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A Meta-Analysis of the Prevalence of Low Anterior Resection Syndrome and Systematic Review of Risk Factors

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A META-ANALYSIS OF THE PREVALENCE OF LOW ANTERIOR RESECTION SYNDROME AND SYSTEMATIC REVIEW OF RISK FACTORS

Running Title: A Meta-analysis of Low Anterior Resection Syndrome

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PRISMA Checklist

Attached

A Meta-Analysis of the Prevalence of Low Anterior Resection Syndrome and Systematic Review of Risk Factors

Abstract

Aim:

To summarize the reported prevalence and causative factors of Low Anterior Resection Syndrome (LARS) from studies using the LARS score.

Methods:

A systematic literature search was conducted using Pubmed, Ovid Medline and the Cochrane database. Searches were performed using a combination of MeSH (medical subject headings) terms and key terms. Studies that were included used the LARS score as their primary collection tool. Studies were excluded if initial surgery was not for malignancy, or if the majority of LARS scores were from patients less than 1 year post initial surgery or closure of diverting stoma. Eligible studies were assessed with a validated quality assessment tool prior to performing a meta-analysis with quality effects model. Meta-analysis was conducted with prevalence estimates that had been transformed using the double arcsine method.

Results:

Following the initial search and implementation of inclusion and exclusion criteria 11 studies were deemed suitable for meta-analysis. Meta-analysis found the estimated prevalence of major LARS was 41% (95% CI 34 -48). Where possible outlier studies were excluded, the prevalence was 42% (95%CI 35-48). Radiotherapy and tumour height were the most consistently assessed variables, both showing a consistent negative effect on bowel function. Defunctioning ileostomy was found to have a statically significant negative impact on bowel function in 4 of 11 studies. The majority of reported data has been produced by groups in Denmark and the United Kingdom with limited numbers provided by other locations. Available data is heterogenous with some variables having limited numbers, making meta-analysis of certain variables impossible.

Conclusions:

There is significant prevalence of Low Anterior Resection Syndrome following oncological rectal resection. A low anastomotic height or history of radiotherapy are major risk factors.

Key Words

Low anterior resection; Rectal Neoplasms; Bowel Dysfunction; Quality of life; Prevalence

1.0 Introduction

With advances in both surgical and adjuvant therapies for rectal cancer, there has been a decrease in the need for abdominoperineal resection (APR) with end colostomy. Low anterior resection with total mesorectal excision (LAR) has become the preferred procedure in suitable patients with mid and low rectal cancers [1]. Since then, there has been an increasing recognition of Low Anterior Resection Syndrome (LARS) which includes incontinence (to faeces and flatus), urgency, diarrhoea, frequency and clustering of bowel motions [2,3]. Patients with LARS often experience either a pattern of urgency and incontinence, or alternately, obstructed defecation. Bowel adaptation is thought to occur by about 18 months post operatively, after which, further improvement with time is unlikely. This means that a proportion of patients will have permanent alteration in bowel function [4]. Furthermore, with improved oncological outcomes, patients with persistent symptoms will be burdened with LARS into the longer term [5].

Currently the volume of literature related to this topic is growing, however there is variability of results with estimated prevalence of LARS ranging from 19-52% [6]. This variability arises from the use of different data collection tools which are not specific to LARS and often don't take quality of life into consideration. This has made any meta-analysis impossible. The LARS score was thus developed to allow for the collection of comparable data which would make such a meta-analysis possible and allow for a more accurate estimation of the true prevalence of LARS. The LARS score is a validated a scoring system which is specific for LAR patients, taking into account impact of bowel dysfunction on overall quality of life

[3]. The aim of this review was to collate and analyse published data on the prevalence of LARS after 1 year follow-up, from studies which utilise the LARS score. Risk factors continuing to contribute to LARS after 1 year were also assessed.

2.0 Methods

2.1 Database search

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines. A systematic literature search was conducted using Pubmed, Ovid Medline and the Cochrane database. A date range for the search was set from 2005 to March 2017. Searches were performed using a combination of MeSH (medical subject headings) terms and key terms; “Low anterior resection syndrome”, “Anterior Resection syndrome”, “Prevalence”, “Incidence”, “bowel function”, “Quality of life” and “Low anterior resection syndrome score”. All articles collected by the initial search were screened by title and abstract to determine their relevance to the study questions. The bibliographies of relevant articles were cross referenced with the list of journals from the initial search and appropriate articles were subsequently added.

2.2 Study selection

The criteria for inclusion were primary studies which assessed prevalence of LARS using LARS score (Figure 2.) and assessed causative factors for LAR. Only articles written in English were included. Studies that were excluded i) used alternate data collection tools, ii) majority of functional data was from patients with period of intestinal continuity of less than 12 months, iii) patients with non-malignant indication for surgery.

2.3 Quality Assessment

Prior to meta-analysis the selected articles were critically assessed and scored using the validated quality assessment QUADAS2 tool, independently by 2 authors.

2.4 Data Extraction

The measured prevalence (percentage of population studied) of major, minor and no LARS was recorded for each study along with patient numbers and follow up period (see Table 1). Variables for systematic review including patient variables (age and gender) and treatment variables (anastomotic height, neoadjuvant therapy, anastomotic technique, anastomotic leak and duration of ileostomy) were recorded for each study, see (Tables 2 & 3).

