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ORIGINAL SCIENTIFIC REPORT

Pelvimetric and Nutritional Factors Predicting Surgical Difficulty in Laparoscopic Resection for Rectal Cancer Following Preoperative Chemoradiotherapy

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Abstract

Aim Laparoscopic total mesorectal excision (LaTME) following preoperative chemoradiotherapy (PCRT) in locally advanced rectal cancer (LARC) is technically demanding. The present study is intended to evaluate predictive factors of surgical difficulty of LaTME following PCRT by using pelvimetric and nutritional factors.

Method Consecutive LARC patients receiving LaTME after PCRT were included. Surgical difficulty was classified based upon intraoperative (operation time, blood loss, and conversion) and postoperative outcomes (postoperative hospital stay and morbidities). Pelvimetry was performed using preoperative T2-weighted MRI. Nutritional factors such as albumin-to-globulin ratio (AGR) and prognostic nutritional index (PNI) were calculated. Multivariable logistic analysis was used to identify predictors of high surgical difficulty. A predictive nomogram was developed and validated internally.

Results Among 294 patients included, 36 (12.4%) patients were graded as high surgical difficulty. Logistic regression analysis demonstrated that previous abdominal surgery (OR = 6.080, $P = 0.001$), tumor diameter (OR = 1.732, $P = 0.003$), intersphincteric resection (vs. low anterior resection, OR = 13.241, $P < 0.001$), interspinous distance (OR = 0.505, $P = 0.009$), and preoperative AGR (OR = 0.041, $P = 0.024$) were independently predictive of high surgical difficulty of LaTME after PCRT. Then, a predictive nomogram was built (C-index = 0.867).

Conclusion Besides previous abdominal surgery, type of surgery (intersphincteric resection), tumor diameter, and interspinous distance, we found that preoperative AGR could be useful for the prediction of surgical difficulty of LaTME after PCRT. A predictive nomogram for surgical difficulty may aid in planning an appropriate approach for rectal cancer surgery after PCRT.

Introduction

Laparoscopic total mesorectal excision (LaTME) for rectal cancer has been widely accepted due to well-established advantages over open surgery, such as reduced postoperative pain, rapid recovery, and shorter hospital stay [1–4]. However, LaTME could be technically challenging in mid/low rectal cancers, especially within a deep and narrow pelvis. Recently, novel minimally invasive techniques, including robotic and transanal TME, may help to overcome difficulties encountered during LaTME [5]. Preoperative chemoradiotherapy (PCRT) is an essential part of the multimodality treatment of locally advanced rectal cancer (LARC) [6, 7]. It can induce tumor downsizing and

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thus facilitate surgical exposure in the pelvis, whereas PCRT-induced tissue edema and fibrosis may hamper dissection around the mesorectum. Therefore, it is advisable to predict surgical difficulty in LaTME after PCRT to preoperatively plan the appropriate surgical approach (e.g., open, laparoscopic, robotic, or transanal) [5].

Surgical difficulty of LaTME is affected by surgical skills as well as the patient's clinical factors, such as male sex, a high body mass index (BMI), previous abdominal surgery, low rectal cancer, and advanced-stage tumors [8, 9]. Difficult pelvic structures could also add to surgical difficulty of LaTME. Recently, MRI-based pelvimetry, radiologic measurement of pelvic dimensions, has been proposed as a usefull tool for prediction of surgical difficulty of LaTME [10, 11]. A recent meta-analysis[12] has demonstrated that bony pelvic measurements based on MRI pelvimetry may predict surgical difficulty of TME. The influence of pelvic anatomy on surgical difficulty of LaTME is expected to be more pronounced due to radiation-induced tissue edema or fibrosis. However, the evidence is sparse regarding the prediction of surgical difficulty of LaTME following PCRT [13, 14].

