A Predictive Nomogram Model for LARS after Rectal Cancer Resection

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Abstract

Background: The aim of this study was to identify risk factors associated with the low anterior resection syndrome (LARS) and to construct a nomogram capable of predicting the risk of LARS in patients who undergo rectal cancer resection.

Methods: 538 patients who had undergone anterior resection were recruited as a development group at the Fujian Cancer Hospital between January 2017 and June 2019. In addition, 114 patients with rectal cancer who had been treated between February 2020 and April 2021 at the Zhongshan Hospital Affiliated to Xiamen University, were analyzed as a validation set to test the new nomogram. The diagnosis of LARS was determined using the LARS Score. Patients in the development set were grouped into two separate cohorts: those with major LARS and those with minor or no LARS. Multiple logistic regression was conducted to detect risk factors for major LARS. A nomogram was performed and verified by a calibration plot and analysis of a receptor operating characteristic (ROC) curve.

Results: The prevalence of major LARS was 40.7%, of minor LARS was 28.6% and the proportion with no LARS was 30.7%. In multivariate analysis, female gender, preoperative chemoradiation, low tumor height, diverting ileostomy, postoperative anastomotic leakage were shown to be independently associated with major LARS occurring in patients after rectal cancer resection. The area under the curve (AUC) values of the nomogram were 0.726 (95% CI: 0.682-0.769) and 0.750 (95% CI: 0.655-0.845) in the development and validation sets, respectively. The calibration curves and Hosmer-Lemeshow goodness of fit tests showed that the model was acceptably accurate.

Conclusions: There is a significant prevalence of major LARS following oncological rectal resection. A nomogram model based on risk factors could be valuable as a predictor of the probability of major LARS after rectal cancer surgery, and provides a guide that clinical staff can use to take preventive measures for high-risk patients.

Introduction

Colorectal cancer is the third most common cancer globally and rectal cancer accounts for approximately 33% of diagnosed cases[1]. The introduction of the concept of total mesorectal excision (TME) and neoadjuvant chemoradiotherapy, and the rapid development of laparoscopic technology have facilitated sphincter-preserving surgery in 62-85% of rectal cancer patients, and have dramatically improved the oncological outcomes[2-4]. Improved survival has increased attention to quality of life, including bowel dysfunction[5].

Sphincter-preserving rectal cancer surgery can avoid a permanent stoma, but 50-90% of the patients are affected by varying degrees of neorectal dysfunction, commonly known as low anterior resection syndrome (LARS)[6, 7]. LARS encompasses a wide array of symptoms, including frequent bowel movements, fecal urgency, incomplete evacuation, incontinence and sexual or urinary dysfunctions[8]. These symptoms appear shortly soon after restoration of intestinal continuity. They are more intense in

the first month, may improve in the first 6 months, and can persist more than 5 years after surgery[9, 10]. LARS has a significant long-term negative impact not only on the quality of life, but also for occupational life, invalidity, and material independence, and more severe LARS has a greater detrimental impact[11]. This current study was performed to identify risk factors for LARS, and to develop a nomogram for accurate prediction of LARS in patients undergoing rectal cancer resection.

Methods

Patients

Between January 2017 to June 2019, 538 patients who had undergone anterior resection at the Fujian Cancer Hospital were screened in this study as a development set. The patients were selected according to the following criteria: (1) pathologically confirmed rectal adenocarcinoma; (2) low anterior resection; (3) complete clinicopathological data and a reliable follow-up. Detailed exclusion criteria were: (1) emergency surgery due to bleeding or obstruction; (2) palliative surgery; (3) simultaneous multiple primary tumors; (4) unclosed ileostomy; (5) tumor recurrence or metastasis; and (6) other intestinal diseases such as Crohn's disease or ulcerative colitis. 114 patients with rectal cancer who had been treated at the Zhongshan Hospital affiliated to Xiamen University between February 2020 and April 2021 were used as a validation set.

Definition of LARS

The international consensual definition of LARS is that a patient must have had an anterior resection (sphincter-preserving rectal resection) and must experience at least 1 of 8 symptoms resulting in at least one of 8 consequences. The 8 symptoms are unpredictable bowel function, altered stool consistency, increased stool frequency, repeated painful stools, emptying difficulties, urgency, incontinence and soiling. The 8 consequences are toilet dependency, preoccupation with bowel function, dissatisfaction with bowel conditions, strategies and compromises, impact on mental and emotional well being, impact on social and daily activities, effect on relationships and intimacy and impact on commitments and responsibilities[12].

