Awareness and Knowledge of Low Anterior Resection Syndrome (Lars) in Colorectal Surgeons: A Cross-sectional Survey

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Research

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Abstract

Background More than 50% patients suffered from low anterior resection syndrome (LARS) after low anterior resection, and their quality of life is predominantly determined by colorectal surgeons' awareness and knowledge of LARS. We conducted the survey to find out the weakness in the management of patients' functional recovery after surgery and explore targeted training pathways to improve doctor's ability to deal with LARS.

Methods An anonymous paper-based survey among colorectal surgeons was performed across the country.

Results 252 questionnaires were collected and analyzed with the effective rate of 86.6%. Most of the respondents were highly educated and experienced in gastroenterology. The mean age was 39.9 ± 9.20 years. In multivariate Logistic regression analysis, surgeons with MD, PhD degree (OR: 2.843, 95%CI: 1.441-5.609, $p = 0.003$) and national academic membership (OR: 2.063, 95%CI: 1.010-4.214, $p = 0.047$) were associated with surgeons' emphasis on follow-up. 65.1% of respondents underestimated the prevalence of LARS. Chief/deputy chief, national academic membership and annual surgeries ≥ 50 (42.7% vs 29.4%, $p=0.033$; 46.4% vs 30.0%, $p=0.007$; 46.0% vs 31.6%, $p=0.021$) were associated with high diagnostic rate of LARS but none of these factors were statistically significant in multivariate analysis. LARS score was the most popular scale in the evaluation of LARS severity. The feedback of the most common postoperative anorectal disorders by colorectal surgeons was significantly different from the items listed in the LARS score. 48.4% of respondents use drugs to treat LARS but therapies varied from surgeons to surgeons. *C*

onclusions There is a lack of knowledge relating to LARS in colorectal surgeons. Clinical guidelines should be developed to guide medical staff in effective management of patients with LARS.

Backgrounds

Rectal cancer is one of the most common cancer with the mortality of 3.2% of cancer death worldwide [1]. The treatment for rectal cancer requires a multidisciplinary approach with surgical resection as the cornerstone of treatment. Fortunately, with the progress of surgical techniques and neoadjuvant therapy, an increasing number of patients accept sphincter-preserving surgery [2]. At present, the mean 5-year survival rate after the treatment of rectal cancer is approximately 65%. If the disease is detected in an early stage, 5-year survival can even be as high as 90% [3].

With increasing survival there is a growing need for knowledge about the long-term side effects and functional results after the treatment [4]. It is reported 52%-76% of patients will suffer anorectal dysfunctions including fecal incontinence, urgency, frequency, constipation from low anterior resections (LAR) with total mesorectal excision (TME) [5,6]. LAR may modify anorectal anatomy and physiology inevitably and result in postoperative complications [7,8]. These combination of abnormal clinical manifestations after LARs was referred as “low anterior resection syndrome (LARS)” [9].

The quality of the assessment is predominantly determined by the instrument administered [10]. However, such assessment has been inconsistent due to the lack of a uniform definition of LARS [11], and the use of a large variety of nonvalidated questionnaires [12]. Although the prevalence of LARS is high, evidence-based therapeutic options are not currently available and postoperative strategies varied from surgeons to surgeons [5].

Early diagnosis and treatment of LARS are potential measures to improve quality of life, thus the improvement of colorectal surgeons' knowledge and awareness of LARS is necessary [13]. In this study, a paper-based questionnaire was used to inquire about Chinese colorectal surgeons about their follow-up, assessment, and treatment of patients with LARS. The purpose of this cross-sectional survey was to find out the weakness in the management of patients' postoperative functional recovery and lay the foundation for further doctor training.

Methods

Study Design and Participants

This project is designed and carried out between January 2015 and May 2017. 291 colorectal surgeons from twenty-eight regions in mainland China were enrolled in the survey. The formal ethical review was waived by our institutional review board.