3.0 Statistical Analysis

Meta-analysis was undertaken using a quality-effects model (factoring the QUADAS2 scores) conducted using the MetaXL (www.epigear.com) add-in for Microsoft Excel. A pooled prevalence figure was calculated with 95% CI. We conducted the meta-analysis with prevalence estimates that had been transformed using the double arcsine method. This method avoids variance moving towards zero as a result of estimate of the study tending towards 0% or 100%, resulting in over estimation of weight in meta-analysis.

4.0 Results

The initial search identified 271 articles. See figure I., for selection of final 11 articles.

Using the quality assessment tool (QUADAS2) these 11 studies were found to be good quality however there were a number of weakness identified. Although anastomotic height is one of the main recognised causative factors for LARS, it was only clearly described in the data of 3 studies [6-8]. Although all studies except 1 used LARS score data only for patients who had intestinal continuity for 12months or more, the exact time from initial surgery to closure of diverting stoma was poorly described in the majority of studies [3,7,9-12]. The form of anastomotic technique or pouch formation were also often not described in a large proportion of studies [1,3,9,11,13]. Of the 11 studies which met inclusion criteria, 5 were from Denmark or the United Kingdom (see Table 1) [1,7,9-11]. The largest patient numbers were also from these studies.

The prevalence of LARS from these studies is shown (see Table 1), where major LARS has significant impact and minor and no LARS is considered together as they both have minimal impact on quality of life. All studies, with the exception of 2, [1,14] had a mean or median follow up of 18months or greater (see Table 1) indicating that the majority of questionnaire results would represent mid to long term function following surgery. The prevalence ranged widely from 17.8%-56%, and the estimated meta-analysis prevalence using the quality effect model was 41% (95% CI 34 -48), $I^2=91%$, $p<0.001$ (Table 4, Figure 3). The study with the lowest rate of major LARS excluded patients who had undergone neoadjuvant therapy which has likely played a major role in the low rate of major LARS identified [6]. The same study also had a larger percentage of patients with tumours in the upper rectum (>40%) which again is known to reduce the risk of developing significant bowel disturbance post-operatively. Hughes et al included patients who had had restoration of intestinal continuity for a minimum of only 12weeks, which is a potential reason for their higher rate of LARS being 56% as it is unlike that at this stage there would be any meaningful bowel adaptation.

The same study also identified that the patient group who completed the survey <1yr following surgery had a mean LARS score of 35.5 compared to 27.9 which was the mean score found in patients completing the questionnaire >4years following surgery. However, a sensitivity analysis which excluded the studies by Ekkarat and Hughes found a prevalence rate of 42% (95% CI 35-48), which is close to the original meta-analysis prevalence.

Radiotherapy used in either a neoadjuvant or adjuvant setting was the most consistently assessed variable affecting major LARS (see Table 2) and reached statistical significance in 8 of the studies [1,3,6-9,12,13]. Hughes et al determined that neoadjuvant radiotherapy in their population was associated with a 20-fold increased risk of developing major LARS ($p < 0.01$). Bondeven et al also found that neoadjuvant therapy was an independent risk factor for the development of major LARS (OR:3.5, 95% CI) even with a larger remnant rectum. Ekkarat et al who excluded patients that had neoadjuvant therapy identified through multivariate analysis that post-operative radiotherapy was the only factor associated with major LARS (OR 6.5, 95% CI;2.37-18.15).

Tumour height and hence anastomotic level was the second most commonly analysed variable and 6 of the 11 studies identified a statistically significant association with the development of major LARS [3,7-9,12,13]. Bondeven et al used post-operative Magnetic Resonance Imaging (MRI) to accurately assess remnant anastomotic height to assess its impact of post-operative bowel function. They found that the risk of major LARS was 46% in patients with less than 4cm of remnant rectum preserved compared to 10% in patients with >4cm of remnant rectum preserved ($P < 0.0001$). Ekkarat et al correlated anastomotic level with major LARS to demonstrate that an anastomotic height of <5cm had a higher risk of developing major LARS. Bregendahl et al found that TME was an independent risk factor

for the development of major LARS (adjusted OR for major LARS 2.31, CI;1.69-3.16) due to a likely associated low anastomotic height.

Four studies (see Table 3) looked at the presence of an ileostomy and duration prior to reversal, all of which found an increased risk of major LARS [1,6,12,13]. Having a complication of an anastomosis, in particular an anastomotic leak, was consistently found to be associated with increased risk of developing major LARS and in one study this association was found to be significant [8]. Age was found to have a statistically significant association with the development of major LARS in only one study [13]. Sturiale et al found that having surgery at 70 years increased the risk of developing major LARS whilst most other studies found a trend in younger patients (<65 or 70yo) for developing major LARS which did not reach statistical significance [1,6,8,10-12,14]. None of these studies found any significant or consistent association between gender and the development of LARS.

