Prospective Cohort Study

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Inflammatory stress response after transanal vs laparoscopic total mesorectal excision: a cohort study based on the TaLaR trial

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Background: Transanal total mesorectal excision (taTME) is a novel approach to radical surgery for low rectal cancer; however, it is not clear whether taTME causes a more severe inflammatory stress response than laparoscopic total mesorectal excision (laTME). Therefore, the authors conducted this study to address this question, with the secondary objective of analyzing the predictive effect of inflammatory indexes on postoperative infective complications between laTME and taTME.

Methods: A total of 545 cases of laTME and 544 cases of taTME from the TaLaR randomized controlled trial were included. Inflammatory stress response was assessed via C-reactive protein (CRP), white blood cell count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, and prognostic nutritional index. Inflammatory indexes were measured and calculated preoperatively (t1) and on postoperative days one (t2) and seven (t3). The accuracy of inflammatory indexes as predictor of infective complications was evaluated by areas under the receiver operating characteristic curve.

Results: Preoperative blood parameters were comparable between the two surgical methods. There were no significant differences in CRP, white blood cell count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, or prognostic nutritional index between the two surgical methods at any time point ($P > 0.05$). Among the inflammatory indexes at three time points, CRP on the first postoperative day was the most accurate predictor of infective complications, which is suitable for two surgical methods. The AUC was 0.7671 ($P < 0.0001$) with a cutoff of 39.84 mg/l, yielding 94% sensitivity and 47% specificity.

Conclusions: Compared with laTME, taTME surgery has no obvious disadvantage with respect to the postoperative inflammatory stress response. In addition, inflammatory indexes were favorable in predicting infective complications, with the best results for CRP on the first postoperative day. Defining the specific predictors for laTME and taTME is unnecessary.

Keywords: inflammatory stress response, infective complications, laparoscopic total mesorectal excision, transanal total mesorectal excision

Introduction

The incidence of colorectal cancer (CRC) is increasing every year[1], and surgery remains a critical treatment option. However, surgical trauma induces a systemic stress response affecting the immune system, autonomic nervous system, and hypothalamic-pituitary axis[2,3]. Previous studies have reported correlations between the inflammatory stress response from surgical trauma and the risks of local and distant recurrence, in turn leading to increased recurrence and mortality rates[4,5]. Therefore, the identification of a surgical technique that minimizes trauma and systemic inflammation is of great clinical significance.

As a new surgical method for rectal cancer, transanal total mesorectal excision (taTME) has several unique advantages. This

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surgical method enables the display of the mesorectal plane to ensure better circumferential resection margins and exhibits better feasibility in narrow pelvic spaces[6]. Moreover, taTME allows the resected specimen to be removed through the anus, avoiding the need for an abdominal incision and reducing the trauma caused by the operation[7]. Concerningly, Norway has suspended the use of taTME due to oncological safety concerns[8]. Surgical trauma can induce local and systemic inflammatory reactions, which may promote tumor recurrence[9]. Therefore, until credible evidence of the long-term oncological outcomes of taTME surgery is available, we must determine whether taTME surgery is different from laparoscopic total mesorectal excision (laTME) surgery in terms of inflammatory stress response. The inflammatory stress response caused by surgical trauma can be measured via many indicators, including C-reactive protein (CRP), white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and prognostic nutritional index (PNI). These indicators have been validated with respect to CRC prognosis[10–12]. Levels of surgical trauma can be compared by assessing the effects of different surgical methods on inflammatory indexes. However, there is currently no information to determine whether the novel taTME approach exacerbates the impact of surgical trauma.

Moreover, the inflammatory indexes hold crucial clinical applications in predicting the occurrence of postoperative infective complications[13], thus guiding investigations at an early stage, aiding safe discharge from the hospital, decreasing health care costs, and even improving the survival of patients[14]. At the same time, it has been suggested that the predictive role of inflammatory indexes might need to take differences of surgical approach into account[15,16], but there is a lack of data on taTME versus laTME.

Therefore, the main goal of this study is to clarify whether taTME leads to stronger inflammation-related reactions than laTME, as well as to provide more clinical evidence to guide rectal cancer surgery choices. The secondary objectives were to analyze the predictive effect of inflammatory indexes on infective complications between laTME and taTME. To our knowledge, this is the first report to compare the traumatic stresses associated with taTME and laTME.

