RISE ileocecal valve functional reconstruction for the prevention of postoperative intestinal dysfunction after robotic/laparoscopic right hemicolectomy: a single-blind, two-arm, multicenter randomized controlled clinical study

(Interventional Clinical Study Protocol)

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I. RESEARCH CONTEXT

Colorectal cancer, a prevalent tumor in the digestive tract, has shown an increasing incidence rate year by year. Laparoscopic right hemicolectomy serves as the standard surgical approach for tumors involving the ascending colon, cecum, and partial transverse colon, with its conventional resection scope encompassing portions of the ileum, ileocecal valve, cecum, ascending colon, and transverse colon [1]. The ileocecal valve—a semilunar fold formed by thickened muscular tissue and mucosal lining at the terminal ileum's junction with the cecum—functions as a sphincter-like structure that separates the small intestine from the large intestine. This anatomical feature plays a crucial role in regulating nutrient absorption through intestinal contents [2-3]. However, current right hemicolectomy procedures routinely omit ileocecal valve preservation, neglecting this critical physiological structure. This omission may lead to two major complications: (1) Loss of the ileocecal valve's "gate mechanism": As a bidirectional valve, the ileocecal valve restricts intestinal contents from rapidly flowing into the cecum, thereby maintaining nutrient absorption efficiency. Valve absence allows excessive intestinal contents to enter the colon, disrupting bile acid reabsorption and potentially causing both bile acid malabsorption (BAM) and bile acid diarrhea (BAD)[4]. (2) Disruption of the ileocecal valve's "anti-reflux defense": When colonic bacteria infiltrate the ileum and proximal small intestine, they compromise the intestinal microbiota barrier, triggering severe bacterial overgrowth (SIBO). This condition frequently causes recurrent abdominal bloating, diarrhea, and other chronic gastrointestinal symptoms. In severe cases, it may impair nutrient absorption including vitamin B12 and fatty acid processing − a common complication in right hemicolectomy patients that significantly compromises postoperative recovery outcomes[5].

According to the existing research, there are two ways to preserve the function of the ileocecal valve: one is to reduce the scope of surgical resection and directly retain the ileocecal valve; the other is to reconstruct the corresponding function after the removal of the ileocecal valve as far as possible. However, there are the following

problems in clinical application:

1. For patients with ileocecal valve retention, studies have reported that ileostomy with ileocecal valve preservation in ulcerative colitis can reduce high-volume fluid loss during the stoma. Additionally, solid food intake leads to firmer stools within one week after resuming solid diet post-surgery, with over 10% weight gain observed within one year. This approach also improves quality of life for patients undergoing total colectomy [10]. Current research on right hemicolectomy with ileocecal valve preservation for tumors in the hepatic flexure and transverse colon has demonstrated feasibility and surgical safety. Postoperative recovery shows significant advantages: patients in the valve-preserving group pass gas earlier and resume bowel movements sooner than non-preserved groups [11]. However, due to the extremely low incidence of hepatic flexure and transverse colon cancers (2%-4% for transverse colon, 0.7%-3% for hepatic flexure), this procedure faces practical limitations. For instance, its application to tumors in other colonic regions may result in insufficient resection margins. Consequently, many right hemicolectomy patients still face the necessity of removing the ileocecal valve along with tumor removal.

2. The concept of reconstructing the ileocecal valve was first proposed by Kellogg in 1918 [6]. Later, Itzhak Vinograd applied the concept of reintegrating the ureter into submucosal tubular valves for reconstructing the ileocecal valve, with results showing that the time for intestinal contents to pass through in the reconstructed group was significantly longer than the control group (16.2 ± 1.5min vs 4.1 ± 1.0 min), meaning the submucosal tunnel method quadrupled transit time [7]. Chardavoyn et al. employed a papillary flap technique, where a segment of the distal small intestine was grafted into the colon to form an embedded papilla approximately 4cm in diameter. To stabilize the ileocecal valve and prevent slippage, non-absorbable sutures were reinforced between the opposing serosal surfaces in a circular pattern before implantation. Postoperative analysis of intestinal microbiota revealed significantly reduced bacterial reflux in the papillary flap group compared to conventional anastomosis groups [8]. These methods have achieved satisfactory outcomes in