Nutritional status is also associated with postoperative morbidity and length of hospital stay in the treatment for gastrointestinal cancers [15, 16]. Several hematological nutritional indexes have been utilized to reflect the patient's nutritional status, such as serum albumin, albumin-to-globulin ratio (AGR), and prognostic nutritional index (PNI). Recent studies have demonstrated the predictive value of these nutritional indexes on postoperative complications in gastric [17] and colorectal [18] cancer surgery. In rectal cancers, PCRT could impair the patients' nutritional status and possibly influences surgical and oncological outcome [19]. We hypothesized that these nutritional indexes may be useful in predicting surgical difficulty of LaTME. Herein, we attempted to predict surgical difficulty of LaTME after PCRT by combining clinical, pelvimetric, and nutritional factors and to develop a predictive nomogram for surgical difficulty.

Patients and methods

Patients

Between 2014 and 2016, LARC patients who underwent PCRT followed by laparoscopic surgery were identified from our colorectal cancer database. Patients with pathologically proven mid/low rectal adenocarcinoma (within 10 cm above the anal verge) and T3/4 and/or N + disease (staged by MRI) were included. Patients were excluded if: underwent abdominoperineal resection (APR) or other surgeries (e.g., Hartmann's procedure, emergency surgery, palliative surgery, pelvic exenteration, multivisceral resection, para-aortic lymph node dissection, or lateral pelvic lymph node dissection) and incompletion of preoperative MRI. This study was reported in accordance with the The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (https://www.equator-network.org/reporting-guidelines/strobe/), as shown in Appendix.

Treatment

Preoperative radiation was delivered at a dose of 45 Gy to the pelvis, followed by a 5.4 Gy boost to the tumor over a 5–6 week period. Concomitant chemotherapy was administered using CapeOX or FOLFOX regimen. Radical resection was planned at 8 weeks after the end of radiation. LaTME was performed via an abdominal ''up-to-down'' TME approach as previously described [20, 21].

Definition of surgical difficulty

Since many differences exist between Eastern and Western countries patients, such as weight, BMI, pelvis, medical insurance policy, and strategy of enhanced recovery after surgery, we have made appropriate modifications of the criteria of surgical difficulty modified from that previously proposed by Escal et al. [10]: duration of surgery >300 min (3 points), estimated blood loss >200 ml (1 point), conversion to open procedure (3 points), Clavien–Dindo classifications [22] grade II and III postoperative morbidities (1 point), need for transanal dissection (2 points), and postoperative hospital stay >7 days (2). After calculating the total score, we categorized patients into low (0–2 points) and high (≥3 points) surgical difficulty groups.

MRI-based pelvimetry

MRI images were centrally evaluated by one radiologist (CJH). Pelvimetry parameters and angles were measured using mid-sagittal and axial planes as described previously [23], as shown in Fig. 1. The definitions of pelvimetric parameters were listed in Supplementary Table 1.

Hematological nutritional indexes

Blood samples were obtained within 1–2 weeks before surgical resection. Hematological nutritional indexes were calculated as follows: AGR = albumin/(total serum protein—albumin) and PNI = serum albumin (g/L) + 5 × total lymphocytes count (10^9/L).