5.0 Discussion

Our meta-analysis showed a prevalence of persistent significant (major) LARS of 41% with narrow 95% confidence levels of 34-48%, where the reported prevalence ranged widely from 17.8-56%. This should raise the need of awareness of the condition and its morbidity. This meta-analysis investigating the prevalence of LARS is the first of its kind and has been made possible by the creation of a validated data collection tool that is specific for patients with altered bowel habit following LAR. Early literature investigating LARS used a variety of data collection tools which only reflected a component of the syndrome, such as incontinence, which would thus only identify a proportion of patients with LARS. Also, the use of various data collection tools lead to the collection non-comparable data that could not

be subjected to meta-analysis. Therefore this study offers a more accurate representation of the prevalence of LARS as it has used a specific scoring system designed for this purpose. Although the studies reported from patient populations which are heterogenous for treatment and patient related factors, this nonetheless likely closely represents the patients after LAR presenting for clinic follow-up. The main limitation of the meta-analysis was that most of the larger studies were from Denmark and the United Kingdom. As well as this, 3 of the studies from Denmark have been produced by the same institution with overlapping time periods, which may have resulted in same patient data being used in multiple studies. This may therefore not represent the overall worldwide LARS prevalence, and possibly the prevalence in any locality taking into account the possible impact of factors including diet and life-style adaptations to LARS which impacts upon the quality of life. Nonetheless, we hope that this review will generate interest in LARS prevalence studies over the world using the increasingly accepted standardized LARS score so that comparable results will be generated with a scoring system specific for LAR patients

Our systematic review also showed that LAR patients may have undergone different variations in surgical technique, or reconstruction and adjuvant therapy regimes necessary for the complex management of rectal cancer. Radiotherapy and level of colorectal anastomosis were the most consistently reported factors to significantly negatively impact on major LARS. Radiation both preoperatively and post operatively have also been found to have negative effects on function in LAR patients with greater numbers of incontinent episodes and decreased rectal sensation [15]. The potential effects of radiation on the sphincter complex have been investigated and it is likely that reducing the dose leads to improvement in sphincter function post treatment [16]. With regard to the increased rates of major LARS in patients with a previous diverting ileostomy, the relationship is expected to be due to underlying reason for the ileostomy rather than the ileostomy itself. Given that a temporary

ileostomy is used more commonly in lower resections, which is known to increase the risk of LARS, this would likely account for its association with major LARS. Most treatment regimens for anastomotic leak involve having a diverting ileostomy for a more prolonged period. Since anastomotic leak has been identified as a risk for developing major LARS this association likely plays a major role in patients with long term ileostomies having worse bowel function once reversed. A recent randomised control trial comparing LARS scores for patients treated with a temporary stoma and no stoma found no statistical difference in major, minor and no LARS when comparing the 2. The same study however found that patients treated with a temporary stoma more often reported incontinence for flatus and liquid stools and had a higher total LARS score [17]. The authors of this study conceded that data was still relatively preliminary and further confirmation studies are required.

Although colonic adaption over a period of about 12 months may improve bowel function, we confirm that a significant population of patients continue to suffer into the mid and long term. The cause of LARS is complex and likely multifactorial. Impaired anal sphincter function has been identified in patients following LAR and has been shown to be associated with poorer functional outcome [2,6,18]. It is suspected that the resultant impairment of the anal sphincter could be due to both direct injury to the anal sphincter as well as damage to its innervation with pelvic dissection of the rectum [2,18]. Altered intestinal motility due to disruption of the parasympathetic innervation of the bowel has been suggested to play a role in the development of LARS [2,19]. Emmertsen et al found that a hyperactive postprandial response in the neorectum in non-irradiated TME patients likely played a significant role in the development of LARS and was potentially due to the denervation of the neorectum. Interestingly the same study found no significant differences in sphincter pressure between no LARS and Major LARS patients suggesting a more proximal cause of bowel dysfunction such as neorectum impaired compliance or gastrointestinal dysmotility [19]. Nonetheless, a

further limitation of the metanalysis is the lack of definitive data regarding the pattern of LARS into the longer term. Further studies need to be conducted for follow-up LARS over time, particularly with improved long-term cancer survival.

Our review on the prevalence and morbidity of LARS suggests that the latter must be taken into appropriate consideration in the management of rectal cancer, although oncological considerations need to be prioritized. Further investigating patient selection for neoadjuvant therapy and improving the sensitivity of investigation techniques such as MRI may further improve patient selection and result in less post treatment morbidity [20]. In addition, partial mesorectal excision for upper rectal cancers where appropriate rather than total mesorectal excision should be adhered to as the oncological outcomes are equivalent and functional outcomes appear to be superior [21]. The use of rectal reservoirs to alleviate symptoms following LAR have been shown to improve function with decreased frequency and urgency of defecation [22], at least in the early postoperative period. Prior to resection, patients also require counselling and education as to what their expected functional outcome may be. A consent aid has been developed, which aims to predict post treatment functional outcome for rectal cancer patients based on what surgery, and or other treatment factors they will be receiving for their cancer [23]. Furthermore, there should be a sympathetic awareness and willingness to address LARS in postoperative follow-up rather than focussing only on oncological issues. Therapies such as biofeedback, sacral nerve modulation and rectal irrigation have been reported and are showing promise in improving patients anorectal function and quality of life post LAR [24-27].

6.0 Conclusion

The estimated prevalence of major LARS in this meta-analysis is 41% (95% CI 34 -48), at 1 year after surgery. Radiotherapy, whether pre or post-operative, and low tumour height are the 2 factors which have the greatest negative impact of patients bowel function following LAR. The presence of a temporary stoma and having a stoma for a prolonged period of time are also associated with poorer bowel function. However, this is likely a reflection of the tumour height and possible complications of surgery which may also impact negatively on bowel function. Further studies to better define the prevalence in various parts of the world as well as to clarify the pattern of LARS over time with long term follow-up is required.