HIGHLIGHTS

- Equivalent changes of inflammatory response were observed in transanal total mesorectal excision compared to laparoscopic total mesorectal excision.
- C-reactive protein on the first postoperative day was the most accurate predictor of infective complications.
- Defining the specific infective complications predictor for laparoscopic total mesorectal excision and transanal total mesorectal excision is unnecessary.

Methods

Patients

All analyzed patients were from the TaLaR trial, a Phase 3, open-labeled, multicenter randomized controlled noninferiority trial conducted at 16 centers across 10 Chinese provinces between April 2016 and June 2021 (ClinicalTrials: NCT02966483)[17]. Inclusion criteria: patients were as follows: age 18–75 years; American Society of Anesthesiologists class I–III; clinical stage I–III rectal adenocarcinoma below peritoneal reflection; expectation of sphincter-preserving surgery via TME principles. The exclusion criteria were as follows: patients with T1 cancers that could be locally resected; patients with tumors exhibiting ingrowth in the internal sphincter or levator ani; patients with surgical contraindications. Ultimately, a total of 1089 patients from were included. The trial was approved by the ethics committees of all participating centers. This study has been carried out according to strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria[18] (Supplemental Digital Content 1, http://links.lww.com/JS9/B244).

Peripheral blood examinations

Peripheral venous blood samples were collected into EDTA-anticoagulate tubes. According to the research plan, peripheral venous blood samples were obtained preoperatively (t1) and on postoperative days one (t2) and seven (t3). Indexes such as CRP, WBC, and neutrophil, lymphocyte, monocyte, albumin, and platelet counts were obtained from the hospital information system. PLR was calculated as the absolute count of platelets/lymphocytes, NLR was calculated as the absolute count of neutrophils/lymphocytes, LMR was calculated as the absolute count of lymphocytes/monocytes, and PNI was calculated as the absolute count of albumin + 0.005 * lymphocytes.

Statistical analysis

All statistical correlation analyses in this study were performed using GraphPad Prism 9 and SPSS (version 25.0). Classification parameters were expressed as numbers and percentages and tested by the χ^2 test. Continuous variables were shown as means (SD). Continuous variables were compared using the Student's *t*-test and the Mann–Whitney *U* test, and χ^2 and Kruskal–Wallis *H* tests were applied for

Table 1

Demographic and clinical characteristics for laTME and taTME groups.

Variables	LaTME-group (n=545)	TaTME-group (n=544)
Male sex	333 (61.1)	359 (66.0)
Age [median (IQR)] (years)	60 (52-67)	58 (50-67)
BMI [median (IQR)] (kg/m^2)	22.8 (20.9-24.8)	22.9 (20.7-24.9)
Location from anal verge [median (IQR)] (cm)	5.5 (4.4-6.6)	5.0 (3.9-6.0)
ASA class		
I	219 (40.2)	228 (41.9)
II	270 (49.5)	279 (51.3)
III	56 (10.3)	37 (6.8)
Preoperative clinical stage		
I	89 (16.3)	105 (19.3)
II	243 (44.6)	220 (40.4)
III	213 (39.1)	219 (40.3)
Preoperative therapy	179 (32.8)	211 (38.8)
Chemotherapy plus radiation	59 (10.8)	93 (17.1)
Chemotherapy alone	120 (22.0)	116 (21.3)
Radiation alone	0 (0.0)	2 (0.4)

ASA, American Society of Anesthesiologists; LaTME, laparoscopic total mesorectal excision; TaTME, transanal total mesorectal excision.