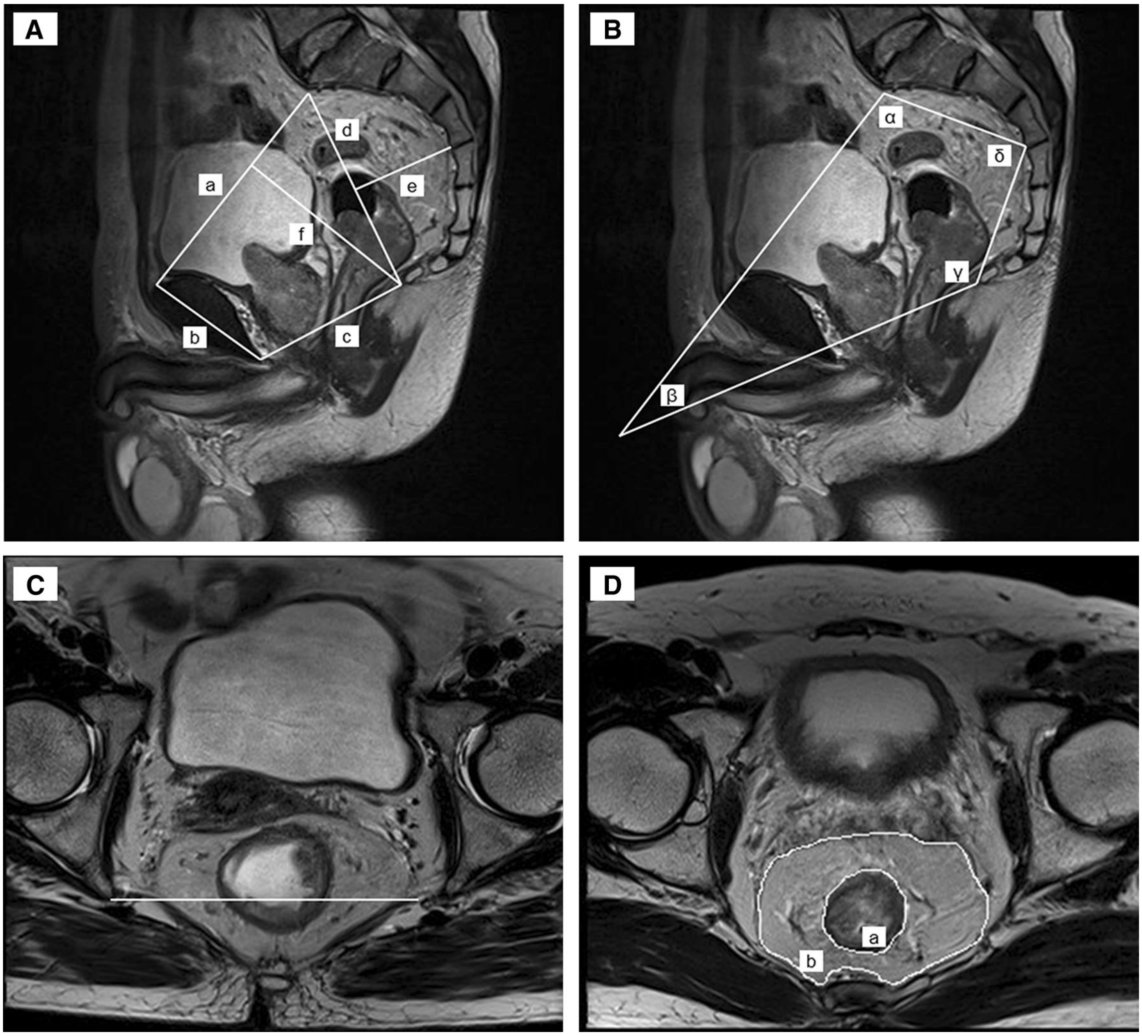

Fig. 1 MRI-based pelvimetry. **a** Sagittal T2-weighted image showing the pelvic inlet (a), pubic tubercle height (b), pelvic outlet length (c), sacral length (d), sacral depth (e), and pelvic depth (f). **b** Sagittal T2-weighted image illustrating the pelvic angles (α, β, δ and ε). **c** Axial T2-weighted image showing the interspinous distance. **d** Axial T2-weighted image showing the manual tracing of the circumference of the rectum (a) that represented the rectal area; axial T2-weighted image showing the manual tracing of the circumference of the mesorectum (b) that represented the mesorectal area

Statistical analysis

SPSS 20.0 software (IBM SPSS INC., Chicago, USA) was used for statistical analyses. Variables were compared using χ^2 test or Student *t* test, as appropriate. Predictive factors for surgical difficulty were identified by using Logistic regression analysis. A predictive nomogram was constructed by R version 3.5.1. The nomogram was internally validated and evaluated by C-index. $P < 0.05$ was considered of statistical significance.