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Table 1. Summary of studies prevalence of LARS and follow up period

<u>Study</u>	<u>Patient Number</u>		<u>Time from Surgery to Survey*</u>	<u>Major LARS</u>	<u>Minor LARS</u>	<u>No LARS</u>
	<u>Total eligible</u>	<u>% Response</u>				
Emmertsen 2012, Denmark	478	92.8%	Mean follow up time 55.5months	190/478 (40%)	119/478 (25%)	169/478 (35%)
Juul et al. 2014, Denmark + UK	579	80%	Median follow up 4.9yrs (range 1.6-12.4yrs)	214 (47%)	103 (23%)	134 (30%)
Bondeven et al 2015, Denmark	125	100% Due to retrospective design	Median follow up 18months (range 12- 24months)	47 (35%)	30 (24%)	48 (35%)
Hain 2016, France	135	87%	Median 43 (range 12- 117months)	36 (23%)	68 (50%)	23 (31%)
Bregendahl 2013, Denmark	1087	90.1%	Median 54months (range 25-97months)	383 (41%)	221 (23.5% %)	334 (35.5%)
Juul et al. 2014, multicentre international Denmark, Spain, Sweden, Germany	1061	76%	Mean 5.6yrs (SEM 2.3)	414 (52%)	155 (19%)	227 (29%)
Luca et al 2016, Italy	23	100%	12months following reversal of ileostomy	5 (23.8%)	4 (19%)	12 (57.1%)
Hughes 2017, Wales	85	80%	Median 248days (range 17- 1664days)	38 (56%)	12 (18%)	18 (26%)
Carillo et al. 2016, Spain	195	70%	Median 37months	62 (47%)	25 (18.9%)	45 (34.1%)
Ekkarat et al. 2016, Thailand	129	Not discussed, however base on study design would be expected to be ~100%	Median 38months (range 11.7-117.5months)	23 (17.8%)	22 (17%)	84 (65.4%)
Sturiale 2016, Italy	110	84.5%	Median 13.7yrs (range 10.9-18yrs)	19 (20.5%)	25 (27%)	49 (52.5%)

Table 2. Risk factors for LARS, Neoadjuvant therapy and Anastomotic Height

<u>Study</u>	<u>Radiotherapy / Chemoradiotherapy</u>	<u>Anastomosis height</u>
Emmertsen 2012, Denmark	<i>Significant (p < 0.0001)</i> Radiotherapy (20.6% of patients) risk factor for LARS	<i>Significant - p < 0.0001</i> tumour height > or < 5cm patient numbers not shown in data.
Juul et al. 2015, Denmark + UK	<i>Significant (p=0.018)</i> Neoadjuvant (n: 141, median LARS: 30) No neoadjuvant (n: 306, median LARS: 28)	<i>Significant (p=0.018)</i> <5cm from anal verge (n=72, median LARS score 32) >5cm from anal verge (n=378, median LARS score 28)
Bondeven et al 2015, Denmark	<i>Significant (p= 0.002)</i> Long course (n. 25/20%) neoadjuvant chemoradiation: independent risk factor for major LARS (OR: 3.5, 95% CI: 1.15-9.4)	<i>Significant (p= 0.0001)</i> <4cm remnant rectum: 46% risk of major LARS - n. 22/48 major LARS in <4cm >4cm remnant rectum: 10% risk of major LARS - n. 5/47 major LARS in >4cm TME performed in anastomoses 2-8cm from anal verge PME performed in anastomoses 5-13cm from anal verge
Hain 2016, France	<i>Significant (p=0.0007)</i> Long course radiotherapy (n.96/71%): independent risk factor for major LARS	Risk factors for major LARS: intersphincteric resection (likely used to tumours <4cm) (p=0.003) hand-sewn CAA (used for tumours <4cm) (p= 0.0008)
Bregendahl 2013, Denmark	Neoadjuvant (n.96/9% short course, n.95/9% long course): increased risk of developing major LARS (OR 2.48; 95% CI: 1.73-3.55)	TME for lower cancers: increased risk of major LARS (OR= 2.31; 95% CI: 1.69-3.16) TME n.555, tumours 0-10cm n.453 PME n.383, tumours >10cm n.478

Juul et al. 2014, multicentre international Denmark, Spain, Sweden, Germany	<i>No statistical analysis discussed</i> Radiotherapy (n.431/41%): major LARS (n.279) minor LARS (n.79) no LARS (n.73)	<i>No statistical analysis discussed</i> Mean tumour distance from anal verge: major LARS – 9 cm n.414/796 minor LARS – 9.6 cm n.155/796 no LARS - 10.6 cm n.227/796
Luca et al 2016, Italy	<i>No significant</i> association with major LARS and long course neoadjuvant (n.18/78%) *This was not displayed in the data	<i>No significant</i> association with major LARS. All patients had tumours within 5cm of anal verge, mean 3.17cm *This was not displayed in the data
Hughes 2017, Wales	<i>Significant (p<0.01)</i> Neoadjuvant radiation (n=19/22%): 20 fold increased risk of developing major LARS	<i>Not significant (p=0.37)</i> Tumour < 8cm increased risk of major LARS (OR 1.6; 95% CI: 0.6-4.1) Major LARS Tumour <8cm n. 18/22 Major LARS Tumour >8cm n. 20/34
Carillo et al. 2016, Spain	<i>Significant (p=0.019)</i> long course radiotherapy (n=30/48) developed major LARS	<i>Significant (p<0.001)</i> Risk factors for major LARS: TME n=56/91 PME n=6/35 * Did not discuss anastomotic/tumour height, however TME for middle and lower tumours, PME for upper rectal tumours
Ekkarat et al. 2016, Thailand	<i>Significant (p<0.001)</i> Association of adjuvant radiotherapy and development of major LARS (OR 6.55; 95%CI; 2.37-18.15) *Neoadjuvant excluded	Anastomotic level <5cm higher risk of LARS (OR 3.76; 95%CI; 1.34- 10.61)
Sturiale 2016, Italy	<i>Significant (p=0.04)</i> Major LARS: Neoadjuvant radiotherapy n=13/19	<i>Significant p=0.003</i> Major LARS: tumours <5cm from anal verge n=8/19