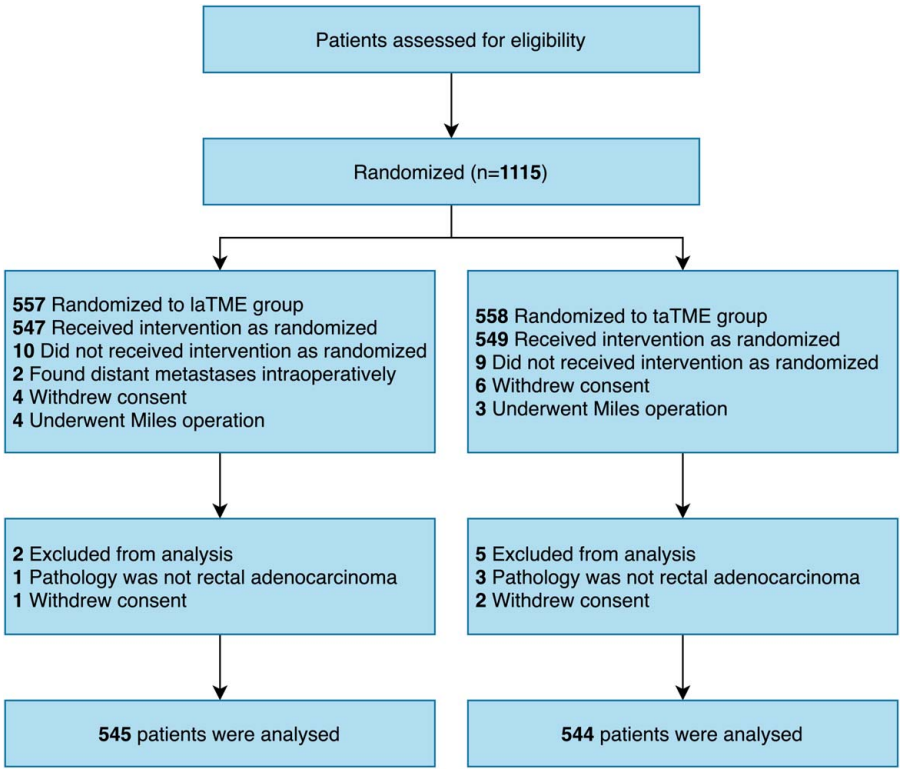

Figure 1. Flow diagram of patient enrollment and randomization.

categorical variables when appropriate. The average value was used to supplement the missing data in some indicators. An unpaired, nonparametric test was used to assess the influences of laTME and taTME on changes in inflammation-related indexes. Receiver operating characteristic curves were used to assess the accuracy of inflammatory indexes in predicting infective complications, and a cutoff was chosen for each inflammatory index. A P-value < 0.05 (two-sided) was considered significant.

Results

Study population and baseline characteristics

A total of 1089 patients were ultimately included, including 544 patients who received taTME and 545 patients who received laTME. The median age of the laTME-group was 60 years old, and it contained 333 males. The median age of the taTME-group was 58 years old, and it contained 359 males. Baseline characteristics of the patients were prospectively recorded for the two groups, which ensured the accuracy and reliability of the data (Table 1). In addition, preoperative imaging showed that there was no difference in clinical staging between the two groups (Fig. 1).

Changes in the inflammatory stress response

Hematological baseline indexes were balanced across the two surgical methods (Table 2). Over the three experimental time points, inflammatory stress response indexes changed significantly ($P < 0.05$). Specifically, CRP gradually increased, WBC increased obviously and then decreased, NLR gradually increased, PLR decreased obviously and then increased, LMR exhibited an upward trend followed by a downward trend, and PNI increased obviously and then decreased (Fig. 2).

Inflammatory stress response at different time points

When we compared the changes in inflammatory stress response indexes between laTME and taTME groups at different time points, we found no statistical differences in CRP or WBC between the two surgical methods during t1-t2, t2-t3 or t1-t3 ($P > 0.05$). Moreover, there were no significant differences between changes to the common inflammatory factor indicators NLR, PLR, LMR, or PNI associated with the two surgical methods at t1-t2, t2-t3 or t1-t3 ($P > 0.05$) (Fig. 3).

Table 2

Comparison of routine blood test index between patients subjected to different surgeries.

Variables	LaTME-group	TaTME-group	*P*
CEA (mean ± SD)	5.62 ± 9.76	4.82 ± 7.47	0.173
CA 19-9 (mean ± SD)	16.29 ± 25.10	14.48 ± 24.40	0.278
CRP (mean ± SD) (mg/l)	4.33 ± 8.32	3.90 ± 8.33	0.394
White blood cell counts (mean ± SD) ($\times 10^9$)	5.89 ± 2.10	5.78 ± 2.48	0.415
Platelet count (mean ± SD)	210.64 ± 68.98	206.95 ± 71.62	0.386
Lymphocyte count (mean ± SD)	1.83 ± 0.62	1.82 ± 0.68	0.903
Neutrophil count (mean ± SD)	3.58 ± 1.29	3.49 ± 1.37	0.274
Monocyte count (mean ± SD)	0.57 ± 0.26	0.59 ± 0.29	0.289
Albumin content (mean ± SD)	40.72 ± 4.41	40.72 ± 4.12	0.991

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, c-reactive protein; LaTME, laparoscopic total mesorectal excision; TaTME, transanal total mesorectal excision.

