

Dear reviewer

I am very grateful to your comments for the manuscript. According with your advice, we amended the relevant part in manuscript. Some of your questions were answered below.

To Reviewer #1:

- 1. Colonoscopy surveillance every 3 months after first year is to me an exaggeration. There is no additional risk of colonic cancer after a complete colonoscopy evaluation. If that was not a mistake, you should better explain why you do that.**

Answer: Thanks for the reminder. It was a mistake, and we have revised the text. According to the guidelines for Diagnosis and Treatment of Rectal Cancer in Taipei Medical University Hospital, colonoscopy is performed in the first year after surgery and every other year thereafter. The original content (Surveillance colonoscopy was performed within 12 months after the initial surgery and every 3 months thereafter.) was changed to (Surveillance colonoscopy was performed within 12 months after the initial surgery and every other year thereafter.). The article has been revised at page 7, line 13-14.

- 2. 7.1% APR is in my experience very low. Is it a bias related to the type of referral? Maybe I discussion a few phrases related to indication of sphincter saving and such a low incidence of APR.**

Answer: Thanks for your comment. Comparing to other previous studies, 7.1% APR rate is very low. However, some studies indicate that APR rate less than 10% is possible. According to the study by Kim et al (1), the APR rate at the Asan Medical Center (Seoul, Republic of Korea) is 6.4% (61/958), even lower than our center. The decrease in APR rate can be attributed to the following points. In the past 20 years, the widespread use of neoadjuvant therapy and the advances in surgical techniques have all contributed to improvement of low rectal cancer treatment. Weiser et al. (2) reported that selected patients with low-lying rectal cancers and responding to preoperative chemoradiation could still be treated with an advanced sphincter-sparing procedure instead of APR with satisfactory oncologic and functional results. Intersphincteric resection has been performed at some specialized institutions as an anus-preserving alternative that avoids the need for permanent colostomy. Intersphincteric resection is indicated for lesions <1 cm from the anorectal ring or lesions invading the internal sphincter but not the intersphincteric plane or the external sphincter, as determined by preoperative imaging (3). Adequate circumferential and distal resection margins have been shown to be independent predictors of local recurrence risk and survival (4). According to our data, there are 391 patients who undergo a sphincter-saving surgery, and 152 (38.9%) are intersphincteric resection. The average distance to anal verge is 6.5cm. The resection margin positive rate in our hospital is 7.4% (29/391). After a mean follow-up of 47 months, the mean local recurrence rate was 8.4% (33/391). Our study confirmed that the CRM positivity rate was comparable to other reported series. For example, in Warrier et al. report, a total of 3367 patients were included in Australasia, with 261 (7.5%) having a positive circumferential resection (5).

Reference:

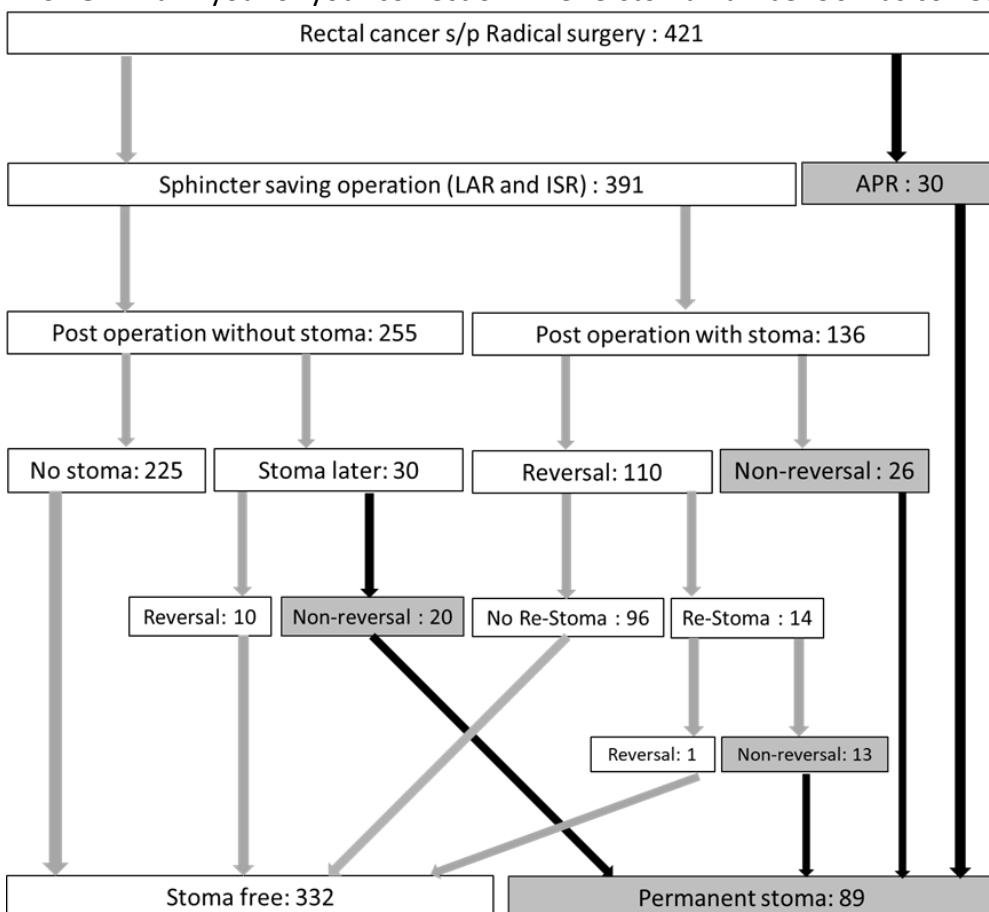
- (1) Kim JC, Lee JL, Bong JW, Seo JH, Kim CW, Park SH, Kim J. Oncological and anorectal functional outcomes of robot-assisted intersphincteric resection in lower rectal cancer, particularly the extent of sphincter resection and sphincter saving. *Surg Endosc.* 2020 May;34(5):2082-2094.
- (2) Weiser MR, Quah HM, Shia J, Guillem JG, Paty PB, Temple LK, Goodman KA, Minsky BD, Wong WD. Sphincter preservation in low rectal cancer is facilitated by preoperative chemoradiation and intersphincteric dissection. *Ann Surg.* 2009 Feb;249(2):236-42.
- (3) Rullier E, Denost Q, Vendrely V, Rullier A, Laurent C. Low rectal cancer: classification and

standardization of surgery. Dis Colon Rectum. 2013 May;56(5):560-7.

- (4) Detering R, Rutgers MLW, Bemelman WA, Hompes R, Tanis PJ. Prognostic importance of circumferential resection margin in the era of evolving surgical and multidisciplinary treatment of rectal cancer: A systematic review and meta-analysis. Surgery. 2021 Aug;170(2):412-431.
- (5) Warrier SK, Kong JC, Guerra GR, Chittleborough TJ, Naik A, Ramsay RG, Lynch AC, Heriot AG. Risk Factors Associated With Circumferential Resection Margin Positivity in Rectal Cancer: A Binational Registry Study. Dis Colon Rectum. 2018 Apr;61(4):433-440.

3. Figure 1 has a small mistake: 5th raw re-stoma is not 96 but 14

Answer: Thank you for your correction. The re-stoma number 96 was corrected to 14 in Figure 1.



4. Figure 2 is almost clear. Easy to understand how you compute the linear predictive value, but not clear how that will translate in predictive value. How do you interpolate the last raw and how do you use this value in clinical setting? I am not a statistician expert, but I fail to fully comprehend how I can use this in my clinic and what do I estimate the chances of permanent stoma. It is my belief that you should discuss a bit more on the information from the nomogram and its usage in real life.