Table 3. Risk factors for LARS, Patient and Ileostomy Factors

<u>Study</u>	<u>Age</u>	<u>Gender</u>	<u>Anastomotic Leak</u>	<u>Timing of Ileostomy Reversal</u>	<u>Anastomosis type</u>
Emmertsen 2012, Denmark	Not discussed as possible causative factor	Not discussed as possible causative factor	Not discussed as possible causative factor	Not discussed as possible causative factor	Type of reconstruction not recorded in database
Juul et al. 2015, Denmark + UK	Not discussed as possible causative factor	Not discussed as possible causative factor	Not discussed as possible causative factor	Not discussed as possible causative factor	Not discussed
Bondeven et al 2015, Denmark	No association found between major LARS and age	No association found between major LARS and gender	Anastomotic leak was an exclusion criteria	Not discussed as possible causative factor	End to side Vs End to End. Not found to have significant impact.
Hain 2016, France	<i>Not significant (p=0.202)</i> >70yo less likely to develop LARS (OR 0.49, CI 95%:0.14-1.42. P= 0.202)	<i>Not significant (p=0.37)</i> Males less likely to develop LARS (OR 0.66, CI95%:0.28-1.64)	<i>Significant (P= 0.02)</i> Symptomatic anastomotic leak: independent risk factor for major LARS	Not discussed as a possible causative factor	Hand-sewn coloanal anastomosis greater risk of Major LARS <i>p = 0.003</i> Side to end anastomosis greater risk of developing major LARS <i>p = 0.01</i>
Bregendahl 2013, Denmark	< 64yo more likely to develop major LARS (OR= 1.9; 95% CI 1.43-2.51)	Females more likely to develop major LARS (OR= 1.35; 95% CI; 1.02-1.79)	Anastomotic leak increased risk of developing major LARS (OR 2.06; 95% CI:0.93-4.55)	Not discussed as possible causative factor	Colonic pouch Vs straight-to-end or side-to-end anastomosis No Statistical difference found
Juul et al. 2014, multicentre international Denmark, Spain, Sweden, Germany	<i>No statistical analysis discussed</i> The mean age of patients with: major LARS: 66.4yo minor LARS: 68.3yo no LARS: 70.2yo	<i>No statistical analysis discussed</i> Major LARS (n=414) males (n=232): 56% females (n=182) = 44% *55% of total patients male	Not discussed as possible causative factor	Not discussed as possible causative factor	Not discussed