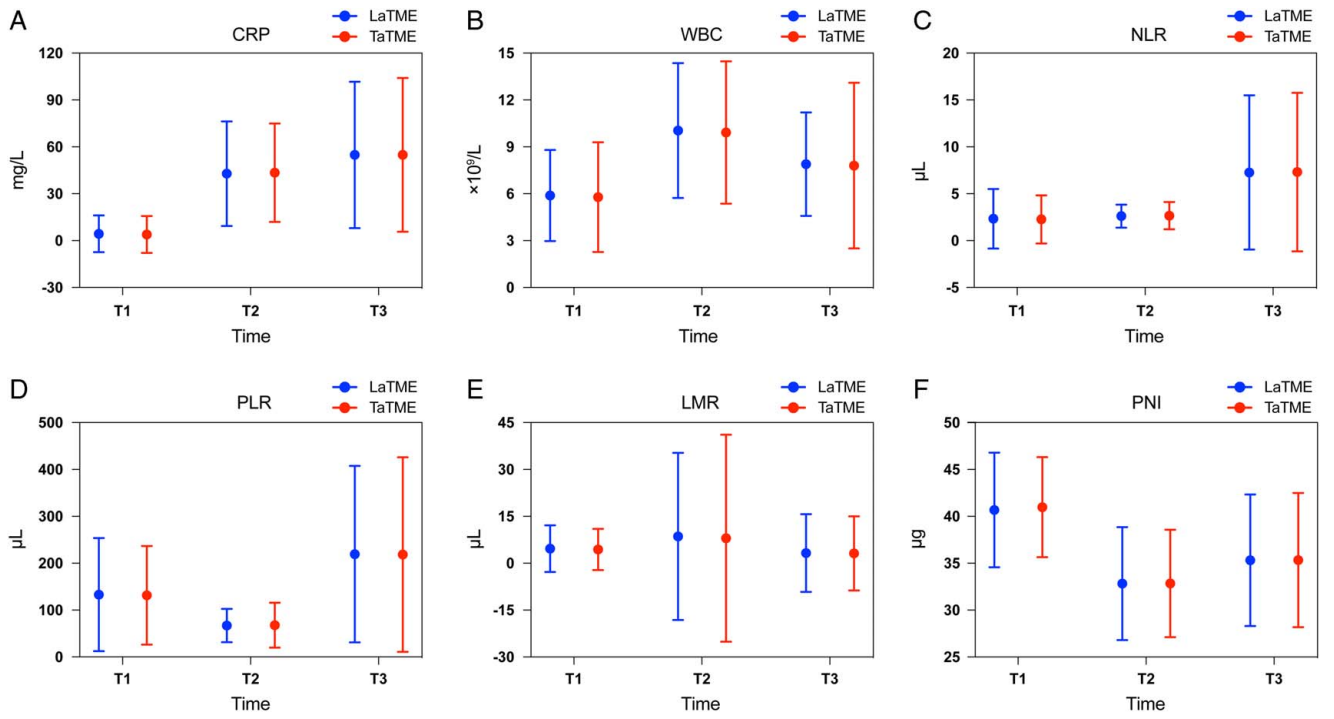

Figure 2. Inflammatory stress response indicators detected in samples from patients who underwent laparoscopic or transanal endoscopic surgery at different time points. (A) C-reactive protein. (B) White blood cell count. (C) Neutrophil-lymphocyte ratio. (D) Platelet-lymphocyte ratio. (E) Lymphocyte-monocyte ratio. (F) Prognostic nutritional index.

