



ORIGINAL ARTICLE

# Prognostic and predictive value of interstitial cells of Cajal populations following stapled transanal rectal resection (STARR) in patients with obstructed defecation syndrome

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## Abstract

**Objective:** The present study was designed to evaluate the functional outcome of stapled transanal rectal resection (STARR) and to examine the relationship between the population density of the interstitial cells of Cajal (ICC) and the efficacy of the STARR operation in the management of obstructed defecation syndrome (ODS) patients.

**Methods:** Full-thickness rectal samples were obtained from 50 ODS patients who underwent STARR. Samples were analysed using ICC immunohistochemistry. Clinical and functional parameters obtained with defecography and anorectal manometry were compared with 20 controls.

**Results:** ICCs were significantly decreased in patients in the submucosal (SM), intramuscular (IM) and myenteric (MY) regions when compared with the control group ( $P < 0.05$ ). The mean pre-operative Cleveland Constipation Score (CCS) was  $24.2 \pm 4.1$ , whilst the CCS at 1, 2, 3, 4 and 5 years post-operatively decreased significantly ( $P < 0.05$ ). At 3 post-operative years, 58.3% (28/48) of the patients reported a favorable outcome ( $CCS \leq 10$ ). On univariate analysis, the functional results were worse in those with pre-operative digitation ( $P = 0.017$ ), a decreased ICC-MY cell population ( $P = 0.067$ ), a higher resting anal canal pressure ( $P = 0.039$ ) and a higher rectal sensory threshold ( $P = 0.073$ ). Multivariate analysis showed the decreased ICC-MY cell population was an independent predictor for low unfavorable functional outcome (odds ratio = 0.097, 95% confidence interval: 0.012–0.766).

**Conclusions:** STARR achieved acceptable results at the cost of a slight deterioration over a more prolonged follow-up. Patients with a decreased ICC number in the rectal specimen showed an unfavorable functional outcome where pre-operative histological assessment of a full-thickness rectal sample might predict for the functional outcome following STARR.

Submitted: 27 April 2018; Revised: 11 July 2018; Accepted: 10 September 2018

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**Key words:** interstitial cells of Cajal; obstructed defecation syndrome; stapled transanal rectal resection (STARR); functional outcomes

## Introduction

Obstructed defecation syndrome (ODS) is a relatively common problem and is mainly characterized by prolonged or repeated straining at stool, an excessive time spent in the toilet, variably reported rectal discomfort and perineal pain, and a sense of incomplete evacuation. Frequently, perineal support and/or digital insertion into the vagina or anus to assist defecation is volunteered as ancillary information and in many there is a history of laxative abuse and repeated enema use [1]. Along with functional causes in the genesis of ODS, there may also be anatomical causes, most notably rectocele and rectal intussusception, both of which may require selective surgical correction. For this purpose, a variety of surgical techniques that include abdominal, vaginal, transanal and perineal approaches have been devised. More recently, several stapled surgical approaches, such as the stapled transanal rectal resection (STARR) procedures (including the PPH-STARR, the Transtar and the TSTStarr Plus) have all been proposed as variant techniques designed to provide a transanal full-thickness rectal resection. One of the goals of these comparative procedures is the correction of the demonstrable ODS-related anatomical and structural anomalies [2–4].

The selective use of the STARR procedure is accepted as an effective therapy for ODS management. Despite the fact that a decision-making algorithm defining its place has been previously published, it is anticipated, however, that the levels of improvement reported in patient symptoms may decline over time. For this reason, further objective data better defining the precise pre-operative characteristics that would indicate patient suitability for a STARR operation and that are predictive of post-STARR outcome are required [5, 6].

The interstitial cells of Cajal (ICC) have been postulated to play an important role in the control of gut motility [7], where there are extensive reports demonstrating the association between chronic constipation and either a loss of or injury to the ICC population [8]. There are currently, however, limited data that examine the ICC distribution in the subgroup of ODS patients presenting with intractable symptoms [9]. The purpose of the present study was to explore the prognostic factors for functional outcomes of the patients who underwent STARR, with a particular focus on assessment of the impact of the ICC population in patients with ODS undergoing a STARR procedure and to determine whether there was any correlation between morphological abnormalities and either symptoms or surgical outcome. An aim was to establish in this group potential predictive factors for both STARR indication and success.

## Patients and methods

Approval for the conduct of the study was obtained from the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University. Written informed consent was signed by each patient prior to his/her inclusion in the study after discussion of the principles of the TSTStarr Plus procedure and its potential morbidity. The study prospectively assessed patients derived from the Department of Coloproctology between November 2012 and June 2015.