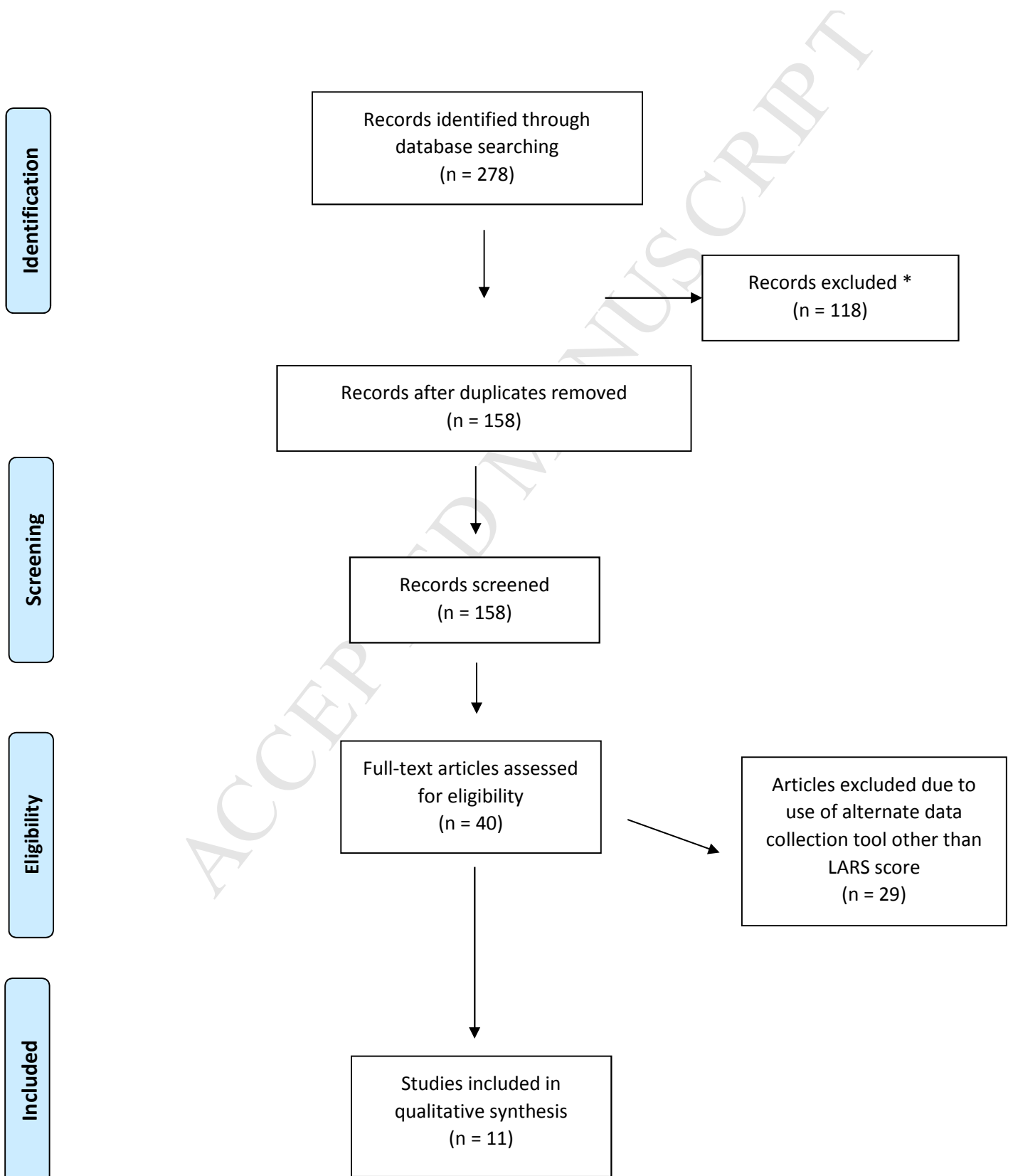
Luca et al 2016, Italy	<i>No significant</i> association with major LARS. *This was not displayed in the data	<i>No significant</i> association with major LARS. *This was not displayed in the data	Not discussed as possible causative factor	Not discussed as possible causative factor	All patients had hand-sewn coloanal anastomosis
Hughes 2017, Wales	<i>Not significant</i> ($p=0.14$) >70yo reduced risk of major LARS (OR 0.5; 95% CI:0.2-1.3)	<i>Not significant</i> ($p=0.73$) Male gender increased risk of developing LARS (OR 1.2; 95% CI:0.4-3.5)	<i>Not significant</i> ($p=0.26$) Anastomotic leak increased risk of major LARS (OR 3.4; 95% CI; 0.4-32.2)	<i>Significant</i> ($p=0.03$) ileostomy closure after 1 year increased risk of major LARS (OR 3.7; 95% CI: 1.1-13.1)	Not discussed
Carillo et al. 2016, Spain	<i>Not significant</i> ($p=0.45$) Average age of: Major LARS - 69.1yo Minor LARS 66.3yo No LARS 68.3yo	<i>Not significant</i> ($p=0.82$) Major LARS: Males n=43/90 Females n=19/42	<i>Not significant</i> ($p=0.641$) Major LARS: With anastomotic complication n= 1/3 With no anastomotic complication n=61/129 * Reported <u>anastomotic complications</u> not leak specifically.	<i>Significant</i> ($p=0.003$) Major LARS: No diverting stoma n=19/59 Diverting stoma n=43/73 *Timing not discussed, however presence of stoma vs no stoma noted	Lower rates of major LARS reservoir (colonic pouch or colopalsty) $p= 0.017$
Ekkarat et al. 2016, Thailand	<i>Not significant</i> ($p=0.72$) Major LARS: <60yo n=12/63 >60yo n=11/66	<i>Not significant</i> ($p=0.18$) Major LARS: Males n=9/67 Females n=14/62	Not discussed as a possible causative factor	<i>Significant</i> ($p=0.024$) Major LARS: No diverting stoma n=11/88 Diverting stoma n=12/41 *Timing not discussed, however presence of stoma vs no stoma noted	For ULAR (n. 38) 27anastomosed with stapler, and 11 with handsewn. Hand-sewn found to have higher rates of LARS. Not significant
Sturiale 2016, Italy	<i>Significant</i> ($p=0.003$) Major LARS: >70yo n=10/19	<i>Not significant</i>	<i>Not significant</i>	<i>Significant</i> ($p=0.002$) Median time of closure of ileostomy: major LARS: 5.4 months minor LARS: 3.3 months no LARS: 2.6 months	Colorectal end to end stapled anastomosis

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Table 4. Meta-analysis results of LARS score prevalence

	Major LARS	Minor LARS	No LARS
Prevalence	41%	24%	35%

Figure 1 Flow chart of study selection. * Studies excluded as they did not primarily focus on assessment of post operative bowel function following anterior resection.



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Figure 2. English validated version of Low Anterior Resection Syndrome (LARS) score.

The aim of this questionnaire is to assess your bowel function. Please tick only one box for each question. It may be difficult to select only one answer, as we know that for some patient's symptoms vary from day to day. We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into account and focus on answering questions to reflect your usual daily bowel function.

Q.1 : Do you ever have occasions when you cannot control your flatus (wind)?

<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	4
<input type="checkbox"/> Yes, at least once per week	7

Q.2 : Do you ever have any accidental leakage of liquid stool?

<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	3
<input type="checkbox"/> Yes, at least once per week	3

Q.3 : How often do you open your bowels?

<input type="checkbox"/> More than 7 times per day (24 hours)	4
<input type="checkbox"/> 4-7 times per day (24 hours)	2
<input type="checkbox"/> 1-3 times per day (24 hours)	0
<input type="checkbox"/> Less than once per day (24 hours)	5

Q.4 : Do you ever have to open your bowels again within one hour of the last bowel opening?

