

Prevalence and risk factors of low anterior resection syndrome: Meta-analysis with Subgroup Analysis

Prévalence et facteurs de risque du syndrome de résection antérieure: Méta-analyse avec analyse en sous-groupes

Mohamed Mehdi Trabelsi, Neirouz Kammoun, Salsabil Nasri, Amine Ben Safta, Imen Samaali, Ramzi Nouira, Chadli Dziri

Department B of Surgery - Charles Nicolle hospital. Faculty of medicine of Tunis. University of Tunis El Manar, Tunisia

ABSTRACT

Background: The prevalence of major LARS and its associated risk factors remains variably reported in the literature. This meta-analysis aimed to assess the pooled prevalence of major LARS and to identify its predictive factors.

Methods: We conducted a meta-analysis in accordance with PRISMA 2020 and AMSTAR 2 guidelines to identify studies reporting the prevalence of major LARS or its associated risk factors. Subgroup analyses was used to explain heterogeneity.

Results: A total of 21 studies comprising 3,730 patients were included. The pooled prevalence of major LARS was 36.8% (95% CI: 30.1%–44.0%), with a 95% prediction interval of 12.0%–71.2%, indicating substantial heterogeneity. Tumor location < 5 cm from the anal margin ($p < 0.001$) and neoadjuvant radiochemotherapy ($p = 0.006$) were significantly associated with increased major LARS risk. No significant associations were found with anastomotic leakage, surgical approach, or stoma closure timing.

Conclusion: Our meta-analysis showed a prevalence comparable to previously published data. Low tumor location and neoadjuvant radiochemotherapy were identified as two independent risk factors for major LARS. Prospective randomized trials are necessary to improve risk stratification for the development of major LARS.

Keywords: low anterior resection syndrome, rectal cancer, prevalence, risk factors, meta-analysis

RÉSUMÉ

Introduction: La prévalence de syndrome de résection antérieure du rectum (LARS) majeur LARS et ses facteurs de risque associés restent variables dans la littérature. Cette méta-analyse visait à évaluer la prévalence globale des LARS majeur et à identifier leurs facteurs prédictifs.

Méthodes: Nous avons réalisé une méta-analyse conformément aux directives PRISMA 2020 et AMSTAR 2 afin d'identifier les études rapportant la prévalence des LARS majeur ou les facteurs de risque associés. Une analyses de sous-groupes ont été utilisées pour expliquer l'hétérogénéité.

Résultats: Au total, 21 études portant sur 3 730 patients ont été incluses. La prévalence de LARS majeur était de 36,8 % (IC à 95 % : 30,1 %-44,0 %), avec un intervalle de prédiction à 95 % de 12,0 %-71,2 %, indiquant une hétérogénéité importante. La localisation de la tumeur à moins de 5 cm de la marge anale ($p < 0,001$) et la radiochimiothérapie néoadjuvante ($p = 0,006$) étaient significativement associées à un risque accru de LARS majeur. Aucune association significative n'a été trouvée avec la fuite anastomotique, l'approche chirurgicale ou le moment de la fermeture de la stomie.

Conclusion: Notre méta-analyse a montré une prévalence comparable aux données publiées précédemment. La localisation basse de la tumeur et la radiochimiothérapie néoadjuvante ont été identifiées comme deux facteurs de risque indépendants de LARS majeur. Des essais prospectifs randomisés sont nécessaires pour améliorer la stratification du risque de développement d'un LARS majeur.

Mots clés: Syndrome de résection antérieure basse, Cancer du rectum, Prévalence, Facteurs de risque, Méta-analyse

Correspondance

Mohamed Mehdi Trabelsi

Department B of Surgery - Charles Nicolle hospital. Faculty of medicine of Tunis. University of Tunis El Manar, Tunisia

Email: mehdi.trabelsi1991@gmail.com

INTRODUCTION

The management of the rectum has seen significant progress in recent years, improving both oncological and functional outcomes(1). Anterior resection with excision of the mesorectum remains the standard treatment for rectal cancer with sphincter preservation(2). It is a major procedure that can lead to changes in bowel function over the medium and long term (3).