Answer: Thanks for your comment. In recent years, statistical prediction models have been developed across most cancer types. One such predictive tool is the nomogram, which maps the predicted probabilities into points on a scale from 0 to 100 in a user-friendly graphical interface. The total points accumulated by the various covariates correspond to the predicted probability for a patient (1). Nomograms play an increasingly important role in predicting prognosis for various kinds of cancers by incorporating assorted effective factors to quantify individual risk (2). The following is an explanation of the nomogram and our example, hoping to make the interpretation of the model clearer. According to the form of Figure 2 and by contrast with the point on the top

line, local recurrence would get 70 score, perineural invasion would get 38, rectal stenosis would get 89, perirectal abscess would get 100. Based on the tumor size and operative time. Once the data number is different, the score would be different too. The greater the data number is, the higher the score will be. If the biggest tumor size is 120 mm, the score will reach 78 according to the top line of point. The longest operative time will last for 750 minutes by contrast with the top line of point, and the score will be 47. The sum of above 6 items will gain the total point. And the predicted value at the bottom line of Figure 2 will be the last odds of the permanent stoma. The next step, take a detailed look on the predicted value. For example, if the patient's total value is 150, the predicted value will be 0.7 when checking with the bottom line, and it will show the patient has 70 % permanent stoma rate.

Reference:

- (1) Iasonos A, Schrag D, Raj GV, Panageas KS. How To Build and Interpret a Nomogram for Cancer Prognosis. *J Clin Oncol*. 2008 Mar 10;26(8):1364-70.
- (2) Balachandran VP, Gonan M, Smith JJ, DeMatteo RP. Nomograms in Oncology: More Than Meets the Eye. *Lancet Oncol* (2015) 16(4): e173–80. 10.1016/S1470-2045(14)71116-7

To Reviewer #2:

1. Whether preoperative clinical staging was carried out using MRI?

Answer: Currently, MRI plays a critical role in the staging and restaging of rectal cancer. The high-quality images of MRI can help doctors formulate corresponding treatment plans. In primary staging, rectal MRI can describe the tumor location and morphology, provide its T and N categories, detect extramural vascular invasion, and identify its relationship with surrounding structures, including the sphincter complex and involvement of the mesorectal fascia (1). These features help diagnose locally advanced rectal tumors for which neoadjuvant chemoradiotherapy is indicated. In restaging after neoadjuvant chemoradiotherapy, in addition to reassessing the features noted during primary staging, rectal MRI can help in the assessment of treatment response. If pathologic complete response could be accurately identified, nonoperative treatment strategies could instead be used, potentially allowing organ preservation (2). Therefore, all rectal cancer patients in our hospital will use MRI for preoperative staging.

Reference:

- (1) Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ. MRI of Rectal Cancer: Tumor Staging, Imaging Techniques, and Management. *Radiographics*. 2019 Mar-Apr;39(2):367-387.
- (2) Kalisz KR, Enzerra MD, Paspulati RM. MRI Evaluation of the Response of Rectal Cancer to Neoadjuvant Chemoradiation Therapy. *Radiographics*. 2019 Mar-Apr;39(2):538-556.

2. Whether all patients received preoperative chemoradiotherapy was performed prophylactic stoma?

Answer: Evidence from randomized clinical trials revealed that a defunctioning stoma reduces the rate of symptomatic anastomotic leakage in rectal patients undergoing LAR (1). This complication occurs in 2%–19% of patients that have undergone such surgery (2). According to our data, symptomatic anastomotic leakage rate in defunctioning stoma group is 2.9% (4/136), while no defunctioning stoma group is 7.5% (19/255). Even without a stoma, the symptomatic leakage of the anastomosis in our hospital is low, which was still better than the average level of other series. Therefore, not all the neoadjuvant chemoradiotherapy rectal cancer patient in our hospital accepted prophylactic stoma. If the patient's conditions are eligible, the doctor will tend not to make temporary stoma. Most of time, the decision to create a stoma was made intraoperatively by

the surgeons based on several factors: bowel edema after radiation; bowel obstruction and dilation; tension, integrity, and blood supply of the anastomosis; prolonged surgery; intraoperative adverse events; tolerability of the anastomotic leakage and surgeon's discretion by experience.