<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	9
<input type="checkbox"/> Yes, at least once per week	11

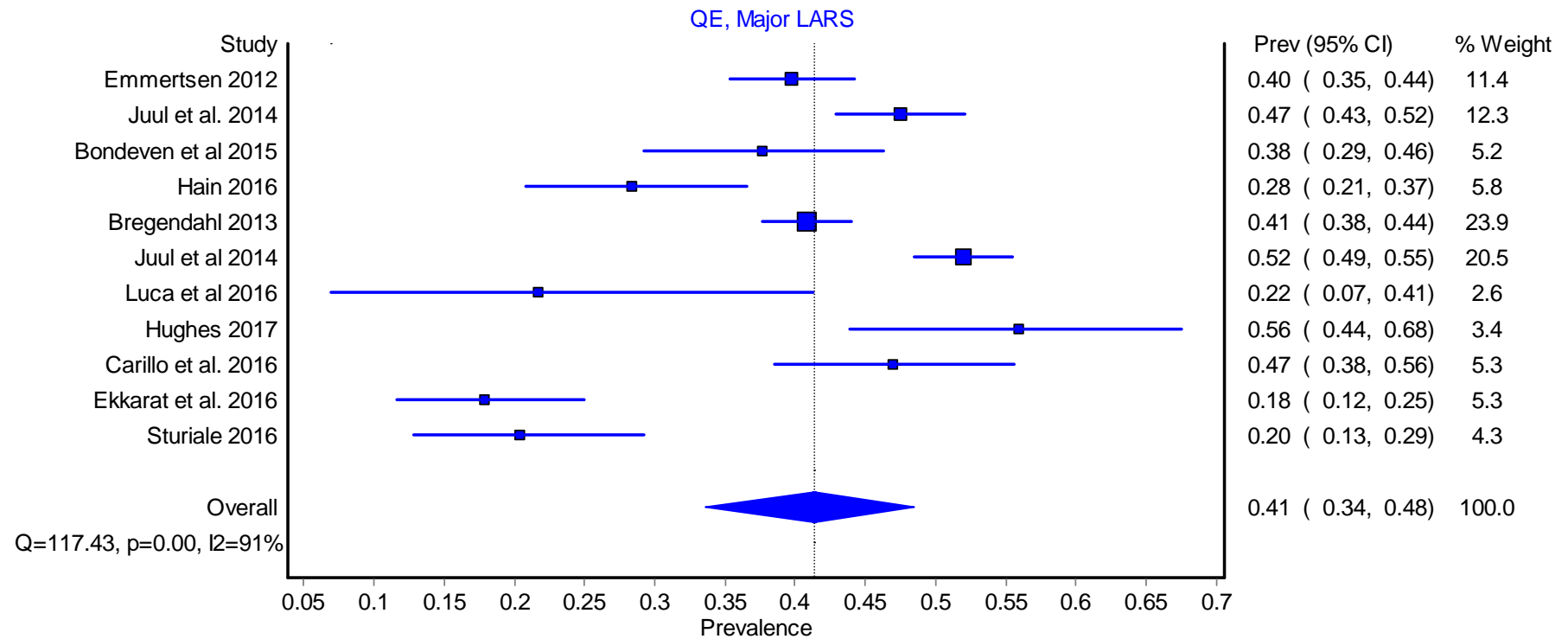
Q.5 : Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

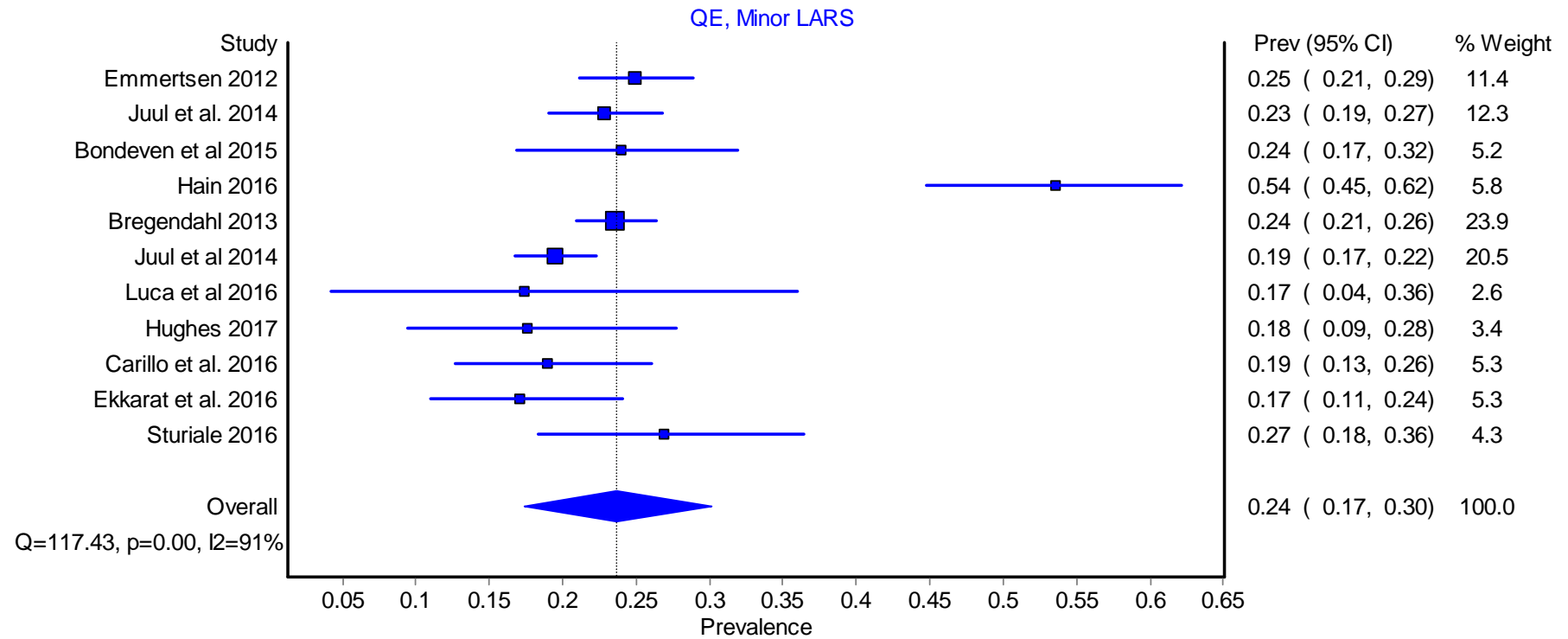
<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	11
<input type="checkbox"/> Yes, at least once per week	16