The symptoms of these digestive functional complications are collectively referred to "Low Anterior Resection Syndrome" (LARS) (4). The initial definition of LARS proposed in 2012 (4), described it as a group of bowel function disorders following rectal resection, resulting in a decline in quality of life (2). In 2020, an international consensus of the LARS was published (5) defining LARS based on input from a large patient panel, leading to the identification of eight symptoms: variable and unpredictable bowel function, altered stool consistency, increased stool frequency, repeated painful stools, emptying difficulties, urgency, incontinence and soiling; and its consequences: Toilet dependence, Preoccupation with bowel function, Dissatisfaction with bowels, Strategies and compromises, Mental and emotional wellbeing, Social and daily activities, Relationships and intimacy, Roles, commitments and responsibilities; which reflect the essential aspects of the syndrome and its impact on quality of life (5). The "LARS score", since its validation, (4) was designed as a simple tool for the clinical assessment of anterior resection syndrome and was used to classify disorders into three categories: no LARS, minor LARS, and major or severe LARS.

Major LARS is defined by a LARS score (4) greater than or equal to 30 out of 42. The prevalence of LARS, ranging from 40% to 49.7% (6–9), remained stable from 2018 to 2023.

The publication of articles on LARS cited in Pubmed database has increased from 2012(8 articles) to 2022 (129 articles), highlighting the importance of this issue and its impact on quality of life(5), as well as on overall health, professional functioning, social functioning, fatigue, and pain (10,11). This meta-analysis aimed to evaluate the prevalence of major LARS, to identify the associated risk factors, and to establish recommendations according to GRADE criteria (12,13)

METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines (14) and AMSTAR 2 (15)(Assessing the methodological quality of systematic reviews) Guidelines. The protocol was registered in PROSPERO with the ID: CRD42025636030

Electronic database searches

An electronic search of the relevant literature from January 1st,2012, to December 31st, 2024, was performed using the following databases: Registry and

Database of Systematic Reviews, PubMed/MEDLINE of the United States National Library of Medicine, Google Scholar, Scopus. The keywords used were "low anterior resection syndrome", "rectal cancer", "functional outcomes", "prevalence", "risk factors". In addition, we manually identified other eligible studies.

Eligibility criteria

All articles, reporting the prevalence of LARS or risk factors of major LARS by comparisons between two groups "Major LARS" and "No major LARS" (i.e. Minor and No LARS), descriptive and comparative studies including adult patients (aged 18 or older) of either gender undergoing anterior resection for rectal cancer were considered for the analysis. Were excluded isolated abstracts (without full text), articles written in languages other than English, French, or Spanish, editorial, case report, literature review, systematic review, and meta-analysis

Outcomes measures

The main endpoint was the occurrence of major LARS after restoring immediate digestive continuity or after reversal of protective stoma.

Data collection and analysis

Study selection: Two authors (MMT and NK) independently reviewed all abstracts. The full texts of all studies that met the inclusion criteria were retrieved.

Assessment of the study quality: All retrieved studies were independently assessed by two authors (MMT and NK) according to the methodological index for non-randomized studies (MINORS) (16). Discrepancies were resolved by discussion or after consulting a third author (CD)

Data extraction: Two authors (MMT and NK) independently extracted the data from the retrieved studies. Disparities were settled after discussion with a third author (CD). The studies were fully matched in terms of the study period, journal and year of publication, the number of major LARS cases among the total number of patients, surgical approach (open or laparoscopic) or tumor characteristics (located < or ≥ 5 cm from anal margin). If studies presented the results as the median and interquartile range (IQR) or range, we converted the values to mean and standard deviation (SD) according to Hozo et al.,(17) as appropriate.

Evaluation of effect size: The mean effect size of prevalence of major LARS was calculated with its 95% confidence interval. We also calculated the mean effect size for associated risk factors (Tumor location, Neoadjuvant radio chemotherapy, Anastomotic leakage, Surgical approach, Duration on diversion stoma) using Risk Difference (RD) with their 95 % confidence intervals (CIs) for dichotomous variable when appropriate (18). Cohen's d index is the Standard difference in means [difference in

mean outcome between two groups / standard deviation of outcome among participants] was used to calculate the mean effect size of continuous variable. Forest plots were performed using a random model.