## Inclusion/exclusion criteria

All patients underwent a thorough clinical examination, with performance of colonoscopy and defecography and selected use assessment of gastrointestinal transit. Patients were considered for surgery after failing medical therapy that comprised 1.5L/day fluid intake, the institution of a high-fiber diet, regular laxative use and biofeedback therapy for a minimum period of 3 months. Surgery was indicated if there was persistence of at least three of the specific symptoms of ODS, namely a feeling of incomplete evacuation, painful evacuatory effort, failure to defecate with a long time spent in the bathroom, defecation with the use of perineal support and/or odd posture, digital evacuatory assistance or defecation obtained only with the use of enemas. Further inclusions occurred if there was radiologically proven internal rectal prolapse (>10mm) and/or an associated rectocele (>3cm) with significant rectal barium entrapment after defecation.

Patients were not considered for surgery if they met the exclusion criteria previously published in the Pioneer Consensus Statement for the use of STARR [10] or if there were any additional exclusion criteria as listed by Corman *et al.* [1]. These latter characteristics included: active anorectal infection, anorectal stenosis, secondary proctitis (e.g. inflammatory bowel disease, radiation-induced), enterocele at rest (low, stable, fixed), chronic diarrhea, prior anterior resection with rectal anastomosis, foreign material (mesh, slings) adjacent to the rectum, coincident severe psychiatric disorder, rectovaginal fistula, anal incontinence (Cleveland Clinic Florida Incontinence-CIS Score >7) [11] or gynecological and/or urinary pelvic floor pathology requiring specific treatment. Intra-operative technical factors that precluded the safe execution of the operation such as significant rectal or perirectal fibrosis discovered during surgery were also excluded from analysis.

## Data collection

Clinical data as above were collected with the defecographic findings that included the measured mean rectocele size, the degree of perineal descent, the presence of an enterocele, puborectalis dyssynergia and/or a sigmoidocele. Anorectal manometric findings including the mean resting pressure, the functional anal canal length, and the maximal squeeze pressure were recorded. Anorectal sensitivity was assessed on balloon distension of the minimum threshold volume, the rectal sensory threshold and the maximal threshold volume. Patients were assessed before and after surgery with the Cleveland Constipation Score (CCS) for constipation [12].

## Surgical technique

The TSTStarr Plus technique has been previously described [4]. Briefly, the procedure is performed using a specialized stapler kit (Touchstone, Suzhou, China) that consists of a large-head diameter stapler (36 mm), a circular anal dilator (CAD), an anoscope and an obturator that can be inserted into the CAD. After repeated gentle anal dilatation, the lubricated obturator is inserted and a gauze swab assists in prolapsing the rectal wall. The parachute technique is used to insert a purse-string with six short running sutures (2/0 Vicryl suture) at the 1, 3, 5, 7, 9 and 11 o'clock positions. Following insertion of the stapler anvil above the purse-string suture, the rectal tissue is pulled into the stapler housing by traction on the sutures, checking the vagina in

women so as to avoid inadvertent incorporation of the vaginal mucosa. In order to ensure a dry anastomotic line, we frequently supplement the staple edge with additional hemostatic sutures.

### Sample disposal and immunohistochemistry evaluation

Surgical specimens were immediately fixed in 10% neutral-buffered formalin for 24 hours with transverse sections obtained. Hematoxylin and Eosin staining were performed on conventional histology 3- $\mu$ m paraffin-embedded sections. A minimum of 10 slides per patient were processed for immunohistochemistry. For this, consecutive formalin-fixed, paraffin-embedded sections were de-waxed and rehydrated through decreasing alcohol series and distilled water. ICCs were defined using an anti-Kit antibody (rabbit polyclonal antibody, IgG, dilution of 1:400, Dako, Carpinteria, CA, USA). All immunohistochemical assessments were made using a Benchmark XT automated staining system (Ventana Medical Systems, Inc., Tucson, AZ, USA). For antigen retrieval, the slides were heated with the Cell Conditioning Solution 1 (CC1; Ventana) for 30 minutes and the acid of a suitable kit was used to block the endogenous biotin. After completion of the staining process, the slides were removed from the autostainer, counterstained with Hematoxylin, dehydrated and mounted in permanent mounting medium. Kit-positive mast cells served as the internal control; a Ventana dispenser filled with non-immune serum at the same concentration of the primary antibody was assessed as the negative control substituting the primary antibody.