treating children with congenital ileocecal valve atresia and patients requiring combined resection due to non-neoplastic causes [9], indicating potential clinical benefits of ileocecal valve reconstruction. However, these approaches also present notable limitations: (1) The relatively thin colon wall makes submucosal tunnel reconstruction prone to bowel perforation; (2) The complex procedural steps hinder clinical application and promotion.

Building on these findings, this study proposes an innovative ileocolonic anastomosis approach based on the integrated reconstruction concept of mucosal folds within the ileocecal valve and the annular muscle outside the valve. The "Revolute Insert Side-End ileocecal valve reconstruction (RISE)" method combines "revolute insertion of the ileocecal valve" with "sleeve embedding reconstruction of the colonic muscle" in the ileal pouch. Preliminary small-sample clinical data demonstrate that this RISE-based ileocecal valve reconstruction technique features simple operation and a distinct "gate effect". Compared to conventional ileocolonic side-to-side anastomosis, patients with RISE anastomosis exhibit faster postoperative intestinal function recovery and significantly improved bowel function quality, highlighting the unique advantages of RISE. Notably, there was no significant difference in short-term complications between RISE and conventional anastomosis groups, indicating good surgical safety. This study plans to conduct a multicenter clinical comparative trial combining complete laparoscopic/robot-assisted right hemicolectomy with RISE anastomosis, observing its effects on short-term and long-term complication rates, quality of life, bowel function, gut microbiota, nutrient absorption, and long-term oncological outcomes.

II. RESEARCH OBJECTIVES

1. Main objectives:

To evaluate the efficacy of total laparoscopic/robot-assisted right hemicolectomy combined with ileocolonic RISE anastomosis (intervention) in improving postoperative stool formation time (primary outcome) in patients with right hemicolectomy for colorectal cancer compared with traditional side-to-side

anastomosis.

2. Secondary purposes:

(1) Compare the surgical safety of the two groups (RISE anastomosis group vs. traditional anastomosis group), including intraoperative bleeding, anastomotic leakage rate (Clavien-Dindo classification), and complication rate within 30 days after surgery;

(2) To evaluate the effects of RISE anastomosis on postoperative nutritional and metabolic disorders, including serum albumin, vitamin B12, bile acid levels, and body composition analysis (body fat percentage, muscle mass);

(3) To analyze the improvement effect of RISE anastomosis on postoperative quality of life, and evaluate it by EORTC QLQ-C30 and QLQ-CR29 scale scores;

(4) To explore the long-term effects of RISE anastomosis on overall survival (OS) and progression-free survival (PFS);

(5) Detect the dynamic changes of intestinal flora abundance (such as Proteus, streptococcus, obligate anaerobic bacteria, etc.) and metabolites (such as short chain fatty acids) in the two groups after surgery to clarify the regulatory effect of RISE anastomosis on intestinal microecology.

III. RESEARCH DESIGN

1. Research on the overall design

This prospective, single-blind, double-arm, multicenter, randomized controlled clinical trial with superiority design aims to compare postoperative intestinal function recovery between complete laparoscopic/robot-assisted right hemicolectomy combined with RISE anastomosis and traditional side-to-side anastomosis in patients with right-sided colon cancer. Eligible participants will be randomly assigned into RISE anastomosis and conventional anastomosis groups through zonal randomization, with evaluation of key outcomes including postoperative bowel function recovery (primary endpoint), complications, nutritional metabolism, quality of life, and oncological prognosis. Patients must provide informed consent prior to surgery, and all procedures are performed by senior physicians with extensive experience at each

center to ensure standardized protocols.