Publication bias was evaluated using the Funnel plot with Egger regression test and the Duval and Tweedie's Trim & Fill methods.

Assessment of heterogeneity: The Cochrane test (Q test), Tau2, and the 95% predictive interval (PI) were used to assess heterogeneity (18,19). To explain heterogeneity, we assessed potential interactions between relevant factors called moderators [neoadjuvant chemoradiotherapy, tumor location (< 5 cm or ≥ 5 cm), surgical approach, anastomotic leakage, duration of stoma closure] and effect size. Subgroup analysis for dichotomic variable was performed. Comprehensive meta-analysis software version 4 was used for all calculations (20).

Summary findings

Two authors (MMT and NK) evaluated the certainty of evidence according to the Oxford Centre for Evidence-Based Medicine Levels of evidence (12,13). Discrepancies were resolved by discussion and after consulting a third author (CD).

RESULTS

literature search results

We identified twenty-nine relevant articles published between January 1st, 2012 and December 31, 2024 of which eight studies were withdrawn: Four studies were meta-analyses (6–9), and four studies were done in general populations, not in populations with rectal cancer (21–24) (Figure 1 and Table 1)

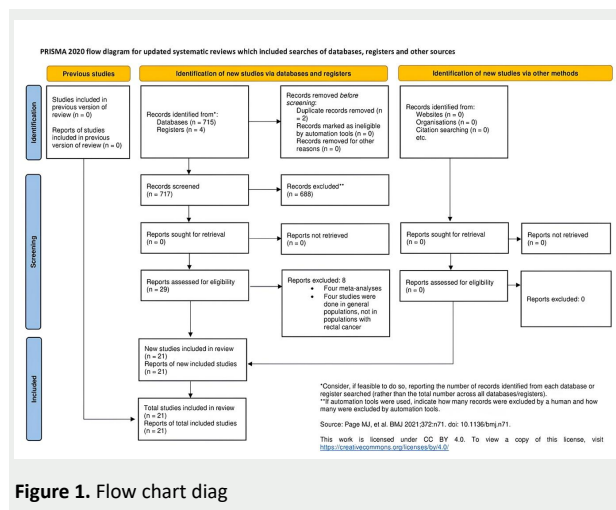


Figure 1. Flow chart diag

The retained twenty-one studies(25–45) included 3730 patients, of whom 1329 had “major LARS”. The practice of radio chemotherapy was reported in 13 studies including 575 patients. Tumor location was reported in all the studies, but only 11 studies stratified tumor location into

three categories, allowing for the identification of low tumor location, defined as less than 5 cm from the anal margin, in 468 patients. The approach was also evaluated in 10 studies, finding that 1250 patients underwent surgery via a laparoscopic approach. The characteristics of the patients included, quality assessment according to MINORS (global score ranging from 0 to 16 since these were non-comparative studies) (16), and details of the included studies were summarized in Table 1. No publication bias was found, as shown by the funnel plot (Figure 2). Egger's regression test did not show a statistical significance (p=0,651).

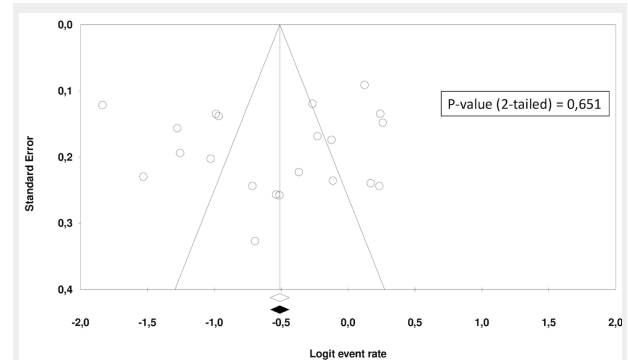


Figure 2. Funnel plot of standard error by Logit event rate showing no publication bias

outcomes measure

Prevalence of major LARS

Of the twenty-one studies, major LARS was reported in 1329 patients. The pooled prevalence of "major LARS" was 36.8%, with a 95% Confidence Interval ranging from 30.1% to 44.0% (Figure 3). Assuming that the true effect size of LARS prevalence was 36.8%, the 95% Prediction Interval (PI) ranged from 12.0% to 71.2% (Figure 3).