Rectal tissue from 20 patients, who did not undertake radiation therapy pre-operatively, undergoing rectal resection for cancer was obtained as comparative control tissue with sections that were confirmed as tumor-free taken at least 2 cm from the neoplastic edge.

All slides were examined by two independent pathologists blinded to the sample origin. The number of immune-positive cells was calculated and expressed as the mean of cells on 10 well-stained and well-oriented microscopic fields at 40 $\times$ , 100 $\times$  and 400 $\times$  magnification for each region of interest (ROI), respectively. If there was disagreement, a consensus was reached after joint review. There were three identified populations of ICC taken into consideration: ICC-SM (along the submucosal surface of the circular muscle bundle), ICC-MY (within the inter-muscular space between the circular and longitudinal muscle layers where the highest yield of ICC was expected) and ICC-IM (within the muscle fibers of the circular or longitudinal layers).

### Statistical analysis

Analyses were performed using the SPSS Version 20.0 software package (SPSS Inc., Chicago, IL, USA). Parameters were recorded as medians and inter-quartile ranges. The two-sample t-test or the Mann-Whitney U test were used where appropriate to compare quantitative variables between the groups with the Chi-square or Fisher's exact test being used for qualitative variables where indicated. Univariate analysis and multivariate regression modeling were used with logistic regression in order to analyse the risk factors affecting recurrence. The independent variable  $P < 0.10$  in univariate analysis was incorporated into the multivariate logistic regression equation. The forward method was used to screen the independent variables. A two-sided  $P$ -value  $< 0.05$  was considered statistically significant.

## Results

Between November 2012 and June 2015, a total of 50 patients underwent the STARR procedure using the TSTStarr Plus. The

**Table 1.** Functional results following stapled transanal rectal resection (STARR) in patients with obstructed defecation syndrome

Time	No.	Cleveland Constipation Score	P-value
Pre-operative	50	24.2 $\pm$ 4.1	–
Post-operative 1 year	50	8.4 $\pm$ 3.1	<0.001
Post-operative 2 years	49	9.6 $\pm$ 4.6	<0.001
Post-operative 3 years	48	11.4 $\pm$ 5.5	<0.001
Post-operative 4 years	27	11.0 $\pm$ 3.8	<0.001
Post-operative 5 years	17	11.7 $\pm$ 3.7	<0.001

study cohort included 46 women, with a mean age of 52  $\pm$  12 years. Patients were grouped according to their complete follow-up periods of 1, 2, 3, 4 or 5 post-operative years with a median follow-up of 52 months (range, 36–65 months) (Table 1).

### ICC expression

Conventional histology showed no specific abnormalities in the sample. Concerning the immunohistochemistry of ODS patients and controls, there was a significant decrease in the patients of ICC-MY expression compared with normal controls (100  $\pm$  26 vs 190  $\pm$  29 cells,  $P < 0.05$ ). Similar changes were noted in ICC-SM expression (11  $\pm$  4 vs 17  $\pm$  5 cells,  $P < 0.05$ ) and ICC-IM expression (17  $\pm$  9 vs 30  $\pm$  11 cells,  $P < 0.05$ ). Representative images are shown in Figure 1.

### Constipation severity score

The mean CCS was 24.2  $\pm$  4.1 prior to surgery and decreased significantly to 8.4  $\pm$  3.1 after the STARR procedure by the first post-operative year ( $P < 0.05$ ). There was a further, less steep decline in the CCS over more prolonged follow-up (9.6  $\pm$  4.6 at 2 years, 11.4  $\pm$  5.5 at 3 years, 11.0  $\pm$  3.8 at 4 years and 11.7  $\pm$  3.7 at 5 years) with each score during follow-up showing significant improvement over the pre-operative score ( $P < 0.05$ ) (Figure 2).

### Univariate and multivariate analysis of predictors of functional outcome

Univariate analysis of potential prognostic factors predictive of functional outcomes after the STARR procedure divided those with favorable (CCS  $\leq$  10) and unfavorable (CCS  $>$  10) post-operative outcomes according to CCS at 3 post-operative years. Independent patient-related variables included patient age, multiparity and constipation-specific symptoms that included any feeling of incomplete evacuation, painful evacuatory effort, failure to defecate (with a long time spent in the bathroom), the need for perineal support and/or odd posturing during defecation, digital evacuatory assistance or defecation induced only with the use of enemas. Defecographic findings of relevance included the mean rectocele size, the degree of perineal descent and the presence of a concomitant enterocele, puborectalis dys-synergia or a sigmoidocele. Anorectal manometric findings of importance included the mean resting anal canal pressure, the length of the anal canal, the maximal anal squeeze pressure and the rectal sensation (minimal sensory threshold volume, rectal sensory threshold and maximal rectal sensory threshold volume). The number and different types of rectal ICC were also factored into the analysis.