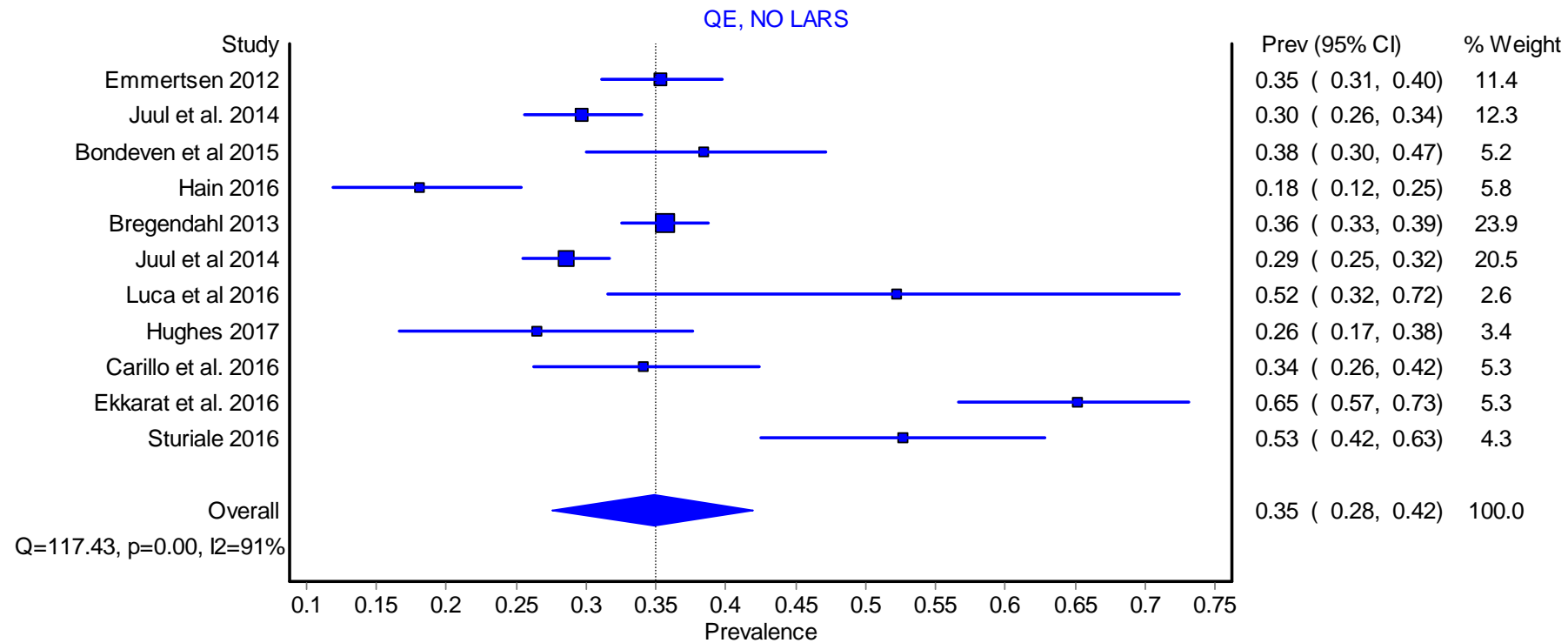
Add the scores from each of the five answers to one final score.

Interpretation: 0-20 = No LARS 21-29 = Minor LARS 30-42 = Major LARS

Figure 3. Forest plots of meta-analysis for major minor and no LARS prevalence with a 95% confidence interval.







Highlights

- Low anterior resection syndrome (LARS) more common due high rates of sphincter preserving surgery
- The LARS score was designed to make a meta-analysis of the syndrome possible
- Risk factors need to be defined in order to attempt preventing LARS
- Need to increase awareness of syndrome to appropriately council patients

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

The authors of this study have no conflicts of interest to disclose

Please state any sources of funding for your research

At present there has been no funding supplied to the authors of this study

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

No ethical approval was sought for this study as it is a meta- analysis and systematic review.

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry and the unique identifying number of the study. You can register your research at <http://www.researchregistry.com> to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Alex Croese- Study design, Data collection, Quality assessment, writing
James Lonie- Quality assessment and writing
Alexandra Trollope- Study design and writing
Vankat Vengaveti- Data analysis .
Yik-Hong Ho- Study design, writing and supervisor

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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