Questionnaire

The questionnaire was sent to surgeons who were older than 25 years, had board certifications and received colorectal specialist training for more than one year. The questionnaire consisted of 13 questions. The questionnaire included the following four parts: (1) general information: gender, age, educational background, clinical title academic membership and hospital categories; (2) surgical information: sub-special (colorectal or surgical oncology), years in practice, the number of LAR completed every year as an surgeon in charge or first assistant, the number of LAR completed in the career, and the most commonly used surgical procedure; (3) follow-up: follow-up methods, the ratio of patients suffered from LARS after LAR as estimated, and the most common chief complaints of bowel dysfunction; (4) assessment and treatment of LARS: the method to assess and treat LARS. To minimize response bias, all the items in the questionnaire are objective questions. The value of “general information” and “surgical information” were encoded only if a single element is checked in each question. However, the options of Q9 and Q11 are not mutually exclusive (Fig. 1). The questionnaires underwent a rigorous scientific review

to ensure that they are of high quality. Respondents were required to finish the questionnaire within 15 minutes independently. The incomplete questionnaires and those finished overtime were discarded.

statistical analysis

Characteristic variables were presented as n (%), and tested by the chi-square test. Continuous variables were presented as mean $\pm$ SD. Univariate Logistic analysis was conducted for the assessment of factors associated with surgeons' emphasis on follow-up and their opinion on the prevalence of LARS. Variables with a $p < 0.1$ were included in the multivariate Logistic analysis which model was constructed. The results of multiple-choice question are shown as frequencies.

All statistics analyses were conducted using SPSS for Windows (version 25.0; IBM Corp., Armonk, NY). A 2-sided $p < 0.05$ was considered statistically significant.

Results

General information of the respondents

From January 2015 to May 2017, 291 questionnaires were sent out and 252 were retrieved with an effective rate of 86.6%. 39 questionnaires were discarded because of incomplete information ($n=35$) and complete the task overtime ($n=4$). All the colorectal surgeons eventually enrolled were from 28 provinces, autonomous regions and municipalities in mainland China. The mean age was 39.9 ± 9.20 years. Most of the respondents (174/252, 69.0%) have worked for more than 5 years as colorectal surgeons. 82.5% of participates were in tertiary comprehensive hospitals while 11.2% were from cancer hospitals. There were 62 respondents who completed more than 100 colorectal surgeries annually (Table 1).

Results of follow-up after LAR surgery

94 doctors said that their medical team would also conduct regular telephone follow-up or regular patient meetings in addition to outpatient follow-up. 124 doctors said that face-to-face follow-up was the only way to know patients' postoperative recovery, and 34 doctors said they never follow up after surgery. 94 respondents with multipath follow-up were regarded as "emphasize follow-up" and the remaining 158 were regarded as "ignore follow-up".

In univariate analysis, surgeons who emphasize follow-up were associated with MD, PhD diploma (OR: 2.916, 95%CI: 1.719-4.948, $p=0.001$), national academic memberships (OR: 2.684, 95%CI: 1.587-4.539, $p=0.001$), over 10 years' working experience (OR: 2.495, 95%CI: 1.477-4.214, $p=0.001$), LAR surgeries ≥ 50 per year (OR: 1.603, 95%CI: 0.953-2.696, $p=0.075$) and those take laparoscopic or robotic surgery as the most common surgical method (OR: 1.704, 95%CI: 1.017-2.857, $p=0.043$). No differences were observed in age, title, and hospital categories. In the multivariate Logistic regression analysis, MD, PhD degree (OR: 2.843, 95%CI: 1.441-5.609, $p=0.003$) and membership in national academy of gastroenterology (OR: 2.063, 95%CI: 1.010-4.214, $p=0.047$) were associated with consciousness of follow-up (Table 2).

Prevalence of LARS in colorectal surgeons' estimate

158 (62.7%, 158/252) surgeons reported that defecation dysfunction was less than 50%, 94 surgeons reported the prevalence of LARS was common (prevalence $\geq$ 50%) in postoperative patients (Fig. 2).

In univariate analysis, surgeons who thought LARS was common were associated with LAR $\geq$ 50 every year (OR: 1.846, 95%CI: 1.096-3.108, $p = 0.021$), national academic membership (OR: 2.022, 95%CI: 1.204-3.395, $p = 0.007$), and chief/deputy chief title (OR: 1.786, 95%CI: 1.046-3.049, $p = 0.033$). No difference was observed in age, educational background, years in practice, hospitals and surgical procedures. In the multivariate Logistic regression analysis, no factor was significant (Table 3).