Results

Patient characteristics

Totally, 294 patients were eligible for the analysis, including 203 men and 91 women. The median BMI was 22.7 kg/m^2, and the average distance from the anal verge was 6.8 cm, as seen in Table 1. An overview of the bony pelvis and soft tissue measurement based on MRI pelvimetry was shown in Table 2. The mean interspinous distance was 9.0 ± 1.0 cm. The mean mesorectal and rectal area was 26.6 ± 6.1 cm^2 and 7.6 ± 3.2 cm^2, respectively, and the mean mesorectal fat area was 19.1 ± 5.5 cm^2. As shown in Table 2, the average

Table 1 Clinicopathological characteristics and surgical outcomes in LARC patients following PCRT and LaTME

Characteristics	Values
Gender, male/ female (%)	203 (69.0%) / 91 (31.0%)
Age (years)	56.4 ± 11.9
BMI (kg/m^2)	22.7 ± 2.8
Distance from the anal verge (cm)	6.8 ± 2.0
Tumor diameter (cm)	2.0 ± 1.1
Prior abdominal surgery	36 (12.2%)
Time interval from completion of radiation to surgery (week)	9.6 ± 5.4
Surgical procedure	
Low anterior resection	94 (32.0%)
Ultra-low anterior resection	151 (51.3%)
Intersphincteric resection	49 (16.7%)
Lymph nodes harvested	13.6 ± 6.9
Pathological T stage	
T0	68 (23.1)
T1	17 (5.8)
T2	77 (26.2)
T3	122 (41.5)
T4	10 (3.4)
Pathological N stage	
N0	212 (72.1)
N1	62 (21.1)
N2	20 (6.8)
Pathological TNM stage	
0	67 (22.8)
I	72 (24.5)
II	73 (24.8)
III	82 (27.9)

Data are expressed as number (percentage) or as median ± standard deviation, where appropriate

LARC locally advanced rectal cancer, *PCRT* preoperative chemoradiotherapy, *LaTME* laparoscopic total mesorectal excision, *BMI* body mass index, *CEA* carcinoembryonic antigen

*Grade II or III in the Clavien–Dindo classification of postoperative morbidity

Table 2 Pelvimetry and immunonutritional indexes in LARC following PCRT

Characteristics	Values
Pelvic inlet length (cm)	11.5 ± 1.0
Pubic tubercle height (cm)	5.1 ± 0.3
Pelvic outlet length (cm)	8.0 ± 0.7
Sacral length (cm)	12.2 ± 1.1
Sacral depth (cm)	3.7 ± 0.5
Pelvic depth (cm)	10.7 ± 0.9
Interspinous distance (cm)	9.0 ± 1.0
Mesorectal area (cm^2)	26.6 ± 6.1
Rectal area (cm^2)	7.6 ± 3.2
Mesorectal fat area (cm^2)	19.1 ± 5.5
Angle α (°)	86.7 ± 8.1
Angle β (°)	43.6 ± 7.3
Angle γ (°)	118.6 ± 9.5
Angle δ (°)	110.8 ± 10.4
Serum total protein level (g/L)	68.4 ± 7.8
Serum albumin level (g/L)	38.8 ± 5.5
Serum lymphocyte count (10^9/L)	1.4 ± 0.7
Preoperative PNI	46.0 ± 6.4
Preoperative AGR	1.3 ± 0.2

Data are expressed as median ± standard deviation

LARC locally advanced rectal cancer, *PCRT* preoperative chemoradiotherapy, *PNI* prognostic nutritional index, *AGR* albumin-to-globulin ratio

preoperative PNI was 46.0 ± 6.4, and the average preoperative AGR was 1.3 ± 0.2.

Surgical outcomes

The duration of surgery was 224.8 ± 69.7 min, and the estimated blood loss was 67.0 ± 69.7 ml. A total of four (1.4%) patients were converted to open procedure; 13 (4.4%) patients experienced the use of transanal dissection. The postoperative hospital stay was 8.0 ± 5.1 days, and 42 (14.2%) patients developed postoperative morbidity (Clavien–Dindo classification grade I n = 26, and Clavien–Dindo classification grade II/III n = 16). Accordingly, surgical difficulty was classified as low in 258 (87.6%) patients and high in 36 (12.4%) patients, as seen in Table 3.