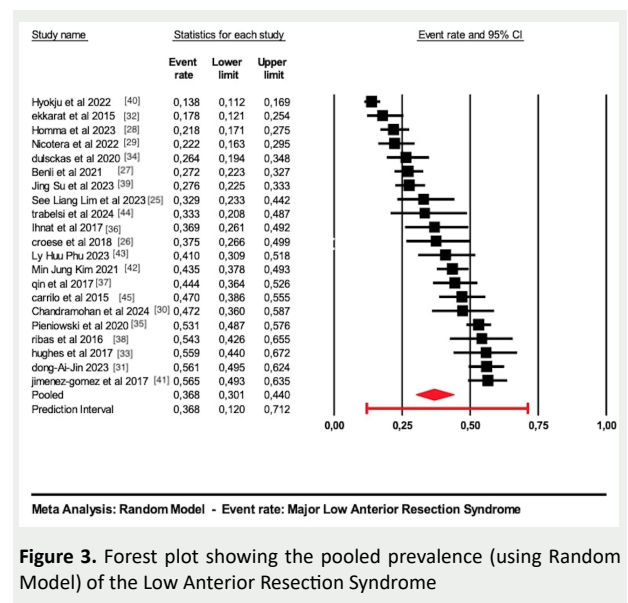


Figure 3. Forest plot showing the pooled prevalence (using Random Model) of the Low Anterior Resection Syndrome

Table 1. List of the non-randomized included studies of Low Anterior Resection Syndrome (LARS)

First author	Study design	Study period	Journal	Major LARS/ population	nRCT	Tumor < 5cm from anal margin	Laparoscopy	MINORS
See Liang Lim et al., 2023 [25]	Retrospective	2011–2020	Ann coloproctol	25/76	23	-	13	9
Croese et al., 2018 [26]	Retrospective	2004–2015	ANZ J Surg	24/64	21	37	-	9
Benli et al., 2021 [27]	Retrospective	2010–2019	Turk J Med Sci	75/276	-	-	-	8
Homma et al., 2024 [28]	Retrospective	2014–2019	Ann Gastroenterol Surg	52/238	24	82	-	11
Nicotera et al., 2022 [29]	Retrospective	2013–2018	Surgical Endoscopy	34/153	-	41	153	9
Chandramohan et al., 2024 [30]	Retrospective	2021–2023	Cureus	34/72	40	-	29	10
Dong-Ai-Jin et al., 2023 [31]	Retrospective	2013–2020	World J Gastrointest Surg	125/223	-	-	-	11
Ekkarat et al., 2015 [32]	Retrospective	2004–2013	Asian Journal of Surgery	23/129	-	29	-	10
Hughes et al., 2017 [33]	Retrospective	2009–2015	Int J Colorectal Dis	38/68	19	5	-	8
Dulscas et al., 2020 [34]	Prospective	2010–2015	Scientific Reports	33/125	13	23	-	13
Pieniowski et al., 2020 [35]	Retrospective	2007–2013	BJS Open	254/478	-	-	-	10
Ihnat et al., 2017 [36]	Prospective	2013–2015	ANZ J Surg	24/65	38	-	65	9
Qin et al., 2017 [37]	Prospective	2012–2014	DISEASES OF THE COLON & RECTUM	63/142	83	47	141	11
Ribas et al., 2016 [38]	Retrospective	2000–2014	Int J Colorectal Dis	38/70	32	-	45	8
Jing Su et al., 2023 [39]	Retrospective	2015–2021	BMC Surgery	72/261	75	-	-	11
Hyokju et al., 2022 [40]	Retrospective	2017–2019	Front. Surg	78/566	160	112	514	8
Jimenez-gomez et al., 2017 [41]	Retrospective	2001–2009	Colorectal Dis	104/184	-	-	-	8
Min Jung Kim et al., 2021 [42]	Prospective	2017–2019	Scientific Reports	123/283	-	56	182	9
Ly Huu Phu et al., 2023 [43]	Retrospective	2022–2023	Cureus	34/83	21	27	-	8
Trabelsi et al., 2024 [44]	Retrospective	2009–2021	Tunisie médicale	14/42	26	9	3	9
Carrilo et al., 2015 [45]	Retrospective	2007–2014	CIRUGIA ESPANOLA	62/132	-	-	105	10