The common complaints of LARS

Among the 17 common complains of defecation dysfunction listed in the questionnaire, the most frequently selected options were: incomplete defecation (160/252, 63.5%), loose stool incontinence (138/252, 54.8%), frequent defecation (126/252, 50.0%), constipation (76/252, 30.2%), and urgent defecation (70/252, 27.8%) (Fig. 3).

Assessment and treatment of LARS

LARS score was the most widely used instrument to assess the severity of LARS (40.6%), followed by Wexner score (11.3%), Mark's score (9.0%), Fecal Incontinence Severity Index (FISI) (6.3%) and others (1.6%). 29.7% of respondents assess the severity of LARS according to the subjective judgement.

Drug was chosen by 48.4% of surgeons, 26.6% of respondents prefer traditional Chinese medicine (TCM), 7.0% of them did not know how to treat with LARS. 5.5 % colorectal surgeons selected radical strategy such as permanent colostomy (Fig. 4).

Discussion

In this study, a questionnaire was used to investigate the awareness and knowledge of colorectal surgeons on LARS. In this sample of highly educated, rich surgical experience colorectal surgeons in China, some interesting findings regarding their awareness and knowledge of LARS emerge. The major findings of the study were divided into four parts, including colorectal surgeons' follow-up, the frequency of LARS, the assessment and treatment of LARS.

LARS may have a serious adverse impact on the quality of life of patients after rectal cancer surgery. Although most improvements of the functional impairment are known to accomplish by 6 to 12 months after the operation, long-term studies recently reported the duration of symptoms can last up to 15 years after operation [14,15]. Plenty of patients are likely to face challenges in recovery, some even have postoperative mental problems which wearing away their quality of life [16]. Some patients have to accept permanent colostomy because of intolerant LARS. Colorectal surgeons are facing serious challenges in the course of follow-up, diagnosis and treatment of LARS.

LARS usually became apparent after discharge from hospital, and it was important that it can be identified in follow-up. However, postoperative follow-up was completely neglected by a large number of colorectal surgeons (34/252,13.5%). Appropriate and effective follow-up methods are also very important. There are some inevitable disadvantages in outpatient follow-up. On the one hand, the time of outpatient service are limited, and some patients are unable to elaborate on their abnormal bowel movements. On the other hand, outpatient follow-up may not realize dynamic monitoring on defecation function and some out-of-town patients may not be reviewed by their surgeon in charge. From the above, the effectiveness of traditional outpatient follow-up was dubious. Routine follow-up has been delivered by telephone in some settings. The advantages of telephone follow-up have been well documented [17,18]. Telephone consultations may be preferable to patients because it may improve healthcare quality and decrease patients' burden [19]. In addition, telephone follow-up may decrease outpatient resource use [20]. We believe that doctors who use telephone or regular patients meeting follow-up as a supplement to outpatient emphasize more on postoperative follow-up of LARS. Highly educated surgeons and those joined national academy focus more on follow-up. The reason may be that they have a deeper understanding of LARS, possibly due to their wider access to the latest clinical and research findings. Besides, surgeons who preferred laparoscopic and robotic surgeries emphasized follow-up more. These minimally invasive procedures have been increasing in China recently [21]. Several randomized controlled trials indicated that minimally invasive surgeries showed satisfied short-term and long-term survival, but with less evidence on functional performance [22,23]. Therefore, these surgeons may retrieve functional information via follow-up.

The prevalence of LARS may be underestimated by Chinese colorectal surgeons. Literature shows that more than 50% of patients with rectal cancer will have different degrees of anorectal disorders after sphincter-preserving surgery [24]. Nevertheless, only 37.3% (94/252) of surgeons estimated the prevalence of LARS over 50%. In our survey, the frequency of colorectal surgeons encountering LARS patients has no relationship with surgeons' age, degree, clinical title, experience, hospitals and procedures. However, surgeons got membership of national academy and those performed more than 50 rectal cancer surgeries annually meet LARS patients more frequently (46.4% vs 30.0%, $P=0.007$; 46.0% vs 31.6%, $p = 0.021$). The reason may be that experienced surgeons have better diagnostic ability.