Predictors of high surgical difficulty of LaTME after PCRT

In the univariate analysis, higher BMI ($P = 0.038$), shorter tumor distance from the anal verge ($P = 0.006$), previous abdominal surgery ($P < 0.001$), larger tumor diameter ($P < 0.001$), type of surgery ($P < 0.001$), defunctioning ileostomy ($P = 0.015$), shorter interspinous distance ($P = 0.026$), larger mesorectal area ($P = 0.017$), larger mesorectal fat area ($P = 0.018$), larger angle δ ($P = 0.012$), smaller angle ε ($P = 0.024$), lower serum albumin level ($P = 0.004$), lower preoperative AGR ($P = 0.002$), and lower preoperative PNI ($P = 0.010$) were significantly associated with high surgical difficulty of LaTME following PCRT (Table 4). Logistic regression analysis demonstrated that previous abdominal surgery (OR = 6.080, 95% CI 2.150–17.190, $P = 0.001$), tumor diameter (OR = 1.732, $P = 0.003$), type of surgery (ISR vs. LAR, OR = 13.241, $P < 0.001$), interspinous distance (OR = 0.505,

Table 3 Perioperative outcomes of LaTME for LARC after PCRT stratified by surgical difficulty

Factors	Total	Surgical difficulty		*P* value
		Low (n = 258)	High (n = 36)	
Duration of surgery (min)	224.8 ± 69.7	211.9 ± 57.7	317.5 ± 78.7	<0.001
Estimated blood loss (ml)	67.0 ± 69.7	62.1 ± 59.1	102.5 ± 116.6	0.001
Conversion to open procedure	4 (1.4%)	0	4 (11.1%)	<0.001
Use of transanal dissection	13 (4.4%)	3 (1.2%)	10 (27.8%)	<0.001
Postoperative hospital stay (days)	8.0 ± 5.1	7.8 ± 5.0	9.6 ± 5.5	0.044
Postoperative morbidity*	42 (14.2%)	31 (12.0%)	11 (30.6%)	0.003
Clavien-Dindo classification I	26 (8.8%)	23(8.9%)	3(8.3%)	0.908
Clavien-Dindo classification II/III	16 (5.4%)	8 (3.1%)	8 (22.2%)	<0.001

Data are expressed as number (percentage) or as median ± standard deviation, where appropriate

LaTME laparoscopic total mesorectal excision, *LARC* locally advanced rectal cancer, *PCRT* preoperative chemoradiotherapy

$P = 0.009$), and preoperative AGR (OR = 0.041, $P = 0.024$) were independently predictive of high surgical difficulty of LaTME following PCRT (Table 4).

A predictive nomogram for high surgical difficulty of LaTME following PCRT

A predictive nomogram for high surgical difficulty of LaTME after PCRT was then developed (Fig. 2A). A higher total score indicated a higher likelihood of high surgical difficulty of LaTME after PCRT. The AUC of the predictive nomogram was 0.867 (Fig. 2B). The nomogram was validated internally (C-index: 0.867, 95%CI 0.838–0.896). The calibration curve demonstrated good accordance of the predicted and observed probability of high surgical difficulty of LaTME after PCRT (Fig. 2C).

Discussion

The present study demonstrated that besides previous abdominal surgery, type of surgery (ISR), tumor diameter, and interspinous distance, preoperative AGR could be useful in the prediction of surgical difficulty of LaTME after PCRT. We further developed a predictive nomogram for surgical difficulty of LaTME following PCRT to help select a proper surgical approach preoperatively.

There are several indicators used to estimate surgical difficulty for TME, including operative time, blood loss, postoperative morbidity, and so on [24–26]. To make a more complete outcome definition for surgical difficulty, we employed both intraoperative and postoperative parameters that were previously proposed by Escal et al. [10] and made a slight modification. It is meaningful to include both operative and postoperative parameters because impaired surgical quality and an eventful postoperative course might increase local recurrence and impair survival [27].

During LaTME after PCRT, the mesorectum dissection was hampered by edema and extensive mist and exudates caused by PCRT, as seen in Supplementary Figure S1. Surgical difficulty may depend on surgical expertise; our surgeries were performed by a high-volume surgical team with more experience in LaTME (Supplementary Figure S2). Herein, LaTME after PCRT was performed with a low rate of conversion rate (1.4%) and postoperative morbidity (14.2%). Thus, learning curve factors or surgical skills were not major contributors to surgical difficulty in the present study. Herein, 12.4% of patients were classified as high surgical difficulty of LaTME after PCRT, similar to that (12.8%) of Escal et al. [10].