Reference:

- (1) Gadan S, Brand JS, Rutegård M, Matthiessen P. Defunctioning stoma and short- and long-term outcomes after low anterior resection for rectal cancer-a nationwide register-based cohort study. *Int J Colorectal Dis.* 2021 Jul;36(7):1433-1442.
- (2) Oncological Outcomes After Anastomotic Leakage After Surgery for Colon or Rectal Cancer: Increased Risk of Local Recurrence. *Ann Surg.* 2022 Feb 1;275(2):e420-e427.

3. Reportedly, preoperative chemoradiotherapy for patients with rectal cancer may increase anastomotic leakage, does it increase the risk of permanent stoma?

Answer: As we all know that preoperative chemoradiotherapy may increase anastomotic leakage rate. Some systematic searches have indicated that preoperative chemoradiotherapy is one of common risk factors for anastomotic leakage (1). In addition, symptomatic anastomotic leakage is strongly associated with permanent stoma after low anterior resection. Jutesten et al. reported that out of 144 patients who underwent rectal surgery with anastomotic leakage, 90 (65%) patients end up with permanent stoma (2). However, although some recent studies have indicated that neoadjuvant therapy was one of risk factor to permanent stoma (3), this issue remain controversial. There are still some studies reveal that neoadjuvant therapy as permanent stoma risk factor is no statistical significance (4-5). Back to our data in Table 2, the univariate and multivariable analyses revealed that neoadjuvant chemoradiotherapy is not the risk factor of permanent stoma, no statistically significant.

Reference:

- (1) Meta-analysis of defunctioning stoma in low anterior resection with total mesorectal excision for rectal cancer: evidence based on thirteen studies.
- (2) Jutesten H, Draus J, Frey J et al. High risk of permanent stoma after anastomotic leakage in anterior resection for rectal cancer. *Colorectal Dis.* 2019 Feb;21(2):174-182.
- (3) Back E, Häggström J, Holmgren K, Haapamäki MM, Matthiessen P, Rutegård J, Rutegård M. Permanent stoma rates after anterior resection for rectal cancer: risk prediction scoring using preoperative variables. *Br J Surg.* 2021 Nov 11;108(11):1388-1395.
- (4) Li C, Qin X, Yang Z, Guo W, Huang R, Wang H, Wang H. A nomogram to predict the incidence of permanent stoma in elderly patients with rectal cancer. *Ann Transl Med.* 2021 Feb;9(4):342.
- (5) Kim S, Kim MH, Oh JH, Jeong SY, Park KJ, Oh HK, Kim DW, Kang SB; Seoul Colorectal Research Group (SECOG). Predictors of permanent stoma creation in patients with mid or low rectal cancer: results of a multicentre cohort study with preoperative evaluation of anal function. *Colorectal Dis.* 2020 Apr;22(4):399-407.

To Reviewer #3:

1. It is not appropriate to use abbreviations in the abstract.

Thanks for the reminder. We correct all the abbreviations in the abstract.

- (1) The original content (Approximately 20 per cent of patients with a tumour localized in the low rectum still encounter the possibility of requiring permanent stoma (PS), which can cause drastic changes in lifestyle and physical perceptions.) was changed to (Approximately 20 per cent of patients with a tumour localized in the low rectum still encounter the possibility of requiring permanent stoma, which can cause drastic changes in lifestyle and physical perceptions.). The article has been revised at page 3, line 4.