Diagnostic accuracy of inflammatory indexes for infective complications

All postoperative complications were recorded and listed in Table S1. Infective complications include anastomotic leakage, incisional infection, and abdominal/pelvic infection. A total of 82 patients (7.5%) suffered infective complications after surgery. The best predictive performance according to receiver operating characteristic curves analysis was found at postoperative day 1, with a CRP

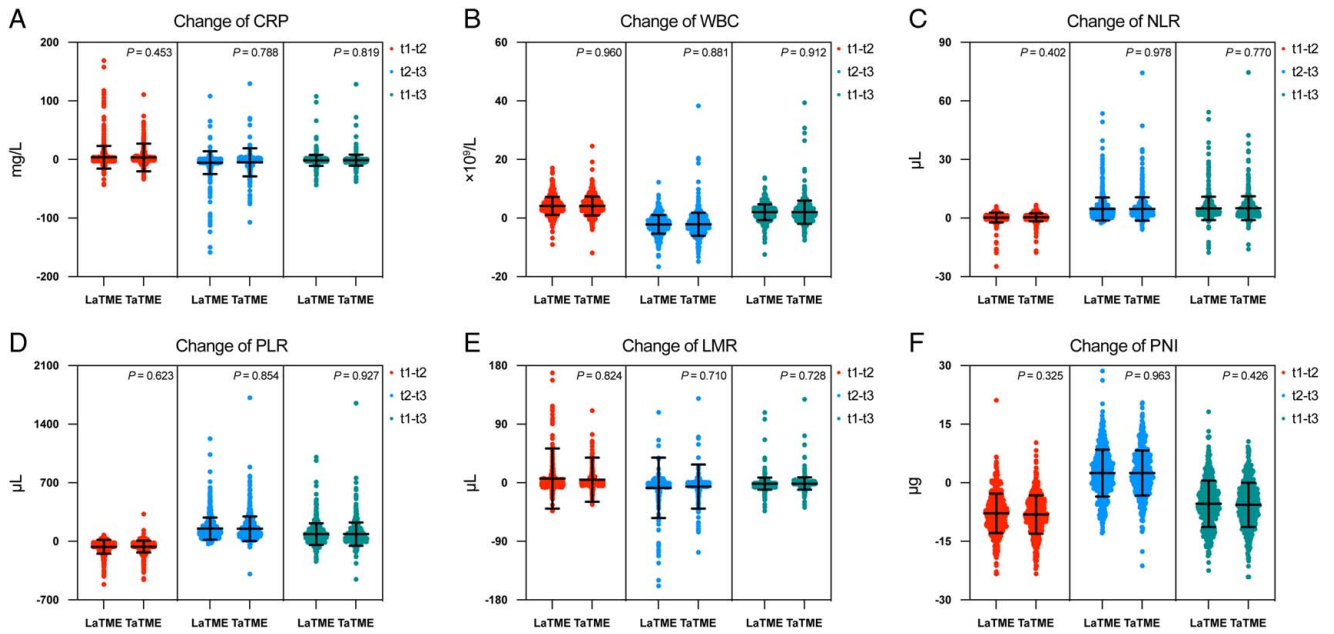

Figure 3. Changes in inflammatory stress response indicators in patients who underwent laparoscopic or transanal endoscopic surgery at different time points. (A) C-reactive protein. (B) White blood cell count. (C) Neutrophil-lymphocyte ratio. (D) Platelet-lymphocyte ratio. (E) Lymphocyte-monocyte ratio. (F) Prognostic nutritional index.

value of greater than 39.84 mg/dl (AUC: 0.7671, sensitivity 94%, and specificity 47%) (Fig. 4). In addition, CRP on postoperative day 7 (AUC: 0.6137, sensitivity 63%, and specificity 56%), WBC on postoperative day 1 (AUC: 0.6040, sensitivity 55%, and specificity 71%) and day 7 (AUC: 0.6096, sensitivity 46%, and specificity 73%), and LMR on postoperative day 1 (AUC: 0.6059, sensitivity 41%, and specificity 69%) were also useful predictors of postoperative complications. The diagnostic accuracy information of inflammatory indexes was summarized in Table 3. Moreover, according to the surgical approach, the predictive role of inflammatory indexes for infective complications was further analyzed. The results showed subtle differences in the predictive effect on different inflammatory indexes, while the best predictor remained CRP on the first postoperative day (Table S2). The relationship between daily inflammatory indexes concentrations and infective complications in the postoperative period are shown in Figure S1 (Supplemental Digital Content 2, http://links.lww.com/JS9/B245). At the time point of inflammatory indexes suitable for prediction, the inflammatory indexes of patients with infective complications have changed obviously.