Pelvic anatomical factors are important in affecting the surgical difficulty of rectal cancer surgery. A narrow pelvis, a prominent sacral promontory, and a shallow sacral angle could impede vision, access, and working space in the operation field during LaTME for rectal cancer [13]. Many efforts have been made in utilization of pelvimetry to predict surgical difficulty of transabdominal TME. Many pelvimetric parameters have been utilized to predict surgical difficulty for LaTME, including both pelvic dimensions and pelvic angles [9, 24–26]. As demonstrated in a recent meta-analysis [12], although the role of MRI pelvimetry in predicting surgical difficulty in rectal cancer surgery has been well demonstrated, it is still controversial that which pelvis parameter weighes heaviest in influencing surgical difficulty. Herein, we employed seven dimensions, four angles, and three areas of the pelvis based on MRI images. Univariate analysis demonstrated that shorter interspinous distance, larger mesorectal area, larger MFA, larger angle δ, and smaller angle ε were associated

Table 4 Logistic regression analysis of predictors associated with high surgical difficulty of LaTME for LARC following PCRT

Factors	Univariate analysis	Multivariate analysis	
	P value	OR (95% CI)	*P* value
Sex (male/female)	0.475		
Age	0.093		
BMI	0.038	1.094 (0.935–1.280)	0.263
Distance from the anal verge (cm)	0.006	0.991 (0.706–1.390)	0.956
Previous abdominal surgery	<0.001	6.080 (2.150–17.190)	0.001
Tumor diameter (cm)	<0.001	1.732 (1.208–2.483)	0.003
Time interval from completion of radiation to surgery (week)	0.388		
Type of surgery	<0.001		
Low anterior resection		Reference	<0.001
Ultra-low anterior resection		0.855 (0.124–5.879)	0.874
Intersphincteric resection		13.241 (3.683–47.602)	<0.001
Defunctioning ileostomy	0.015	0.924 (0.137–6.211)	0.935
Pelvic inlet length (cm)	0.680		
Pubic tubercle height (cm)	0.822		
Pelvic outlet length (cm)	0.388		
Sacral length (cm)	0.308		
Sacral depth (cm)	0.138		
Pelvic depth (cm)	0.534		
Interspinous distance (cm)	0.026	0.505 (0.302–0.844)	0.009
Mesorectal area (cm^2)	0.017	1.016(0.859 -1.203)	0.850
Rectal area (cm^2)	0.657		
Mesorectal fat area (cm^2)	0.018	1.108 (0.908–1.353)	0.313
Angle α (°)	0.240		
Angle β (°)	0.1181		
Angle δ (°)	0.012	1.046 (0.980–1.117)	0.179
Angle ε (°)	0.024	0.996 (0.929–1.068)	0.910
Serum total protein level (g/L)	0.209		
Serum albumin level (g/L)	0.004	0.969 (0.834–1.127)	0.686
Serum lymphocyte count (10^9/L)	0.832		
Preoperative AGR level	0.002	0.041 (0.003–0.652)	0.024
Preoperative PNI level	0.010	1.019 (0.892–1.164)	0.780
Pathological T stage	0.190		
Pathological N stage	0.262		
Pathological TNM stage	0.287		

LaTME laparoscopic total mesorectal excision, *LARC* locally advanced rectal cancer, *PCRT* preoperative chemoradiotherapy, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *MFA* mesorectal fat area, *AGR* albumin-to-globulin ratio, *PNI* prognostic nutritional index

with high surgical difficulty of LaTME after PCRT. After adjusting for confounding factors, shorter interspinous distance remained to be independently associated with high surgical difficulty. Consistent with previous findings [10, 14], our result reaffirmed that shorter interspinous distance could represent an anatomical bottleneck of the deep pelvis that hinders laparoscopic resection maneuvers during LaTME. Besides, a larger tumor within the bony pelvis is associated with surgical difficulty [28]. The present study demonstrated that tumor diameter was independently associated with surgical difficulty of LaTME after PCRT.