- (2) The original content (The purpose of this study was to determine the risk factors for PS and to develop a prediction model to predict the probability of PS in rectal cancer patients after sphincter-saving surgery.) was changed to (The purpose of this study was to determine the risk factors for permanent stoma and to develop a prediction model to predict the probability of permanent stoma in rectal cancer patients after sphincter-saving surgery.). The article has been revised at page 3, line 7-8.
- (3) The original content (Univariate and multivariate analyses were performed to identify the independent risk factors for PS) was changed to (Univariate and multivariate analyses were performed to identify the independent risk factors for permanent stoma). The article has been revised at page 3, line 13-14.
- (4) The original content (The PS stoma rate after sphincter-saving surgery was 15.1% (59/391) in our study after a median follow-up of 47.3 months (range 7–114 months). Multivariate logistic regression analysis demonstrated that local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size, liver disease, and operative time were independent risk factors for PS.) was changed to (The permanent stoma rate after sphincter-saving surgery was 15.1% (59/391) in our study after a median follow-up of 47.3 months (range 7–114 months). Multivariate logistic regression analysis demonstrated that local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time were independent risk factors for permanent stoma.). The article has been revised at page 3, line 18-21.
- (5) The original content (Several risk factors for PS after sphincter-saving surgery were identified.) was changed to (Several risk factors for permanent stoma after sphincter-saving surgery were identified.). The article has been revised at page 4, line 2.
- (6) The original content (Approximately 20 per cent of patients with a tumour localized in the low rectum still encounter the possibility of requiring permanent stoma (PS), which can cause drastic changes in lifestyle and physical perceptions. The study aimed to identify the risk factors for PS in rectal cancer patients after sphincter-saving surgery. Our results showed that the predictive models constructed by clinicopathological features exhibited perfect predictive ability and will allow physicians to inform patients about the possibility of PS prior to surgery.) was changed to (Approximately 20 per cent of patients with a tumour localized in the low rectum still encounter the possibility of requiring permanent stoma, which can cause drastic changes in lifestyle and physical perceptions. The study aimed to identify the risk factors for permanent stoma in rectal cancer patients after sphincter-saving surgery. Our results showed that the predictive models constructed by clinicopathological features exhibited perfect predictive ability and will allow physicians to inform patients about the possibility of permanent stoma prior to surgery.). The article has been revised at page 4, line 11-15.

2. Why do you exclude metastatic patients for this study?

Answer: Here are the reasons for excluding Stage IV patients. First, most of these metastases are irresectable with reported resection rates of 5–15%. Prognosis for stage IV disease is poor with a five-year survival rate of 3-10% (1-2). The patient may have died before the stoma was closed, making it difficult to evaluate risk factors for permanent stoma. Second, there is no standardized treatment for stage IV cancer currently, and there are still many ongoing studies for stage IV cancer treatment. The therapy methods will vary depending on the patient's physical condition, the hospital's medical resources, and the physician's judgment (3). Therefore, the timing of stoma closure may be influenced by different treatment modalities. Third, stage IV patients often have many problems, such as organ function affected by metastases, immunocompromised, frailty,

malnutrition, prolonged bed rest, and other comorbidities (3). Stoma closure has limited improvement in the patient's quality of life and carries a high surgical risk. Therefore, Patient factors and treatment uncertainty make it more difficult to assess risk factors for stoma closure. That's why we excluded stage IV patients and focused on patients who could have radical surgery.

Reference:

- (1) Afshari K, Chabok A, Naredi P, Smedh K, Nikberg M. Prognostic factors for survival in stage IV rectal cancer: A Swedish nationwide case-control study. *Surg Oncol*. 2019 Jun; 29:102-106.
- (2) Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. *Cancer Med*. 2020 Jan;9(1):361-373.
- (3) Stillwell AP, Ho YH, Veitch C. Systematic Review of Prognostic Factors Related to Overall Survival in Patients with Stage IV Colorectal Cancer and Unresectable Metastases. *World J Surg*. 2011 Mar;35(3):684-92.

3. Redundant in the Methodology: Inclusion criteria: No evidence of distant metastasis at the time of surgery. Exclusion criteria: patients with stage IV disease.

Answer: The original content {The inclusion criteria were as follows: (1) patients older than 18 years, (2) no evidence of distant metastasis at the time of surgery, (3) underwent radical surgery [low anterior resection, intersphincteric resection (ISR), or abdominoperineal resection (APR)], (4) pathological diagnosis of malignancy, and (5) lesion located within 12 cm from the anal verge.} was changed to {The inclusion criteria were as follows: (1) patients older than 18 years, (2) underwent radical surgery [low anterior resection, intersphincteric resection (ISR), or abdominoperineal resection (APR)], (3) pathological diagnosis of malignancy, and (4) lesion located within 12 cm from the anal verge.}. The article has been revised at page 6 line 5-7.