Univariate analysis showed significant differences between favorable and unfavorable outcomes in digitation ( $P = 0.017$ ), the decline in the number of ICC-MY cells ( $P = 0.067$ ), the resting

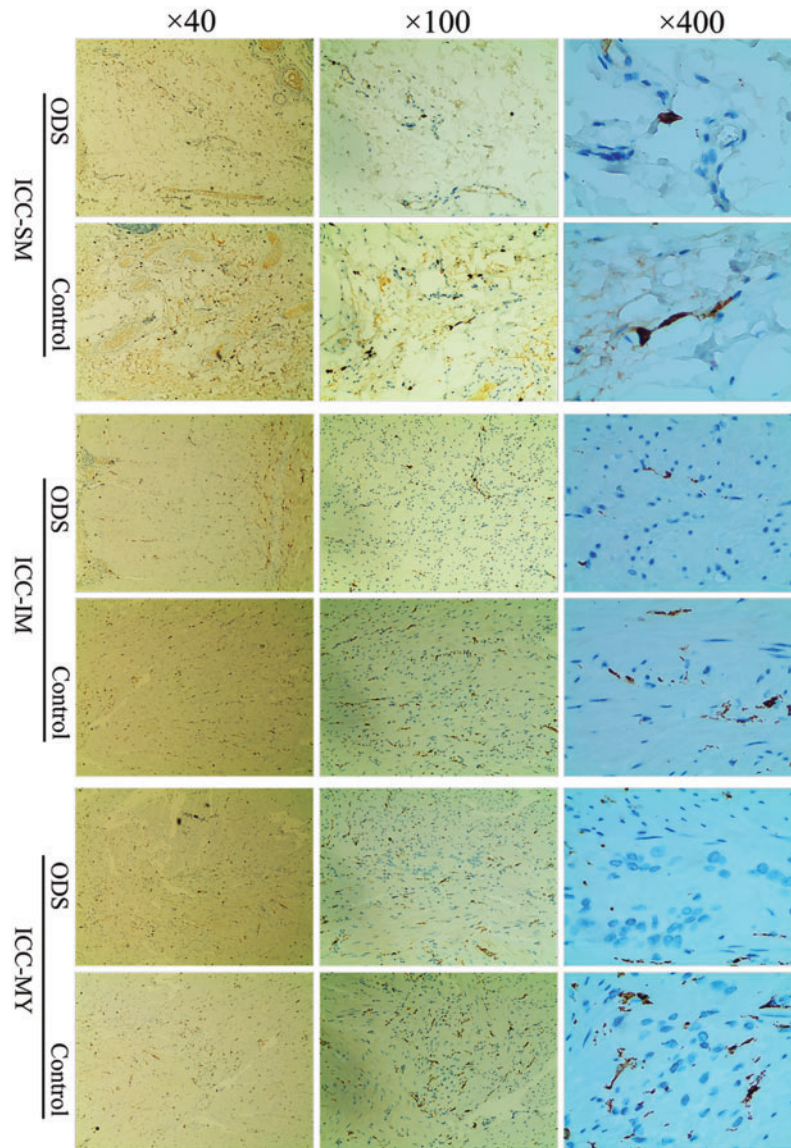


Figure 1. Quantitative alterations of interstitial cells of Cajal (CD117, original magnification: 40 $\times$ , 100 $\times$  and 400 $\times$ ) in patients with obstructed defecation syndrome (ODS). Decreased number of interstitial cells of Cajal (ICC) in the submucosal (SM), intramuscular (IM) and myenteric (MY) regions in ODS patients compared to controls.