nRCT : neoadjuvant radiochemotherapy, MINORS methodological index for non- randomized studies

This wide range reflected substantial heterogeneity, which should be explained by variables called “moderators” such as tumor location, neoadjuvant radio chemotherapy, anastomotic leakage, surgical approach, and duration on diversion stoma.

Tumor location

Eight studies, out of the 11 that specified the number of patients with a tumor located less than 5 cm from the anal margin, reported major LARS in 208 patients. The group “Tumor location < 5cm” had a greater rate of major LARS than the group “Tumor location equal or greater than 5cm” (50,6% vs 18,3%) ($p < 0,001$), PI showed a trivial heterogeneity (0,034 to 0,539), which was in accordance with the 95%CI (0,198 to 0,375) (Figure 4)

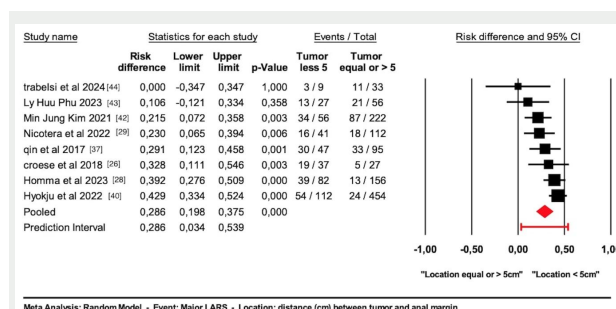


Figure 4. Forest plot comparing tumor location < 5cm versus equal or > 5cm

Neoadjuvant radio chemotherapy

Although 13 studies reported data on neoadjuvant radiochemotherapy, only six studies provided sufficient and extractable comparative data (major LARS vs no major LARS) to be included in the forest plot analysis. These studies found 111 patients with major LARS. The group “no neoadjuvant radio chemotherapy” (No nRCT)

had a lower rate of major LARS compared to the group “neoadjuvant radio chemotherapy” (nRCT) (RD = 0,216) ($p = 0.006$) 95% CI (0,063 to 0,369) (Figure 5).

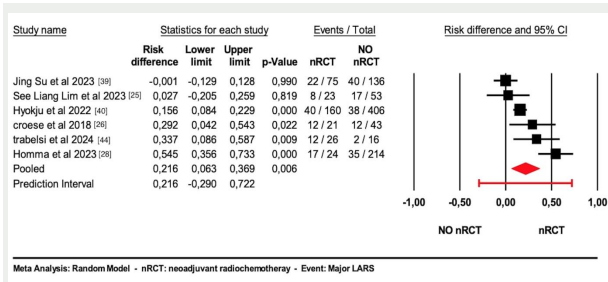


Figure 5. Forest plot of Neoadjuvant radio chemotherapy versus NO.

However, there was substantial heterogeneity that remained unexplained, PI (-0,290 to + 0,722)

Anastomotic leakage

Five studies had compared major LARS in both groups “anastomotic leakage” and “no anastomotic leakage”. There was no significant statistical difference between the two groups and there was no heterogeneity (Tau²: Zero), with a tendency to develop major LARS in the “anastomotic leakage” group (Figure 6).

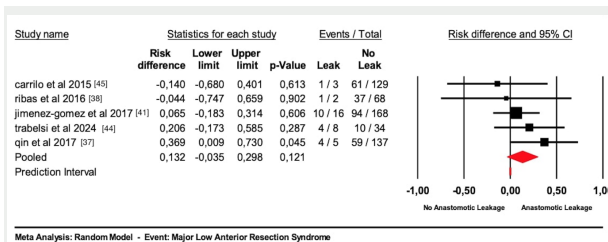


Figure 6. Forest plot of Anastomotic leakage group versus No Anastomotic leakage group regarding the outcome Low Anterior Resection Syndrome.