The manifestations of LARS varied. In recent years, the LARS score has been used for quick clinical evaluation of the severity of postoperative defecation dysfunction. In our survey, LARS score was the most popular instrument to evaluate the severity of LARS. LARS score was widely used since it was proposed in 2012 owe to its precision and simplicity [25]. The rating scale ranges from 0 to 42 points and patients are classified into three groups: "no LARS" (0–20 points), "minor LARS" (21–29 points) and "major LARS" (30–42 points). Major LARS was negatively associated with physical, emotional, and social function [13]. The LARS score quantifies the function of defecation from five most important items: incontinence of flatus, Incontinence of liquid stool, frequency, clustering, and urgency [26]. In our investigation, surgeons considered that the five most common defecation disorders were incomplete defection, incontinence for liquid stool, frequency, constipation, and defection urgency. This is not consistent with the five symptoms listed in the LARS score. 160 surgeons (160/252,63.5%) thought that

incomplete defecation was the most common symptom, which was not even listed in the LARS score. Similarly, symptoms such as constipation tenesmus and painful defecation were also chosen more frequently by surgeons than incontinence of flatus. Incontinence for flatus is the most easily ignored symptom by colorectal surgeons [27], although it is reported that over 40% of patients faced flatus incontinence affecting quality of life [28,29]. Clustering defecation, defined as repeated defecation within one hour, was a troublesome postoperative anorectal disorder. Up to 63.2% of patients undergoing anal preservation surgery with traditional end-to-end anastomosis occurs defecation clustering [30], this proportion was still 30% in patients with modified j-pouch anastomosis [31]. However, defecation clustering has not attracted much attention from colorectal surgeons. There was a significant difference between the items in the LARS score and the defecation disorders reported by Chinese colorectal surgeons. The LARS scale was first proposed by European experts, and the scale is based on the characteristics of Caucasians which may not be fully applicable to Chinese patients.

According to the European guideline, no comparative evidence on different treatments for LARS was available [32]. In our survey, nearly half of respondents use drugs to treat LARS but therapies varied from surgeons to surgeons. More than a quarter of respondents suggested patients seeking treatment at TCM. However, there is no reliable evidence-based medical evidence to support this decision. It deserved attention that 7% surgeons don't know how to treat with LARS and 5.5% of surgeons were very radical. Surgeries should be an alternative choice only if conservative treatment is ineffective [33].

There are a number of limitations in our survey. Firstly, the sample size is relatively insufficient and the sampling error was inevitable. Secondly, our survey was based on mainland China but it is unsure how well generalizable they are. Thirdly, all of the data were based on colorectal surgeons' subjective opinions and we don't know whether it is correspond to reality. Finally, the thirteen questions listed in the questionnaire may not cover all of the problems related to LARS.

In conclusion, according to our survey, Chinese colorectal surgeons do not pay enough attention to LARS and have insufficient awareness of LARS. It is necessary to strengthen medical education for all colorectal surgeons and guidelines should be developed to guide surgeons in better management of patients with LARS.

Abbreviations

LAR: Low anterior resection; LARS: Low anterior resection syndrome; TME: Total mesorectal excision; SD: Standard deviation; OR: Odds ratio; MD: Doctor of medicine; MS: Master of science; PhD: Doctor of Philosophy; REF: Reference; CI: Confidence interval; FISI: Fecal Incontinence Severity Index; TCM: Traditional Chinese medicine

Declarations

Acknowledgments

None.

Competing interests

None.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The formal ethical review was waived by our institutional review board.

Consent for publication

Not applicable

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Authors' contributions

Yingjiang Y designed the research and revised the draft, Sen H and Peng G were the main investigators and data recorders, they analyzed and interpreted the data. Sen H and Fan L wrote the manuscript together. All authors approved the final version of the manuscript.