Diagnosis and classification of LARS

The LARS score consists of 5 questions and is a validated and frequently used tool with which to assess bowel dysfunction after rectal cancer resection. The severity of LARS is calculated on a scale ranging from 0 to 42 as follows: 0-20 = no LARS, 21-29 = minor LARS, and 30-42 = major LARS[13, 14]. Patients with stage II/III rectal cancer were required to receive between 3 and 6 months of adjuvant chemotherapy[15]. To avoid confounding factors caused by chemotherapy in this current study, follow-up data were collected 7-9 months after the primary surgery *via* the outpatient service or a telephone interview.

Carpelan et al. found that patients with major LARS had a significantly lower quality of life and more defecatory symptoms than those with no low anterior resection syndrome[16]. Significant differences in the global quality of life between those with no or minor LARS could not be detected, even in cases where a progression of defecatory symptoms was noted. Thus, the patients in this study were categorized into a group with major LARS and a group with minor or no LARS.

Statistical analysis

IBM SPSS, version 24.0 was used to perform statistical analysis. Continuous variables were expressed as the mean ± SD or median (interquartile range, IQR), and were calculated using a Student's t test or the Mann-Whitney U test. Categorical variables were with whole numbers and percentages. The chi-square tests or Fisher exact tests were used for categorical variables. Multivariable logistic regression models were employed to screen for significant predictors of major LARS. Nomogram construction and validation were performed using the RMS package in the R software. Predictive accuracy of the nomogram was validated using C-index values and ROC and quantified by the area under the curve (AUC). Calibration curves established with the bootstrapping method were used to compare further validation of the nomogram. The Hosmer-Lemeshow test was used to evaluate the goodness-of-fit of the logistic model. A P value < 0.05 was considered significant.

Results

Clinicopathological characteristics and incidence of LARS

The mean age of the 538 patients was 56.9±11.3 years. Of these patients, 68.6% were male and 31.2% of them had received adjuvant chemoradiotherapy. There were 165 (30.7%) patients with no LARS, 154 (28.6%) with minor LARS and 219 (40.7%) with major LARS.

Risk factors for major LARS

In the univariate analysis, the factors significantly associated with major LARS were: gender, preoperative chemoradiation, low tumor height, diverting ileostomy, postoperative anastomotic leakage, all with P < 0.05 (Table 1).

Table 1

Univariate analysis of risk factors related to major LARS

Variables	Major LARS(n=219)	minor/no LARS(n=319)	t/χ2	P value
Sex			6.234	0.013
Male	137	232		
Female	82	87		
Age (years), mean±SD	57.3±11.0	56.6±11.6	0.728	0.467
Marital status			1.279	0.258
Married	153	237		
Single/widowed	66	82		
BMI(kg/m2)			2.167	0.141
26	142	226		
≥26	77	93		
Hypertension			0.444	0.505
Yes	57	75		
No	162	244		
Diabetes mellitus			0.808	0.369
Yes	43	53		
No	176	266		
Smoking			0.573	0.449
Yes	47	60		
No	172	259		
Alcohol use			0.163	0.686
Yes	66	91		
No	153	228		
Preoperative anemia			0.523	0.469
Yes	66	87		
No	153	232		
Preoperative hypoalbuminemia			0.331	0.565
Yes	64	86		
No	155	233		

Preoperative chemoradiation			18.337	0.000
Yes	91	77		
No	128	242		
ASA			0.307	0.579
I-II	158	237		
III-IV	61	82		
Surgical approach			1.902	0.386
Open	32	34		
Laparoscopic	154	236		
Robotic	33	49		
Operational styles			2.149	0.143
TME	177	273		
taTME	42	46		
Tumor height(cm)			10.506	0.001
≤5	130	144		
5	89	175		
Tumor size (cm)			0.922	0.337
≤3	87	140		
3	132	179		
Blood loss (ml), median (IQR)	175 (100-190)	170(90-200)	-1.223	0.221
Operative time (min), median (IQR)	186(155-225)	192(163-228)	-1.295	0.195
Diverting ileostomy			7.171	0.007
Yes	73	73		
No	146	246		
Postoperative anastomotic leakage			4.629	0.031
Yes	27	22		
No	192	297		
Pathological TNM stage			2.932	0.231

I	51	95		
II	110	151		
III	58	73		
Postoperative chemotherapy			2.220	0.136
Yes	141	185		
No	78	134		

ASA american society of anesthesiology, BMI body mass index, TNM tumor, node and metastasis,

TME total mesorectal excision, taTME transanal total mesorectal excision

Multivariate analysis of major LARS factors

Multivariate analysis showed that the following independent risk factors for major LARS in patients after rectal cancer resection are: female, preoperative chemoradiation, low tumor height, diverting ileostomy, postoperative anastomotic leakage, all with $P < 0.05$ (Table 2).