A greater mesorectal volume could restrict the pelvic working space for the TME procedure. Two recent studies have investigated the predictive value of the mesorectal fat area on surgical difficulty of laparoscopic [10] and robotic [23] TME. In the present study, we found that both the mesorectal area and the mesorectal fat area were associated

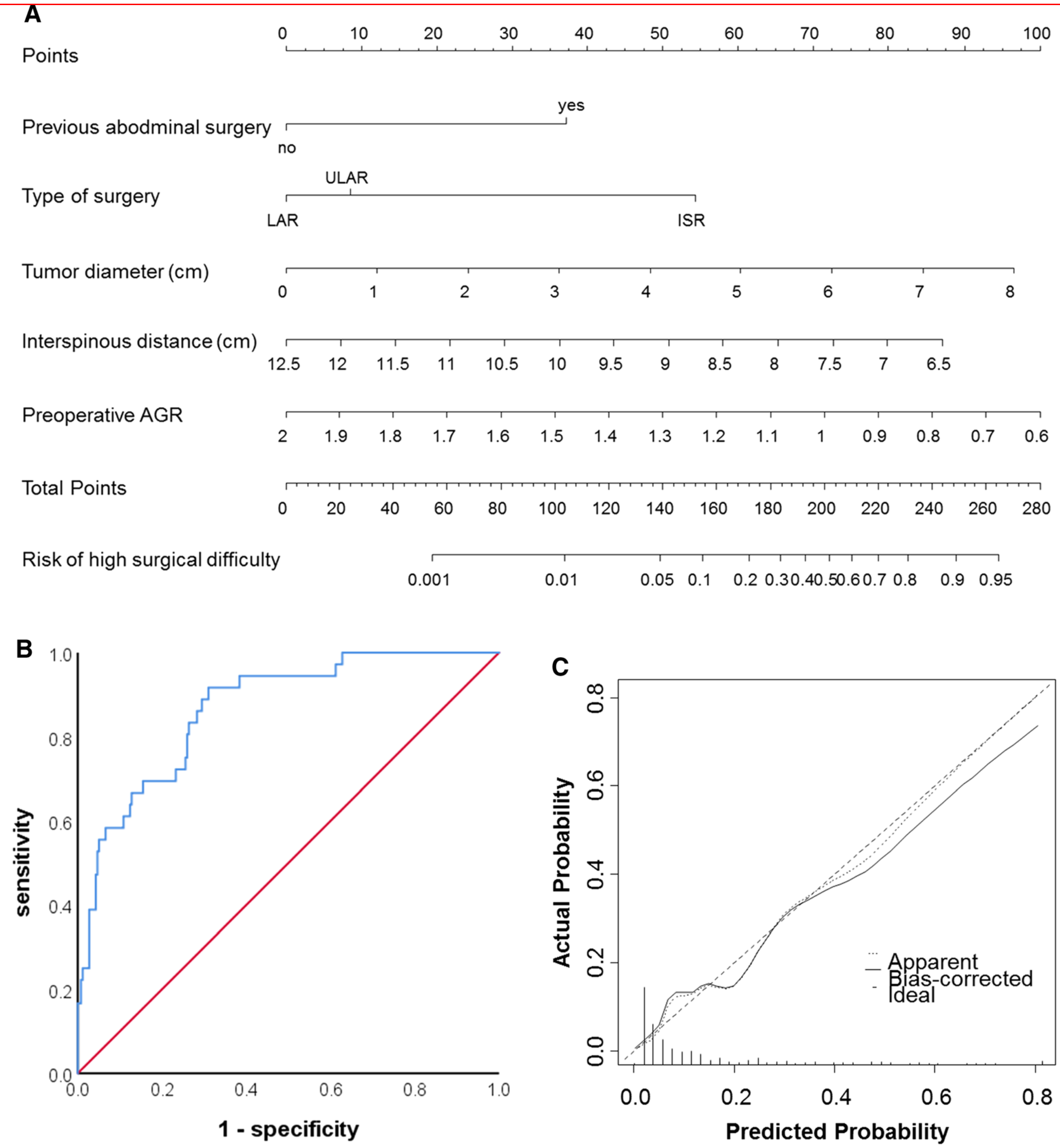

Fig. 2 A nomogram for predicting the probability of high surgical difficulty of LaTME for LARC following PCRT. **a** A predictive nomogram for high surgical difficulty of LaTME for LARC following PCRT; **b** ROC analysis of the nomogram; **c** calibration curves for the nomogram with internal validation. *LaTME* laparoscopic total mesorectal excision, *LARC* locally advanced rectal cancer, *PCRT* preoperative chemoradiotherapy, *AGR* albumin-to-globulin ratio, *ROC* receiver-operating characteristics curve

with high surgical difficulty of LaTME by univariate analysis; however, none of them were independent predictors of surgical difficulty after adjustment for confounders. The lack of statistical significance might be explained that our patients had a much lower BMI and the mesorectal fat area as compared with that of patients in Western countries [10, 23], thus reducing the influence on surgical difficulty.

Nutritional status is a well-established factor associated with postoperative complications for gastrointestinal tumors [15, 16], such as surgical site infection and anastomotic leakage. Interestingly, lower preoperative AGR was independently associated with high surgical difficulty of LaTME after PCRT. It has been reported that PCRT could impair the patients' nutritional status of rectal cancer patients and possibly increase the risk of postoperative complications [19]. In our experience, patients with malnutrition are more likely to encounter tissue edema, a large amount of mist and exudates caused by PCRT, which hinders the dissection of the tissue. Unfortunately, whether nutritional status (as indicated by albumin or AGR) contributes to different tissue reactions to CRT among patients is unclear. In addition, the mechanism underlying the predictive value of AGR on surgical difficulty remains to be further explored.