4. How do the authors could use the variables that affect the quality of the patient, if you included some variables as: local recurrence, anastomosis site stenosis and liver disease (exclusion criteria)? It is at least something to discuss.

Answer: From a statistical point, these risk factors are related to the risk of the stoma. With appropriate multivariate and nomogram statistical methods, we can understand the influence level of these risk factors. Nomogram can map the predicted probabilities into points on a scale from 0 to 100 in a user-friendly graphical interface. The total points accumulated by the various covariates correspond to the predicted probability for a patient. To our nomogram from a clinical point, when a patient has a perirectal abscess, a rectal stenosis, or a local recurrence, the patient has a permanent stoma. It is no surprise that these three factors can lead to permanent stoma. Rectal stenosis or local recurrences can cause mechanical bowel obstruction, which makes stoma reversal contraindicated. Perirectal abscesses mean poor anastomosis healing. Physicians tend to delay stoma closure until imaging or clinical improvement. We exclude liver disease as a variable for nomogram construction because odds ratio less than 1.

To Reviewer #4:

Seven variables extracted in the multivariate analysis were used to construct the nomogram. However, of these, only liver disease did not have a significant P value in the univariate analysis, and I feel uncomfortable about using this as a variable for nomogram construction. What are the authors' views on this matter? If liver disease is to be used as a variable for constructing the nomogram, a discussion of the association between liver disease and permanent stoma should be included in the manuscript.

Answer: Thanks for your comment. We all agree that liver disease as a variable for nomogram

construction unsuitable. Not only univariate analysis reveals no significant P value, but also odds ratio less than 1. If the OR is <1, odds are decreased for an outcome. Therefore, we adjusted Figure 2 nomogram and Figure 3 AUROC curve. All the liver disease item was removed. The corrected figure is shown below.