Surgical approach

Seven studies compared major LARS in both groups “laparoscopic surgery” and “open surgery”. There was no significant statistical difference between the two groups and there was a substantial heterogeneity. In other words, similar population would have less major LARS with the laparoscopic approach and other similar population would have less major LARS with the open approach (Figure 7).

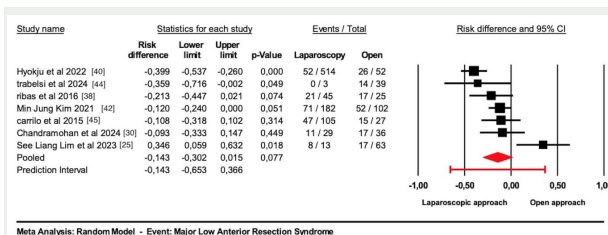


Figure 7. Forest plot comparison between Laparoscopic and Open approaches regarding the outcome Low Anterior Resection Syndrome.

Duration on diversion stoma

The duration of stoma closure was compared in six

studies, which found no statistically significant difference between the 'major LARS' and 'no major LARS' groups ($p=0.081$). However, there was a tendency to conclude that the shorter the time between surgery and stoma closure, the lower the major LARS rate. Nonetheless, there was substantial heterogeneity (Figure 8).

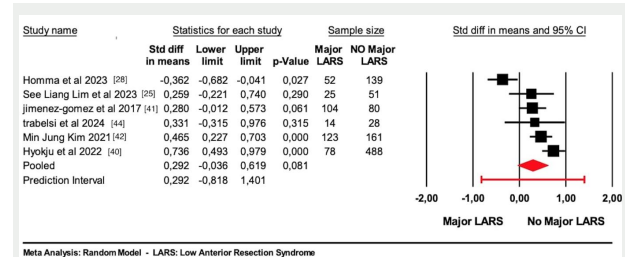


Figure 8. Forest plot comparison between Major LARS versus No Major LARS regarding duration on diversion stoma.

Recommendations according to the literature findings

Regarding our data, the pooled prevalence of major LARS was 36.8% (95% CI 30.1%–44.0%), with a wide prediction interval (12.0%–71.2%) reflecting substantial heterogeneity. This indicated that more than one-third of patients undergoing sphincter-preserving surgery for rectal cancer experience major LARS

For the risk factors:

- Tumor location < 5 cm from the anal margin was associated with a higher risk of major LARS (50.6% vs 18.3%; $p < 0.001$), with trivial heterogeneity. Therefore, tumor location < 5 cm should be considered a strong independent predictor of major LARS (LoE 2a – GoR B).
- Neoadjuvant radiochemotherapy was also significantly associated with increased risk of major LARS ($p = 0.006$), though with substantial unexplained heterogeneity (LoE 2a (-) – GoR B).
- Anastomotic leakage showed no significant association with major LARS, with null heterogeneity (LoE 2b – GoR C).
- Surgical approach (laparoscopic vs open) did not show a statistical difference in the occurrence of major LARS, with substantial heterogeneity between studies (LoE 2b – GoR C).
- Duration of stoma closure was not predictive of Major LARS (LoE 2b – GoR C).

DISCUSSION

This meta-analysis found a “major LARS” prevalence of 36.8%, with a 95% Confidence Interval ranging from 30.1% to 44.0%. It showed a wide Prediction Interval (12.0% - 71.2%) reflecting a substantial heterogeneity of the studies due to the presence of risk factors influencing the prevalence of LARS: neoadjuvant radio chemotherapy and tumor location < 5cm. Other meta-analyses (6–9) reported major LARS prevalence rates that are quite similar, ranging from 40,9% to 49.7%. These four meta-analyses (6-9) did not assess heterogeneity correctly. The authors (6-9) reported I^2 values to evaluate variability between studies which is not the appropriate metric (16).