Discussion

To assess the safety of taTME, this study analyzed changes in inflammatory reaction indexes at different time points following laTME and taTME. Our results revealed no significant differences in the inflammatory stress response between patients treated with taTME and those treated with laTME. Additionally, CRP level on the first postoperative day was helpful to predict postoperative infective complications.

Surgery remains an important treatment option for CRC. However, the trauma caused by surgery induces many changes in physiological and immune functions. Although these changes help promote immune defense under normal circumstances, serious surgical trauma can lead to an intense systemic inflammatory stress response and immunosuppression[19]. The adverse effects of systemic inflammatory stress have been proven by a large number of basic and clinical studies. Severe reactions to surgical trauma may induce rapid secretion of inflammatory mediators, promoting the proliferation and migration of cancer cells and eventually leading to the progression of undetected micrometastases[4]. Based on this concern, many previous studies have investigated whether different surgical approaches have different effects on traumatic stress and immune response. For colorectal surgery, laparoscopic colorectal surgery was shown to have a significant advantage in terms of reduced trauma compared to open colorectal surgery, facilitating the reduction of traumatic stress response and immunosuppression phenomena[20,21]. However, it is still unclear whether taTME is superior or similar to laTME

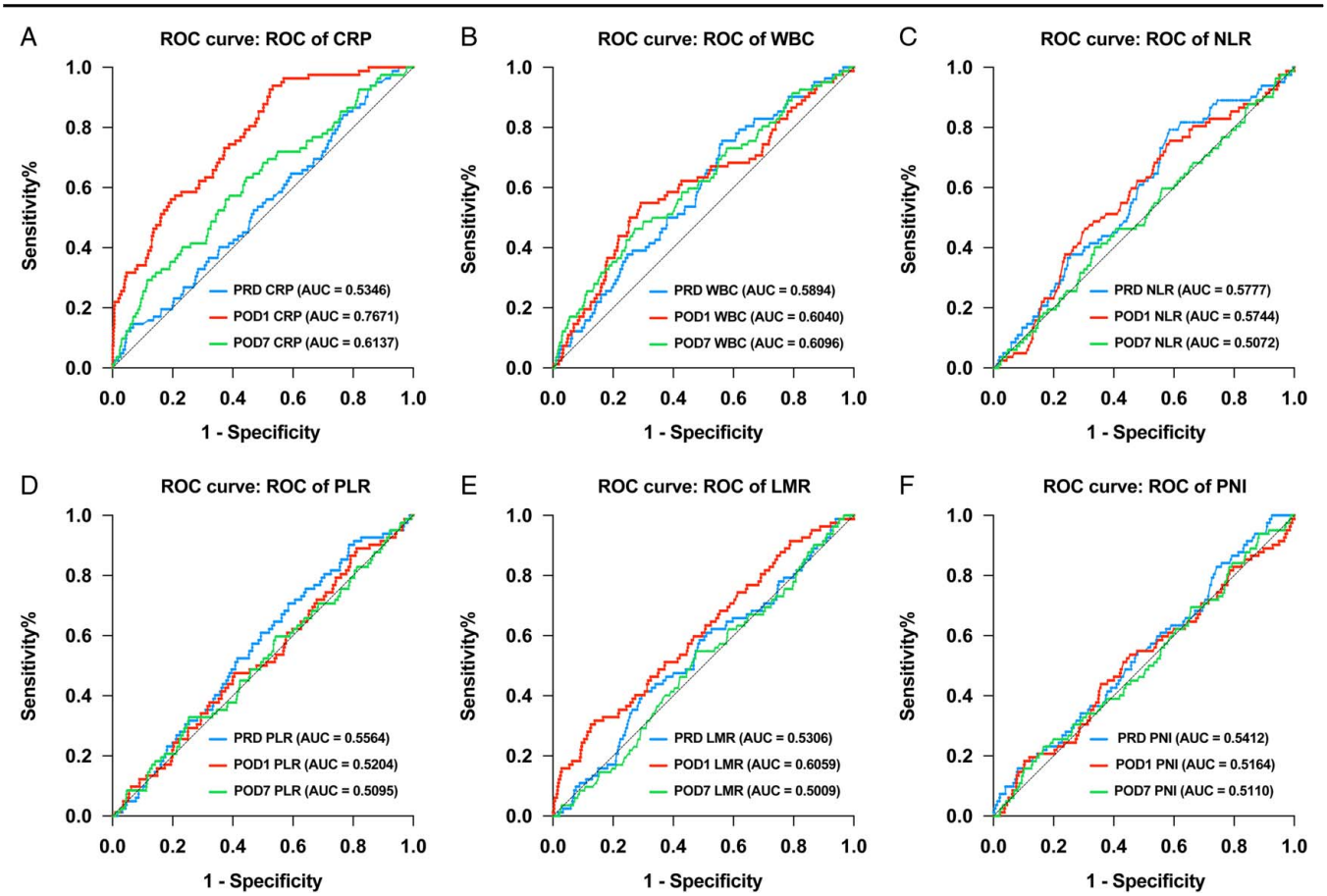

Figure 4. Diagnostic accuracy of inflammatory indexes with regard to the development of infective complications following surgery for rectal cancer. (A) C-reactive protein. (B) White blood cell count. (C) Neutrophil-lymphocyte ratio. (D) Platelet-lymphocyte ratio. (E) Lymphocyte-monocyte ratio. (F) Prognostic nutritional index.

surgery in terms of surgical trauma, necessitating further research and discussion.

In 2010, taTME technology was developed to address some of the shortcomings of laTME, including more accurate display of the distal rectum and surrounding structural features[22]. Therefore, compared with traditional surgical methods, taTME may have the advantage of improving mesorectal excision quality and the negative resection margin ratio, thus improving surgical specimen quality[23]. In addition, taTME is more feasible for narrow pelvic spaces, minimizing the risk of a series of adverse sequelae[24]. Many research reports have demonstrated that taTME is safe in terms of short-term outcomes[25–27]. Most critically, Norway has made the widely publicized decision to suspend the use of taTME because of a higher-than-expected recurrence rate[8]. The Norwegian incident has brought to the forefront a series of safety concerns associated with taTME. Therefore, we urgently need to assess the difference between taTME and conventional laTME in order to better understand the operation. Specifically, the inflammatory reaction caused by surgical trauma stress needs major attention.