Figure 2

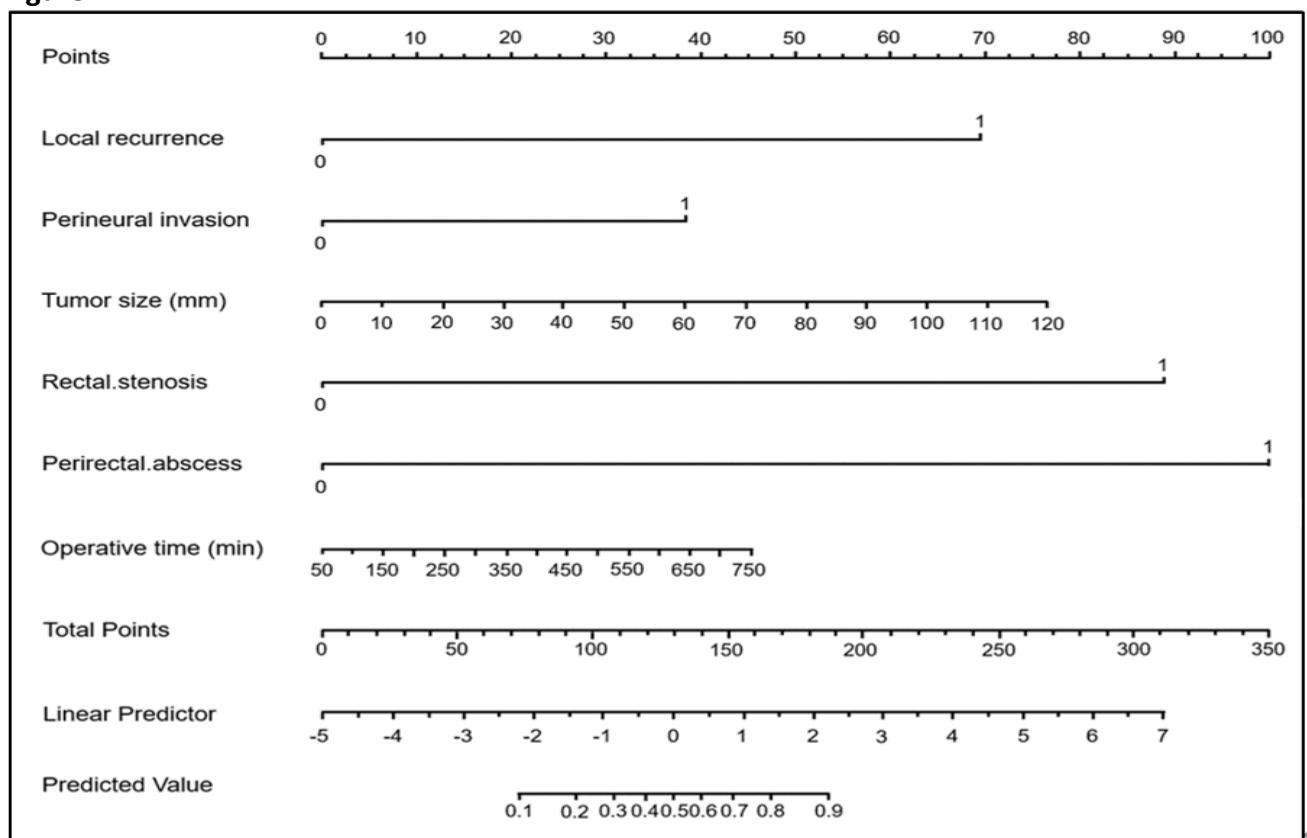
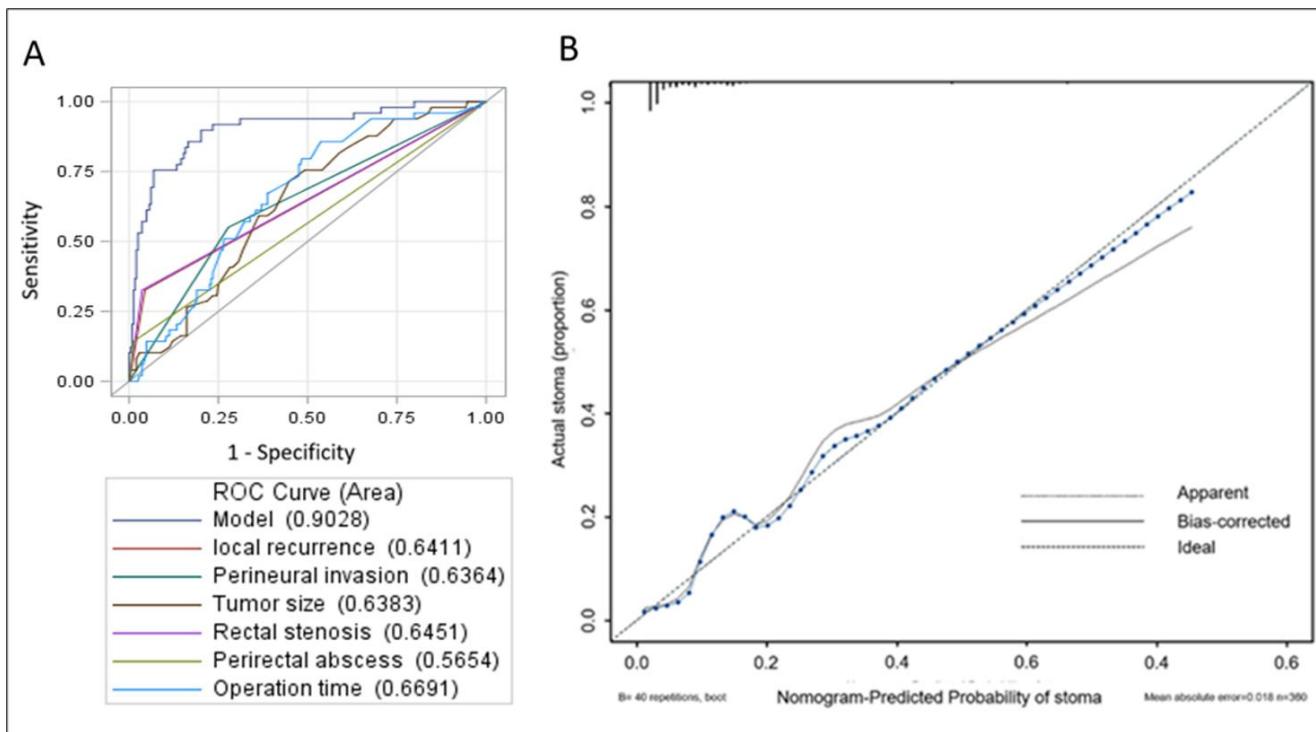