Table 2

Multivariate analysis of risk factors leading to major LARS

Variables	p value	Odds ratio	95% CI for odds ratio
Female	0.002	1.947	1.316-2.881
Preoperative chemoradiation	0.000	2.377	1.613-3.503
Low tumor height	0.022	1.772	1.232-2.549
Diverting ileostomy	0.001	2.073	1.112-3.864
Postoperative anastomotic leakage	0.003	1.825	1.219-2.731

95%CI, 95% confidence interval

Construction and validation of the nomogram

The risk factors identified by multivariate analysis were used to construct a nomogram to predict major LARS after rectal cancer resection (Fig. 1). The nomogram model showed that the C-index for major LARS prediction in the development set was 0.731 (95% CI = 0.689-0.778) and the AUC was 0.726 (95% CI = 0.682-0.769) (Fig. 2), confirming the good discrimination by the model. Bootstrapping (1,000 replications) was applied and the internal calibration curve revealed good agreement between the predicted and actual

observations and the predictive probability (Fig. 3). The Hosmer-Lemeshow goodness of fit tests showed that the model was accurate ($\chi2 = 7.244$, $p = 0.404$).

In the validation set, the AUC was 0.750 (95% CI = 0.655-0.845) (Fig. 4), the external calibration curve demonstrated good agreement between prediction and observation (Fig. 5), and the Hosmer-Lemeshow test result was insignificant ($\chi2=5.881$, $p=0.661$), demonstrating a good fit.

Discussion

Introduction of the concept of total mesorectal excision (TME) led to the lowest rates of local recurrence and it has become the therapeutic gold standard for the rectal cancer resection[17]. However, bowel function was significantly affected after TME. Patients experience loneliness due to being toilet-bound, and as a result of changes in their lives and activities outside their homes and the impact on their family life[18]. The prevalence of LARS and its risk factors are awareness of deficiency noted by a significant number of colorectal surgeons[19]. We found that the incidence of LARS following rectal cancer resection was 69.3% (28.6% with minor LARS and 40.7% with major LARS), which is similar to previous findings. Bolton et al. found that the incidence of LARS was 82.6%, of which 19.7% were minor LARS and 62.9% were minor LARS[20]. A different study indicated that of the 100 patients who underwent total or partial mesorectal excision, 16 had minor LARS and 51 had major LARS[21]. Anterior resection could impair motility patterns in the distal colon, reduce the pressure gradient between the rectum and the anal canal, neural dysfunction, reduction of rectal compliance, dysfunction of the neorectal reservoir and an increase in rectal sensibility[22,23].

The nomogram provides an individualized and easily used tool to identify high-risk patients, and can lead to effective preventive measures in a timely fashion. We developed a nomogram of major LARS based on follow-up data collected 7-9 months after surgery. The internal and external validation of the nomogram was good in measures of discrimination and calibration respectively, which indicated that this predictive model is convenient and highly accurate as a means of estimating the risk of major LARS after rectal cancer resection.

This study demonstrated that being female is an independent risk factor for major LARS. Van Heinsbergen et al. reported that females experienced major LARS significantly more often than males[24], but in another study, it was found that the male gender is predisposed to LARS[25]. Several reasons have been proposed for the female predisposition to LARS and include weaker muscle fibers in females and damage to the levator ani muscle and the perineal muscle due to pregnancy and vaginal childbirth with subsequent pelvic floor dysfunction[26].

Among the current modalities, neoadjuvant chemoradiotherapy is preferred and has become a standard of care in locally advanced rectal cancer[27, 28]. Preoperative chemoradiation played a major role in this predictive model. Consistent findings were demonstrated in a recent study which showed that a neoadjuvant modality is associated with more severe LARS and diminished quality of life[29]. Among the reasons for the more likely major LARS after preoperative radiotherapy are: neoadjuvant

chemoradiotherapy may induce pathological features, including fibrosis, nerve injury, mucosal edema, ulcers, inflammatory cell infiltration and significant vascular lesions in the non-neoplastic mucosa[30]. Furthermore, neoadjuvant chemo-radiotherapy can cause excessive tissue edema, leading to a loss of surgical planes, thereby posing complications and an increased surgical challenge[31].