The inflammatory stress response caused by surgical trauma can be measured through many inflammation-related indicators. Many serum markers of systemic inflammation have proven to be useful in guiding patient prognosis, including CRP, WBC, NLR, PLR, LMR, and PNI[10–12]. For patients with CRC, a large number of studies have corroborated the utility of these inflammation-related indicators in prognostic guidance[28,29]. Changes to inflammatory stress response indexes are closely related to tumor-related inflammation, antitumor immunity, tumor invasion, and metastasis[30–32]. Therefore, it is very important to pay attention to the impacts of different surgical methods on these indexes. This problem is especially critical because high-quality survival data following taTME surgery is still lacking. Our results showed that, although inflammation-related indexes change obviously during the perioperative period, there are no significant differences in these changes between taTME and laTME, indicating that the two methods are equally traumatic. Despite there is an evident difference between taTME and laTME in terms of surgical access, the series of intra-abdominal operations such as detachment and resection performed in the course of rectal cancer resection are similar. There is no doubt that the intra-abdominal operations caused the most significant surgical trauma. Therefore, the contribution of the difference in surgical access in terms of traumatic stress did not significantly affect the overall difference, which makes the stress of the two surgical approaches similar. Consequently, taTME is a safe surgical method in terms of the influence of surgical trauma on the inflammatory stress response in patients with rectal cancer.

Although few markers have been studied as predictors of postoperative complications, in an era of Fast Track Surgery or enhanced recovery after surgery[33] in which patients are discharged rapidly, the identification and utilization of preclinical inflammatory indexes might become important to allow early diagnosis of serious complications. According to our analysis, high concentrations of CRP, WBC, and LMR at postoperative day might be associated with the development of infective complications. Among the inflammatory indexes at three time points, CRP on the first postoperative day was the most accurate predictor of infective complications. Consistently, previous studies also have agreed that CRP value has a vital clinical potential in the prediction or exclusion of infective complications in a sufficiently early stage to facilitate timely interventions[15,34]. Therefore, these thresholds might be useful in identifying interventions targeted at reducing infective complications. And that is of particular interest in modern surgical practice[35]. More importantly, it is unclear whether the predictive role of inflammatory indexes needs to be refined according to the surgical approach[15,16]. Our results revealed that suitable predictors are similar between taTME and laTME, which fills in this knowledge gap. Considering the clinical utility, there is no need for further refinement according to the surgical approach.