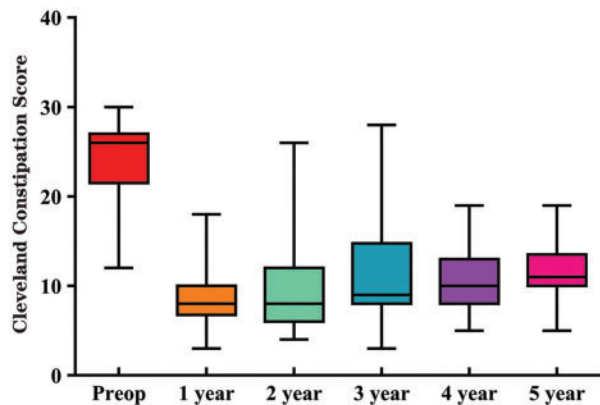


Figure 2. Symptom Severity Score for obstructed defecation. Results are shown for all patients pre-operatively ( $n=50$ ) and for groups with post-operative follow-up periods of 1, 2, 3, 4 and 5 years. The numbers of patients in each post-operative group were 50, 49, 48, 27 and 17, respectively.

anal canal pressure ( $P=0.039$ ) and the rectal sensory threshold ( $P=0.073$ ) (Table 2). Stepwise multivariate logistic regression analysis inserting the significant factors defined on univariate analysis showed two independent variables of significance for functional post-operative outcome, namely the ICC-MY count (odds ratio [OR] 0.097, 95% confidence interval [CI]: 0.012–0.766,  $P=0.027$ ) and the resting anal sphincter pressure (OR 1.044, 95% CI: 1.006–1.084,  $P=0.023$ ).

## Discussion

Several studies have reported the medium-term efficacy of the STARR procedure for the relief of ODS-specific symptoms, generally demonstrating high patient satisfaction rates [13–18]. Similar clinical results were obtained in our present study where we were able to show that defecation difficulties were significantly improved by STARR. There was, however, a slight

Table 2. Univariable analysis of pre-operative factors in relation to constipation at post-operative 3 years

	CCS ≤ 10 (n = 28)	CCS > 10 (n = 20)	Odds ratio (95% CI)	P-value
Mean age, years	52 ± 11	51 ± 12	–	0.903
Multiparous (≥2), n (%)			1.037 (0.173–6.233)	0.968
Yes	9	7		
No	4	3		
Incomplete evacuation, n (%)			0.711 (0.215–2.349)	0.575
Yes	19	12		
No	9	8		
Painful evacuatory effort, n (%)			1.137 (0.338–3.827)	0.836
Yes	9	7		
No	19	13		
Straining, n (%)			<0.001	0.999
Yes	27	20		
No	1	0		
Use of perineal support and/or odd posture, n (%)			0.833 (0.255–2.718)	0.762
Yes	18	12		
No	10	8		
Digitation, n (%)			0.216 (0.061–0.764)	0.017
Yes	17	5		
No	11	15		
Use of enemas, n (%)			0.579 (0.177–1.894)	0.579
Yes	19	11		
No	9	9		
Rectal intussusception, n (%) <sup>a</sup>			0.424 (0.087–2.061)	0.288
Yes	11	7		
No	4	6		
Mean rectocele size, mm <sup>a</sup>	19.3 ± 4.9	23.2 ± 12.6		0.328
Perineal descent, n (%) <sup>a</sup>			0.393 (0.031–4.917)	0.469
Yes	14	11		
No	1	2		
Enterocoele, n (%) <sup>a</sup>			0	1.000
Yes	1	0		
No	14	13		
Puborectalis dyssynergia, n (%) <sup>a</sup>			<0.001	0.999
Yes	0	2		
No	15	13		
Sigmoidocele, n (%) <sup>a</sup>			0.229 (0.022–2.377)	0.217
Yes	4	1		
No	11	12		
Decreasing ICC-SM number, n (%)			2.318 (0.717–7.490)	0.160
Yes	17	8		
No	11	12		
Decreasing ICC-MY number, n (%)			0.321 (0.095–1.083)	0.067
Yes	12	14		
No	16	6		
Decreasing ICC-IM number, n (%)			1.800 (0.559–5.792)	0.324
Yes	18	10		
No	10	10		
Mean anal canal resting pressure, mmHg	57.7 ± 21.4	79.3 ± 38.6	–	0.039
Mean anal canal maximum squeeze pressure, mmHg	146 ± 48	151 ± 35	–	0.736
Mean anal canal length, cm	1.5 ± 0.6	1.8 ± 1.0	–	0.287
Mean rectal minimal volume threshold, ml	48 ± 14	54 ± 13	–	0.190
Mean rectal sensor threshold, ml	72 ± 29	90 ± 27	–	0.073
Mean rectal maximum volume threshold, ml	133 ± 26	130 ± 26	–	0.709
Mean anorectal angle (°) on defecation	128 ± 17	118 ± 35	–	0.361
DUAC on defecation, mm	52.7 ± 13.1	49.5 ± 10.5	–	0.495
Depth of intussusception, mm	23.1 ± 7.3	22.7 ± 4.5	–	0.905

<sup>a</sup>Defecographic results were not available in some patients.