This study also showed that the risk of major LARS was related to low tumor height. The American Society of Colon and Rectal Surgeons (ASCRS) 2020 Clinical Practice Guidelines recommended that for tumors located in the mid to lower third of the rectum, a 2 cm distal margin is deemed adequate and allows for a low colorectal anastomosis. A distal margin of at least 1 cm is acceptable for tumors located at or below the mesorectal margin[32]. Surgical treatment for distal rectal cancer in terms of oncologic and functional outcomes is known to be a technically demanding procedure. The anal sphincters and peripheral nerves are more likely to be injured in surgical treatment of low-lying rectal cancer, and such injury results in impaired normal defecation reflex and rectal defecation function.The closer the tumor is to the anus, the smaller the size of the residual rectal volume, and the more obvious the foreign body sensation caused by the anastomotic material[33].

Our study also revealed that major LARS is more common in diverting ileostomy. The reason for the association between an ileostomy and major LARS may be that the temporary ileostomy is more likely to be used in lower resections and those patients are more likely to receive neoadjuvant therapy. These two factors have both been identified as a risk for development of major LARS[34]. As a result of disuse, atrophy of pelvic floor muscles which are unused for the time of temporary ileostomy, causes bowel function to be possibly impaired. Enteral nutrient deprivation of distal intestinal gut and fecal stream diversion results in alterations to the microbiota composition and impaired intestinal renewal, which consequently has an impact on intestinal structure and function[35].

In this study, postoperative anastomotic leakage was significantly associated with an increased risk of major LARS. It has been demonstrated that anastomotic leakage is a significant factor in the occurrence of major LARS[36]. This may due to an anastomotic leak leading to pelvic inflammation and resulting in pelvic autonomic nerve lesions and excessive fibrotic scarring around the anastomotic stoma. It may lead to a decrease in compliance and in the capacity of the neorectum, which can induce urgency or incontinence[37].

Conclusion

The nomogram developed in this study can more accurately predict the occurrence of major LARS after rectal cancer resection. The model may provide some guide to risk assessment and can facilitate the guidance of clinicians in their development of individualized treatment regimens for patients.

Abbreviations

LARS: Low anterior resection syndrome; ROC: Receptor operating characteristic; AUC: Area under the curve; TME: Total mesorectal excision; IQR: Interquartile range; ASA: American society of anesthesiology; BMI: Body mass index; TNM: Tumor, node and metastasis; taTME: transanal total mesorectal excision; 95%CI: 95% Confidence interval

Declarations

Acknowledgements

None.

Authors' contributions

Mingfang Yan and Zhenmeng Lin collected the data and wrote the paper. Zhiying Wu collected the data. Huizhe Zheng analyzed the data and produced the Figs. Meiqin Shi designed the research. All authors read and approved the manuscript to be published.

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Availability of data and materials

The data are available from the corresponding author on reasonable request. All patients obtained written informed consent.

Declarations

Ethics approval and consent to participate

The study was approved by Institutional Ethics Committee of Fujian Cancer Hospital (NO. SQ2020-007-01) .Written informed consent was obtained from the patients.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Figures