One important factor that could affect our research results is differences in surgical techniques, especially for taTME, a more complicated procedure with a longer learning curve. Undoubtedly, taTME is more likely to be influenced by surgical techniques than laTME. Since the TaLaR trials strictly controlled participating surgeons, the reliability of the results of this study are assured. In addition, the prediction of postoperative infective complications by inflammatory indexes was influenced by the range of data. In conclusion, our study fills a gap in the current knowledge of taTME as related to surgical trauma stress. More research is needed in the future to improve the choices and effects of surgical treatment.

Table 3

Diagnostic accuracy of inflammatory stress response indexes for infective complications.

	AUC	*P*	Sensitivity	Specificity	Youden index	Cutoff
CRP						
PRD	0.5346	0.2964	0.9390	0.1420	0.081	0.6350
POD1	0.7671	< 0.0001	0.9390	0.4667	0.4057	39.84
PRD7	0.6137	0.0006	0.6341	0.5551	0.1892	53.67
WBC						
PRD	0.5894	0.0070	0.7561	0.4369	0.193	5.235
POD1	0.6040	0.0017	0.5488	0.7080	0.2568	11.22
PRD7	0.6096	0.0010	0.4634	0.7279	0.1913	8.720
NLR						
PRD	0.5777	0.0191	0.7927	0.4141	0.2068	1.645
POD1	0.5744	0.0249	0.7561	0.4121	0.1682	2.585
PRD7	0.5072	0.8277	0.4024	0.6634	0.0658	7.105
PLR						
PRD	0.5564	0.0889	0.7073	0.4151	0.1224	103.1
POD1	0.5204	0.5391	0.8902	0.1887	0.0789	87.75
PRD7	0.5095	0.7736	0.3293	0.7468	0.0761	254.4
LMR						
PRD	0.5306	0.3565	0.4146	0.6941	0.1087	2.425
POD1	0.6059	0.0014	0.3049	0.8739	0.1788	11.50
PRD7	0.5009	0.9789	0.5488	0.5243	0.0731	1.575
PNI						
PRD	0.5412	0.2146	0.8293	0.2572	0.0865	43.33
POD1	0.5164	0.6209	0.5366	0.5452	0.0818	33.12
PRD7	0.5110	0.7408	0.2317	0.8332	0.0649	30.51

AUC, Area Under Curve, CRP, C-reactive protein; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; POD, postoperative day; PPV, positive predictive value; PRD, preoperative day; WBC, white blood cell count.

Conclusions

Inflammation-related indexes changed significantly during the perioperative period. Equivalent changes in the inflammatory

stress response index were observed in rectal cancer patients who underwent taTME compared to those who underwent laTME. Therefore, the two approaches are equally traumatic. Apart from this, inflammatory indexes were advantageous to predict postoperative infective complications, with the best results for CRP on the first postoperative day. Defining a specific predictor on account of the surgical approach is unnecessary.

Ethical approval

This study was reviewed and approved by the Institutional Review Board of the Independent Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (2016ZSLYEC-048).

Patient consent

Not applicable.

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Author contribution

L.H. and L.K.: contributed to conception of the study and supervision; M.C., F.J.Y., and P.Z.H.: contributed to data collection, quality assessment, and manuscript draft; Z.X.L. and H. S.L.: contributed to statistical analysis and interpretation of data; X.B.Z., W.X.L., and S.L.L.: contributed to interpretation of data and revision of the manuscript draft. All authors have approved the final draft of the manuscript.

Conflicts of interest disclosure

The authors declare there is no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Transanal Versus Laparoscopic Total Mesorectal Excision For Rectal Cancer.
2. Unique identifying number or registration ID: NCT02966483.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/study/NCT02966483?cond=NCT02966483&rank=1.

Guarantor

Liang Kang and Liang Huang.

Data availability statement

The data that support the findings of this study are available from the corresponding author, LH, upon reasonable request. The data are not publicly available since this could compromise the privacy of research participants.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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