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Table 1. General information of the respondents

Characteristics	n (%)
Total	252(100)
Age(year)	39.9±9.2
Sex (Male)	250 (99.2)
Education background	
MD	44(17.4)
MD, MS	104(41.3)
MD, PhD	104(41.3)
Titles	
Resident	54(21.4)
Attending	54(21.4)
Deputy chief	58(23.0)
Chief	86(34.1)
Memberships of enterology	
National	112(44.4)
Provincial	26(10.3)
Municipal	40(15.9)
None	74(29.4)
Years in practice	
≤5	78(31.0)
5-10	54(21.4)
10-20	52(20.6)
≥20	68(27.0)
Hospitals	
Tertiary comprehensive hospital ^a	208(82.5)
Tertiarycancer hospital ^a	26 (10.3)
Primary comprehensive hospital ^b	16 (6.3)
Primarycancer hospital ^b	2 (0.9)
Number of LARs(cases/year)	

≤20	120 (47.6)
20-50	32 (12.7)
50-100	38 (15.1)
≥100	62 (24.6)
Primary surgical procedure	
Open surgery	144 (57.1)
Laparoscopic surgery	98 (38.9)
Robotic surgery	10 (4.0)

Statistics presented as mean ± SD, or N (%)

MD: Doctor of medicine; MS: Master of science; PhD: Doctor of Philosophy

Tertiary hospital^a: Large and advanced hospitals providing medical and health services across the whole country, with more than 500 beds.

Primary hospital^b: Regional hospital providing health services across several communities, with 100-499 beds.

TABLE 2. Logistic regression analysis of associated factors of surgeons' emphasis on follow-up.					
	Emphasize follow-up	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age(year)			0.854		
<45	62 (36.9)	REF			
≥45	32 (38.1)	1.052 (0.613-1.806)			
Education background			0.001	2.843 (1.441-5.609)	0.003
MD/MS	40 (27.0)	REF			
MD, PhD	54(51.9)	2.916 (1.719-4.948)			
Titles			0.990		
Residents /Attending	38 (37.3)	REF			
Deputy chief / Chief	56 (37.3)	1.003 (0.596-1.688)			
National academic membership			0.001	2.063(1.010-4.214)	0.047
No	44(28.9)	REF			
Yes	50(50)	2.684 (1.587-4.539)			
Years in practice			0.001	1.173(0.558-2.464)	0.674
<10	36(27.3)	REF			
≥10	58(48.3)	2.495 (1.477-4.214)			
Hospitals			0.314		
Comprehensive	86(38.4)	REF			
Cancer	8(28.6)	0.642 (0.271-1.521)			
Number of LAR (case / year)			0.075	0.584(0.289-1.182)	0.135
<50	50(32.9)	REF			
≥50	44(44.0)	1.603 (0.953-			

2.696)

Surgical procedure		0.043	1.476(0.834-2.611)	0.181
Open surgery	46(31.9)	REF		
Laparoscopic / robotic surgery	48(44.4)	1.704 (1.017-2.857)		
Statistics presented as N (%) or OR (95% CI)				
MD: Doctor of medicine; MS: Master of science; PhD: Doctor of Philosophy; REF: Reference; OR: Odds ratio; CI: Confidence interval.				

TABLE 3. Logistic regression analysis of factors associated with colorectal surgeons' estimate for the prevalence of LARS in postoperative patients

	LARS is common (prevalence $\geq$ 50%)	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Age (year)			0.461		
<45	60 (35.7)	REF			
≥ 45	34 (40.5)	1.224 (0.715-2.096)			
Education background			0.750		
MD/MS	54 (36.5)	REF			
MD, PhD	40 (38.5)	1.088 (0.648-1.826)			
Titles			0.033	1.125 (0.559-2.262)	0.741
Resident / Attending	30 (29.4)	REF			
Deputy chief / Chief	64 (42.7)	1.786 (1.046-3.049)			
National academic memberships			0.007	1.656 (0.887-3.090)	0.113
No	42 (30.0)	REF			
Yes	52 (46.4)	2.022 (1.204-3.395)			
Years in practice			0.172		
<10	44 (33.3)	REF			
≥ 10	50 (41.7)	1.429 (0.856-2.385)			
Hospitals			0.519		
Comprehensive	82 (36.6)	REF			
Cancer	12 (42.9)	1.299 (0.586-2.880)			
Numbers of LAR (case / year)			0.021	1.410 (0.754-2.639)	0.282
<50	48 (31.6)	REF			

≥50	46 (46.0)	1.846 (1.096-3.108)
Surgical procedure		0.652
Open surgery	52 (36.1)	REF
Laparoscopic / robotic surgery	42 (38.9)	1.126 (0.673-1.884)
Statistics presented as N (%) or OR (95% CI)		
MD: Doctor of medicine; MS: Master of science; PhD: Doctor of Philosophy; REF: Reference; OR: Odds ratio; CI: Confidence interval.		