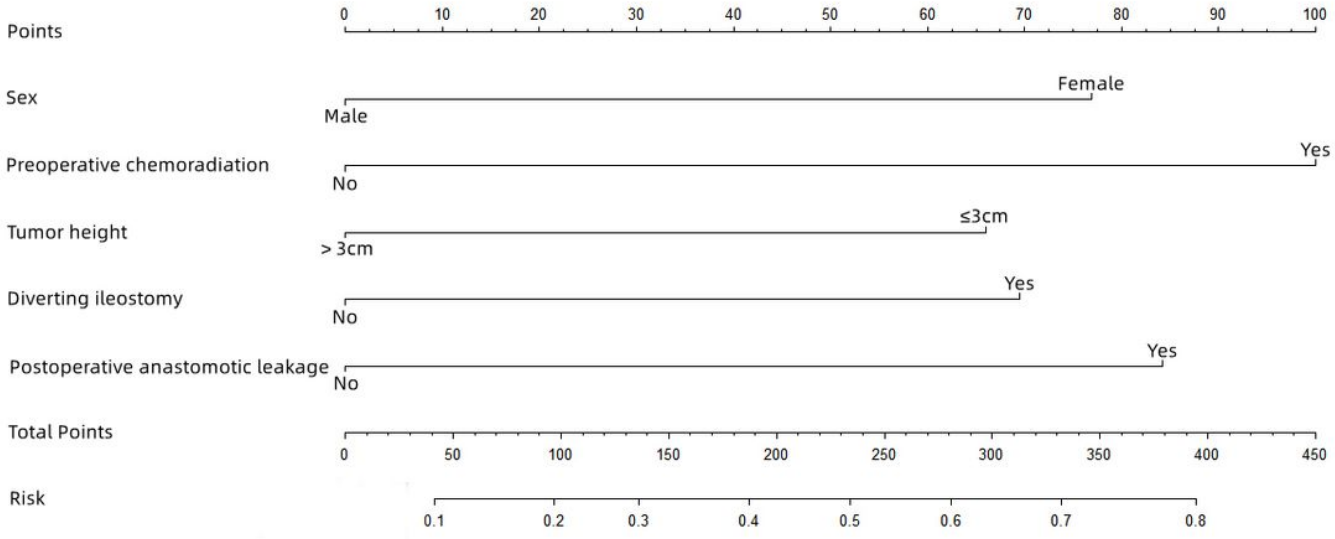

Figure 1

Nomogram predicting the probability of major LARS after rectal cancer resection.