Prior abdominal surgery may increase tissue adhesion and fibrosis, and our study reaffirmed it as an independent predictor of surgical difficulty of LaTME, consistent with previous studies [13, 29]. ISR for low-lying tumors is a technically demanding procedure, in which a distal dissection, transection, and anastomosis proceeding into the sphincter complex structures of the long "tube within a tube," and even more challenging in patients with bulky tumors in a narrow pelvis [21, 30]. Not surprisingly, we herein demonstrated that laparoscopic ISR was independently correlated with high surgical difficulty of LaTME after PCRT. Contrary with previous findings, BMI was not associated with surgical difficulty of LaTME, probably because the average BMI of our patient cohort was much lower than that of Western patients.

Several scoring systems have been proposed for predicting the difficulty of LaTME for rectal cancer [8, 10, 11]. The present study, for the first time, constructed a predictive nomogram for surgical difficulty of LaTME after PCRT. The AUC of the nomogram was 0.867, indicating a good discriminative power. Surgical trainees or early-career surgeons could select appropriate cases during their learning curve to improve surgical quality and to minimize adverse outcomes caused by lack of experience. The present nomogram can help improve doctor–patient communication by informing patients of possible perioperative risks and complications. Finally yet importantly, this nomogram might help to select the appropriate surgical approach (e.g., open, laparoscopic, robotic, or transanal) for LARC patients after PCRT.

There are several limitations. Firstly, the present study was a retrospective single-center analysis. Secondly, we made a modification of the Escal et al. score for surgical difficulty, which may potentially hamper direct comparison with previous similar works. Thirdly, Nicola de'Angelis et al. [31] have demonstrated that pelvimetry and restaging MRI play an important role in predicting surgical difficulties in LARC management. Since some data concerning restaging MRI were missing, we did not include it in the score and nomogram. Fourthly, operations in our patient cohort were performed by highly experienced laparoscopists; thus, the results may not be extrapolated to less-experienced surgeons. Fifthly, the completeness of TME could not be fully assessed in the present study. Finally, our predictive nomogram required further validation in other independent patient cohorts.

In conclusion, besides previous abdominal surgery, type of surgery (ISR), tumor diameter, and interspinous distance, preoperative AGR could also help predict surgical difficulty of LaTME after PCRT.

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Declarations

Conflict of interest None declared.

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