CCS, Cleveland Constipation Score; CI, confidence interval; DUAC, distance between the anorectal junction (the upper part of anal canal) and pubococcygeal line; ICC-SM, interstitial cells of Cajal along the submucosal surface of the circular muscle bundle; ICC-IM, interstitial cells of Cajal within the muscle fibers of the circular or longitudinal muscle layers; ICC-MY, interstitial cells of Cajal within the inter-muscular space between circular and longitudinal muscle layers (myenteric region).

deterioration in clinical status over time, with the principal symptoms minimized at 1 post-operative year but gradually worsening over a more prolonged follow-up. Our results are akin to previously reported literature where there is a trend for constipation scores to increase only after 2 years of post-operative follow-up [19]. It is likely that these findings are indicative of a slow change in the anatomy that ultimately results in late relapse, suggesting the need to assess post-STARR patients beyond a few years.

Puborectalis dyssynergia was present in 4% of patients operated upon and did not represent in our series a contraindication to STARR surgery [20, 21]. However, our findings are inconsistent with other reports [20, 22], which suggest that patients with pre-operative puborectalis dyssynergia are less likely to be satisfied with their surgery and also that they are more likely to develop a recurrence. In interpretation of their analysis, patients with puborectalis dyssynergia (which is one type of marker of slow-transit constipation or rectal inertia) are less likely to benefit from surgery, since this does not address the underlying cause of their symptoms [23]. This view would be supported by those reports that have suggested that the functional outcomes of rectocele repair in those patients with coincident anismus are similar to those in patients without evidence of anismus [24]. These data should be viewed with caution, however, since the methods used for anismus diagnosis (electromyography, balloon expulsion and evacuation proctography) varied widely between studies. The present study showed that patients with an increased pre-operative resting anal canal pressure had an unfavorable operative outcome, suggesting a value in anorectal manometry as an operative discriminator.

The negative finding concerning digitation is controversial. Pre-operative vaginal digitation has been reported in between 20 and 75% of patients presenting with ODS potentially correlating with a successful outcome following surgery [25, 26]. Despite a similarity with our findings, it is accepted that improved fecal evacuation after surgery may be reported by patients independently of any history of digitation [27].

Bassotti et al. [28] examined 17 rectal specimens derived from patients with ODS showing an increased number of ICC-MY and ICC-SM cells when compared with controls with a normal level of ICC-IM cells. In this regard, it is suggested that a decrease in ICCs may be a compensatory mechanistic response to obstructed defecation. In the present study, by comparison, we found that the number of ICC-SM, ICC-MY and ICC-IM cells were all significantly reduced in ODS cases. These results, although inconsistent with other reports, may, however, represent a more accurate ODS pathological phenotype. Of note, the number of ICC-MY, ICC-IM and ICC-SM cells in the colon in patients with slow-transit constipation are significantly decreased when compared with controls reflecting the pathological state in this condition [8]. Since our logistic regression analysis revealed that a reduced ICC-MY cell population correlates with an unfavorable post-operative outcome, we would suggest that the number of ICCs plays an important role in the constipation and ODS pathogenesis. Pre-operative immunohistochemistry of a full-thickness rectal sample specimen may potentially be predictive for the functional outcome following the STARR procedure for ODS. In addition, further studies needed to confirm these findings, since the cause and effect and relationship with ICC is unknown.

In summary, STARR achieved acceptable results at the cost of a slight deterioration over a more prolonged follow-up.

Patients with a decreased ICC cell population in the rectal specimen showed an unfavorable post-operative outcome. This study suggests that pre-operative histological study of a full-thickness rectal sample might predict the functional outcome following the STARR procedure.

## Acknowledgements

This work was supported by the National Key Clinical Discipline. J.-P.W. and D.-L.R. are the principal investigators and responsible for the study plan. H.-C.L., H.-X.C., Y.-X.Z., Q.Z., J.L. and Y.-J.X. drafted the manuscript. D.-L.R. performed all of the surgical procedures and finalized the manuscript. All authors have read and approved the final version of the manuscript.

## Funding

This work was supported by the National Natural Science Foundation of China (No. 81603628), Medical Scientific Research Foundation of Guangdong Province, China (No. A2015180) and Sun Yat-Sen University Clinical Research 5010 Program (No. 2017017).

Conflict of interest statement: none declared.

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