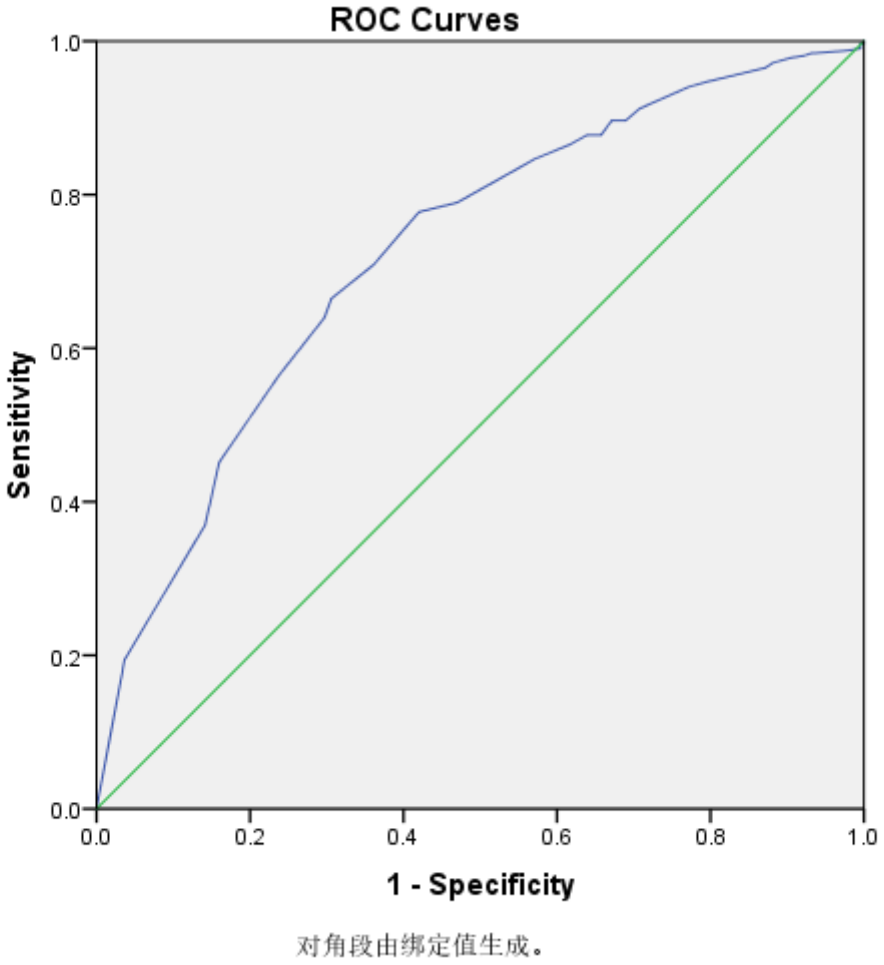

Figure 2

The ROC used to predict major LARS in the development set

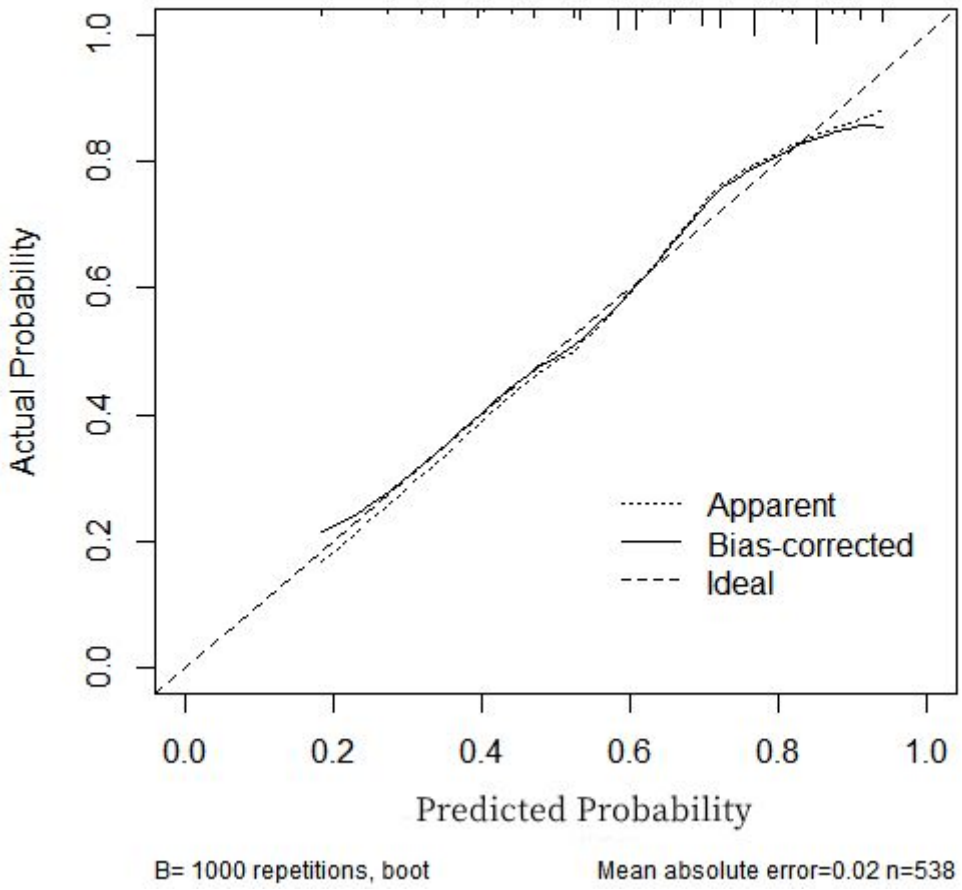

Figure 3

The calibration curve for predicting major LARS in the development set