Figures

Colorectal Surgeon Reported Questionnaire

GENERAL INFORMATION				
Name		Age		Sex ☐ Female ☐ Male
Q1: Education background (Degree)		☐ MD ☐ MD, MS ☐ MD, PhD		
Q2: What is your clinical title?		☐ Resident ☐ Attending ☐ Deputy chief ☐ Chief		
Q3: Do you have academic memberships?		☐ National ☐ Provincial ☐ Municipal ☐ None		
Q4: Which kind of hospitals are you working in?		☐ Tertiary comprehensive hospital ☐ Tertiary cancer hospital ☐ Primary comprehensive hospital ☐ Primary cancer hospital		
SURGICAL INFORMATION				
Q5: How many years have you been in colorectal practice?		☐ < 5 ☐ 5-10 ☐ 10-20 ☐ > 20		
Q6: How many low anterior resections surgeries have you finished in your career?		☐ < 50 ☐ 50-100 ☐ 100-200 ☐ > 200		
Q7: How many low anterior resections have you finished every year?		☐ < 50 ☐ 50-100 ☐ 100-200 ☐ > 200		
Q8: Which is the most common used surgical procedure?		☐ Open ☐ Laparoscopic ☐ Robotic		
FOLLOW-UP				
Q9: Which method do you use in follow-up? (Indefinite selection)		☐ No follow-up ☐ Outpatient ☐ Telephone ☐ Regular patient meetings ☐ Others: (Please specify)		
Q10: How many patients suffer from LARS after low anterior resection as you estimated?		☐ Seldom (0-25%) ☐ Not common (25%-50%) ☐ Common (50%-75%) ☐ Almost all (> 75%)		
Q11: Which are the most common chief complains of bowel dysfunction? (Indefinite selection but no more than FIVE items)		<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;">☐ Clustering</div> <div style="width: 50%;">☐ Constipation</div> <div style="width: 50%;">☐ Force defecation</div> <div style="width: 50%;">☐ Frequency</div> <div style="width: 50%;">☐ Incontinence of liquid stool</div> <div style="width: 50%;">☐ Incontinence of flatus</div> <div style="width: 50%;">☐ Incomplete defecation</div> <div style="width: 50%;">☐ Incontinence of solid stool</div> <div style="width: 50%;">☐ Overnight defecation</div> <div style="width: 50%;">☐ Obstructive defecation</div> <div style="width: 50%;">☐ Painful defecation</div> <div style="width: 50%;">☐ Prolonged defecation</div> <div style="width: 50%;">☐ Urgency</div> <div style="width: 50%;">☐ Tenesmus</div> <div style="width: 50%;">☐ Underwear pollution</div> <div style="width: 50%;">☐ Use paper diaper</div> <div style="width: 50%;">☐ Viscous defecation</div> </div>		
ASSESSMENT & TREATMENT				
Q12: Which method do you use to assess the severity of bowel dysfunction?		☐ LARS score ☐ FISI ☐ Subjective judgement ☐ Mark's score ☐ Wexner score ☐ Others: (Please specify)		
Q13: How do you treat with LARS?		☐ Don't know ☐ Lifestyle changing ☐ Wait and watch ☐ Drug ☐ TCM ☐ Enema ☐ Biofeedback ☐ Sacral nerve stimulation ☐ surgery		

Figure 1

Questionnaire used to assess colorectal surgeons' awareness and knowledge of LARS

Figure 2

Prevalence of LARS after LAR estimated by Chinese colorectal surgeons (n=252)

Figure 3

Frequency of 17 anorectal disorders chosen by respondents (n=252) The first five issue were in LARS score, the last twelve issue were not listed in LARS score. The order of issues in questionnaires were random, and they were rearranged according the cumulative frequencies.

Figure 4

Assessment and treatment of LARS chosen by respondents (n=252) Only one option can be selected. The order of issues in questionnaires were random, and they were rearranged according to the cumulative percentage.

Supplementary Files

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

- [questionnaire.pdf](#)