1.1 Random grouping method-block randomization

Randomized design: Block Randomization was used, and computer-generated random sequences (SAS 9.4) were used to assign subjects to either RISE or traditional groups on a 1:1 basis.

Group setting: The size of the fixed group is 4 cases (2 cases per group) to ensure balanced number of cases between groups. The order of the groups is randomly arranged (e.g., AABB, ABAB, BAAB, etc.) to prevent prediction of the distribution pattern.

Blind assignment: The random results are sealed in an opaque envelope, which only indicates the research center and the subject enrollment number. After signing the informed consent form, the independent research assistant of the sub-center unpacks the envelope to carry out the grouping, ensuring that the assignment process is irreversible and cannot be traced back.

Implementation process:

The random sequence is generated uniformly by the statisticians of the leading unit;

The groups were assigned according to the order of case reception in the sub-center;

If the number of cases in a sub-center is less than one group (4 cases), the remaining quota will be filled according to the random sequence.

1.2 Blinding-single-blind

Blind subjects: Patients were not informed of the specific anastomosis method, and postoperative care and follow-up procedures were kept consistent to avoid inter-group exposure differences.

2. Selection and withdrawal of participants

Research site: General Surgery, Second Affiliated Hospital of Army Medical University

Patients who meet the diagnostic criteria for right-sided colon cancer in the

NCCN Colon Cancer Guidelines and are candidates for radical surgical resection.

Inclusion criteria:

a. The study was conducted with subjects aged 18 to 80;

b. ASA score is less than 3 points;

c. Patients with a first diagnosis of tumor located in the appendix, ileocecal region, ascending colon, hepatic flexure of colon and right 1/3 of transverse colon, or patients who plan to undergo laparoscopic radical resection of the right half of colon;

d. No other history of digestive tract disease (except intestinal polyps and gallstones)

e. Willing to participate in this study and sign the informed consent form;

f. Clinical data is complete.

Exclusion criteria:

a. Patients with other malignant tumors of organs;

b. Tumors invade local surrounding organs;

c. Patients with other infectious or autoimmune diseases (e.g., Crohn's disease);

d. Patients have congenital or acquired metabolic diseases;

e. Have taken antibiotics and other drugs that interfere with the flora within one month before being selected for research;

f. The plan of the operation was changed, and the resection did not include the ileocecal valve;

Exit criteria:

a. Subjective withdrawal: the patient explicitly refuses to continue to participate in the study or adopts the anastomosis method of reconstructing the ileocecal valve.

b. Withdrawal by the investigator:

- During or after the operation, complicated conditions (such as severe abdominal adhesion, more difficult than expected) are found, which make it impossible to complete the operation according to the established plan.
- The patient's postoperative condition changes (such as severe complications, infection, etc.) are not suitable for continued participation in the study after evaluation by the investigator.

c. Missing follow-up: the patient is unable to complete the follow-up (e.g., lost

contact, refusal to further examination).

d. Protocol deviation: the subject did not receive the intervention or follow-up as required by the study protocol, affecting the validity of the data.

Termination criteria:

a. Study intervention-related risks: serious safety problems were found during the study (such as significantly higher incidence of serious complications such as anastomotic leakage and massive hemorrhage than expected), and the study was terminated after evaluation by the ethics committee.

b. Ineffective: The interim analysis showed that the intervention (RISE anastomosis) did not achieve the predefined superiority and efficacy goals, and continued study was clinically meaningless.

c. External request for termination:

The ethics committee or regulatory authorities require the termination of the study due to safety or ethical issues. The research funds or resources are insufficient to sustain the study.

d. Force Majeure: The research cannot be continued due to force majeure such as natural disaster or epidemic.