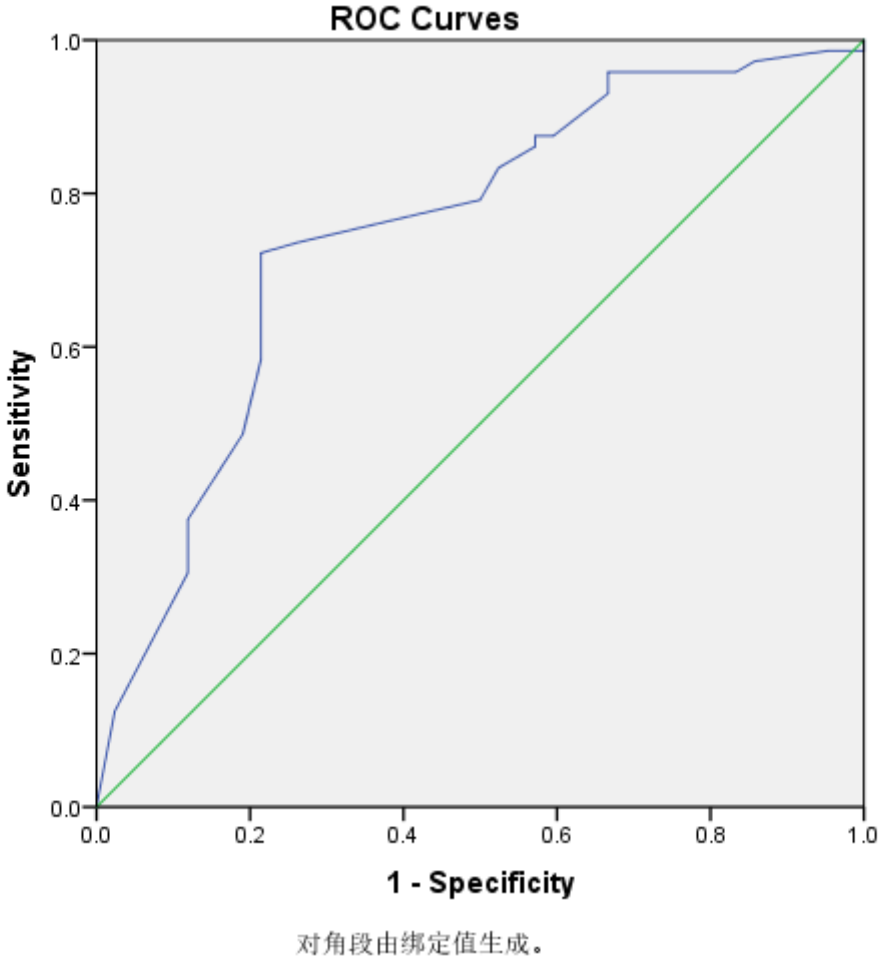

Figure 4

The ROC for the prediction of major LARS in the validation set

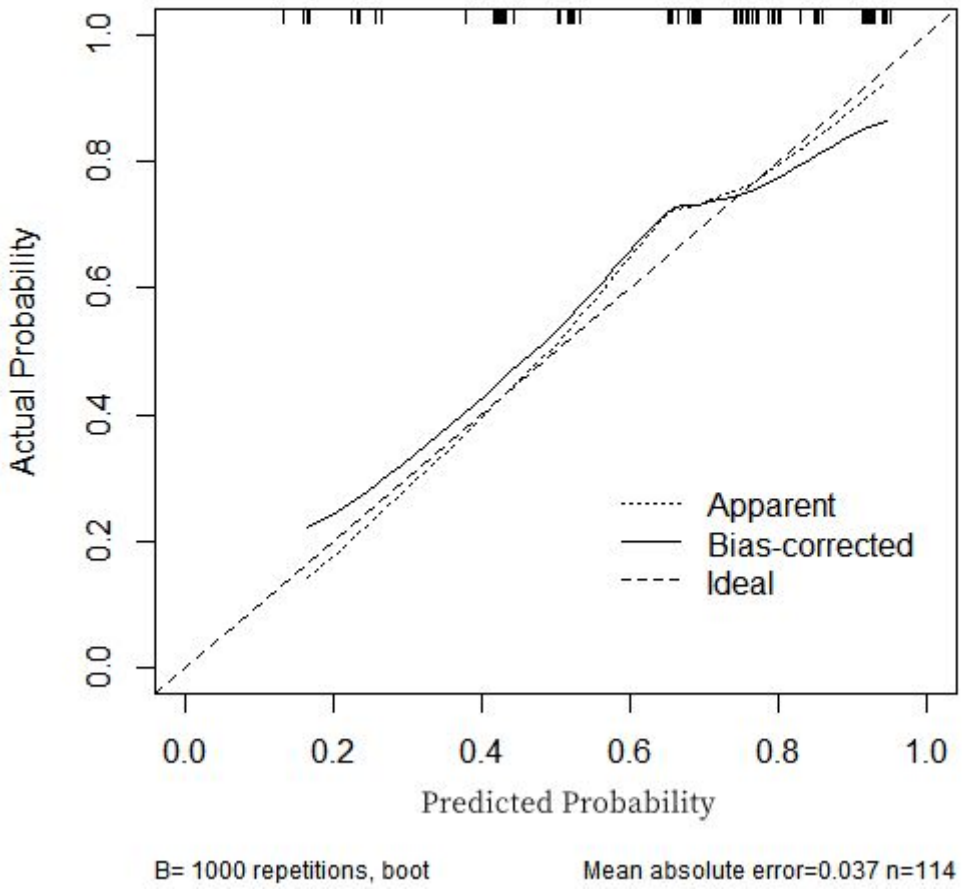

Figure 5

The calibration curve for prediction of major LARS in the validation set