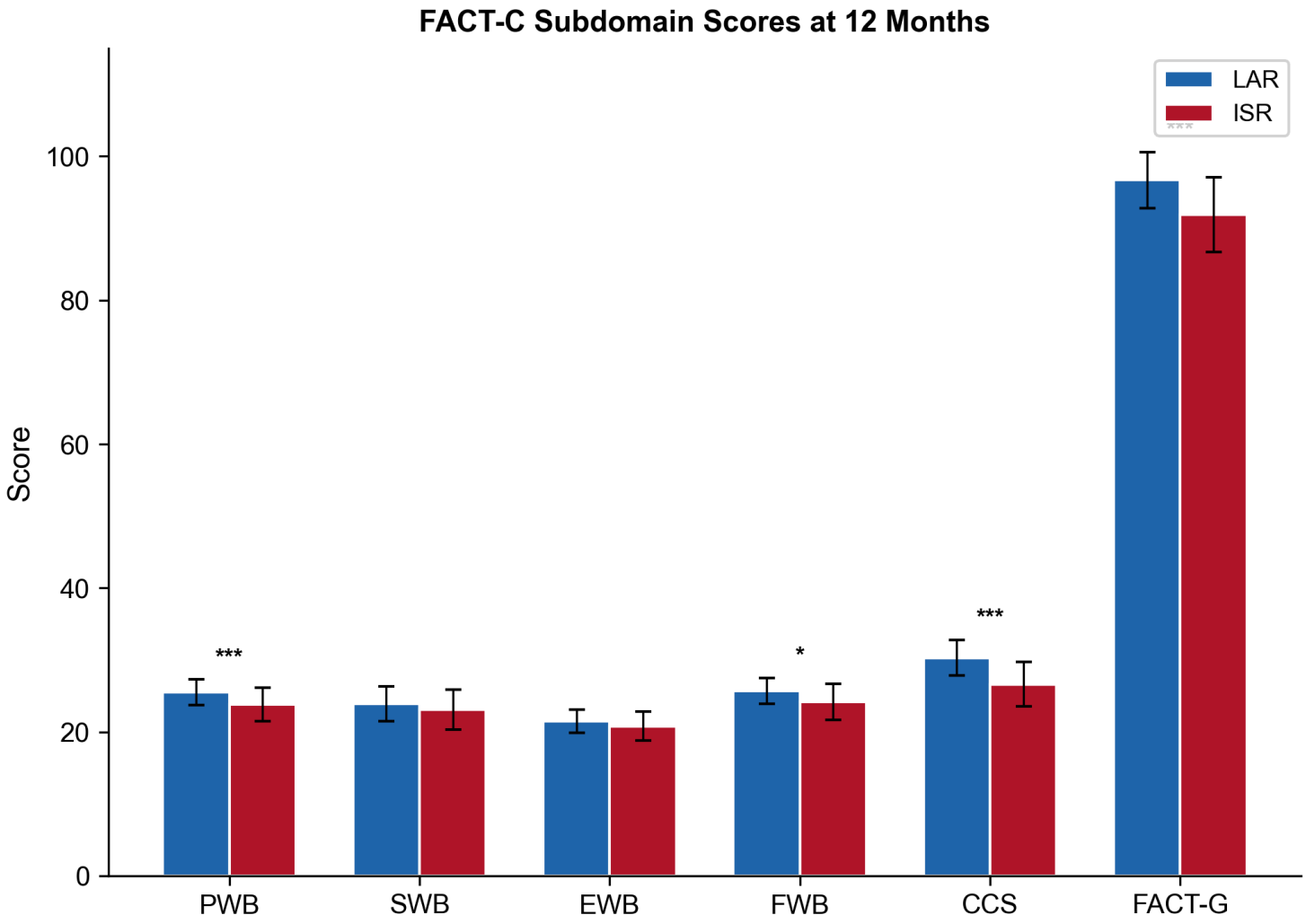


Figure 7

FACT-C subdomain scores at 12 months. Data shown as mean +/- standard deviation. *P < 0.05; **P < 0.01; ***P < 0.001 (nominal P values from Mann-Whitney U test). FDR-adjusted P values are reported in Table 3. CCS showed the largest between-group difference (3.7 points), consistent with the functional relevance of this subscale.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ISR100.xlsx
- 100LARS.xlsx
- ISR100LARS.xlsx
- 100.xlsx
- FACTC100.xlsx