In 2017, Borenstein and Higgins et al. reported a paper entitled “ I^2 is not an absolute measure of heterogeneity” (46). Heterogeneity should be evaluated by the prediction interval with its variance Tau^2 (46). Our Meta-analysis evaluated heterogeneity by using the prediction interval which showed a substantial heterogeneity when we calculated the pooled prevalence.

Neoadjuvant radio chemotherapy was assessed as an important risk factor for major LARS in our study, with results comparable to other meta-analyses (6,8,9); some even investigated the type of protocol used (7), finding that the long-course protocol was associated with a higher risk of developing major LARS.

Seven studies, conducted on LARS, have highlighted the negative effect of neoadjuvant radiotherapy on bowel function after anterior resection of the rectum, with a significant impact on quality of life (8,27,32,33,35,37,47). The potential effects of irradiation on the sphincter complex have also been studied. Arias et al (48) suggested that possibly reducing the radiation dose could improve sphincter function post-treatment.

As concerns tumor location (distance between the lower limit of the tumor and the anal margin), several studies (8,11,27) showed that a low tumor location, and the level of the anastomosis, are considered as a risk factor for major LARS. Furthermore, Croese's meta-analysis(6) showed that, six out of 11 studies identified a statistically significant association between low tumor location and the development of major LARS.

Two studies (3,49) indicated that, in order to remove a low rectal tumor completely, the anal sphincters and peripheral nerves may be damaged, leading to the disappearance of the recto-anal inhibitory reflex, decrease of the distensibility of colonic plasty. Our meta-analysis concluded that low tumor location was a predictive factor of LARS, as mentioned in Figure 3, the confidence interval and the prediction interval were complementary to conclude in the same way: these two intervals were positive, greater than the line zero.

Regarding other risk factors, our meta-analysis did not identify anastomotic leakage as a predictive factor for major LARS. However, the meta-analysis by Ye et al. (8) found that anastomotic leakage was a major risk factor. The discrepancy between our findings and those of the previous meta-analysis may be explained by several factors. The definition of anastomotic leakage varied across studies, ranging from clinically evident leaks to radiologically detected or subclinical leaks. In addition, the small number of studies included in our analysis may have limited the statistical power to detect a significant association. Furthermore, heterogeneity in patient populations, surgical techniques, and perioperative management may also have contributed to these differences. Following anastomotic leakage in rectal cancer patients, the resulting local inflammation can cause infection or fibrosis around the anastomotic site. Consequently, it reduced rectal volume and compliance, affected bowel function, increases LARS scores, and decreased quality of life (50).

Although our meta-analysis indicated a trend toward lower rates of major LARS with shorter intervals between

surgery and stoma closure, this factor wasn't identified as an independent predictor of major LARS. In contrast, a meta-analysis published in 2021 (7) found that the increased risk of major LARS may be attributed to the presence of a defunctioning ileostomy, as well as to the delayed ileostomy closure. Therefore, early reversal should be considered an important part of the patient care pathway (51). Although laparoscopic surgery provides enhanced visualization of the autonomic nerves, allowing for more precise dissection (52), our meta-analysis did not find any difference between laparoscopy and laparotomy in terms of major LARS.

Several limitations should be considered for our meta-analysis. Mainly, most of the included articles are retrospective, and there is heterogeneity in the evaluation of the primary outcome (major LARS). As most of the included studies are retrospective, this may introduce inherent biases. Recall bias could affect the accuracy of patient-reported LARS scores, particularly when long-term functional outcomes are assessed. In addition, selection bias may be present, as patient inclusion and follow-up completeness varied across studies. These biases may have influenced the estimated prevalence and strength of association of risk factors for major LARS. Furthermore, the analysis of predictive factors for LARS varied across studies. For instance, even for the same factor such as tumor location, the definition of a low tumor differed between studies: in the study by See Liang Lim et al. (25), a low tumor was defined as being located less than 8 cm from the anal margin, whereas in the study by Nicotera et al., the cutoff was less than 5 cm (29). Larger future prospective studies with standardized tomographic screening are needed to homogenize the results.

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