Figure 3



We have revised the text.

- (1) The original content (Multivariate logistic regression analysis demonstrated that local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size, liver disease, and operative time were independent risk factors for PS.) was changed to (Multivariate logistic regression analysis demonstrated that local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time were independent risk factors for permanent stoma.). The article has been revised at page 3, line 21.
- (2) The original content (Thus, these seven variables were selected to construct the nomogram.) was changed to (We excluded liver disease because of OR<1. Thus, these six variables were selected to construct the nomogram.). The article has been revised at page 9, line 20-21.
- (3) The original content [After these seven factors were incorporated, the nomogram achieved an outstanding C-index of 0.903 (95% CI: 0.851–0.955).] was changed to [After these six factors were incorporated, the nomogram achieved an outstanding C-index of 0.903 (95% CI: 0.851–0.955).]. The article has been revised at page 10, line 16.
- (4) The original content [The area under the receiver operating characteristic (AUROC) curve of our model (0.903) was higher than that of any single factor (local recurrence: 0.641; perineural invasion: 0.636; tumor size: 0.638; rectal stenosis: 0.645; perirectal abscess: 0.565; liver disease: 0.511; operative time: 0.669), which indicates that this model was more accurate than other models (Figure 3A).] was changed to [The area under the receiver operating characteristic (AUROC) curve of our model (0.903) was higher than that of any single factor (local recurrence: 0.641; perineural invasion: 0.636; tumor size: 0.638; rectal stenosis: 0.645; perirectal abscess: 0.565; operative time: 0.669), which indicates that this model was more accurate than other models (Figure 3A).]. The article has been revised at page 10, line 19.
- (5) The original content [This study reports that risk factors leading to PS were highly correlated with local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size, liver disease, and operative time (min).] was changed to [This study reports that risk factors leading to PS were highly correlated with local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time (min).]. The article

has been revised at page 16, line 3.

- (6) The original content [These identified risk factors were incorporated into the nomogram, and the concordance index of this model was 0.903 (95% confidence interval: 0.851-0.955).] was changed to [After exclude liver disease, these identified risk factors were incorporated into the nomogram, and the concordance index of this model was 0.903 (95% confidence interval: 0.851-0.955).]. The article has been revised at page 18, line 3-4.
- (7) The original content [This study reports that risk factors leading to PS were highly correlated with local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size, liver disease, and operative time (min).] was changed to [This study reports that risk factors leading to PS were highly correlated with local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time (min).]. The article has been revised at page 18, line 10.
- (8) The original content in Figure 2 annotation [The established nomogram for predicting PS was developed by incorporating the following seven parameters: Local recurrence, perineural invasion, tumor size (mm), rectal stenosis, perirectal abscess, liver disease, and operative time.] was changed to [The established nomogram for predicting PS was developed by incorporating the following six parameters: Local recurrence, perineural invasion, tumor size (mm), rectal stenosis, perirectal abscess and operative time.]. The article has been revised at page 27

To Reviewer #5:

This manuscript was described with a very interesting point of view. If possible, a validation cohort should be used to assess this monogram.

Answer: We test the nomogram model on a validation cohort of 32 patients. These patients are all newly collected in 2021, and they are followed up at least 1 year. All of them meet inclusion and exclusion criteria. The overall accuracy was satisfactory to be 72%. The average predicted probability of stoma-free and stoma group was 0.07 and 0.11, respectively.