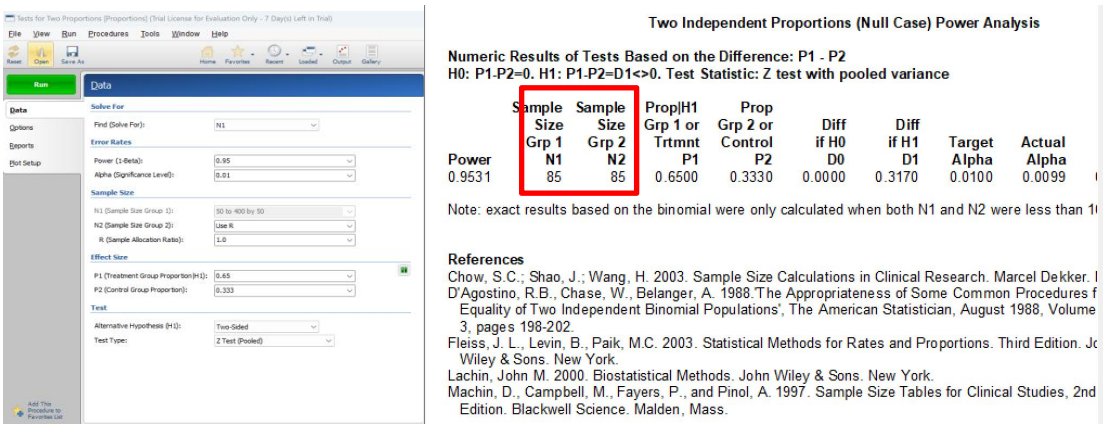
3. Sample size:

This prospective, double-arm, single-blind, multicenter randomized controlled trial evaluated the effectiveness of RISE anastomosis with ileocecal valve reconstruction. The postoperative stool formation time served as the primary endpoint for sample size calculation. Based on our prior trial results, the stool formation rate was approximately 65% in the RISE group and 33.3% in the control group on day 2 postoperatively. With a two-tailed test level α=0.05 and a 1:1 group ratio, PASS11.0 software estimated minimum sample sizes of 85 cases per group. Considering a 10% dropout rate, each group required 94 additional cases (85 + 85 × 10%), totaling 188 cases combined. The study employed block randomization with minimum blocks of 4 samples. Subsequently, sample allocation was determined based on regional average patient intake levels to match block sizes.

According to the number of patients with right-sided colon cancer admitted by each center per year, the number of cases was allocated proportionally among the research centers,

Table 1 Sample size allocation of each sub-center

Center units	**Sample size allocation**
Second Affiliated Hospital of Army Military Medical University	108
The First Affiliated Hospital of Chongqing Medical University	20
Affiliated Hospital of North Sichuan Medical College	20
Guangan People's Hospital, Sichuan Province	20
Third People's Hospital of Yibin City, Sichuan Province	20



Two Independent Proportions (Null Case) Power Analysis

Numeric Results of Tests Based on the Difference: P1 - P2
H0: P1-P2=0. H1: P1-P2=D1<>0. Test Statistic: Z test with pooled variance

Power	Sample Size Grp 1 N1	Sample Size Grp 2 N2	Prop|H1 Grp 1 or Trtmnt P1	Prop Grp 2 or Control P2	Diff if H0 D0	Diff if H1 D1	Target Alpha	Actual Alpha
0.9531	85	85	0.6500	0.3330	0.0000	0.3170	0.0100	0.0099

Note: exact results based on the binomial were only calculated when both N1 and N2 were less than 1

References

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Figure 1 PASS11.0 software interface-sample size calculation results

4. Research process

The research process is divided into screening period, treatment period and follow-up period, the details of which are as follows:

1. Screening period

Time point: preoperative

Research content and items to be collected/detected:

(1) Audit the inclusion and exclusion criteria (according to the inclusion and exclusion criteria);

(2) Sign the informed consent form;

(3) Registration of demographic statistics (age, gender, occupation, contact information);

(4) Record the past medical history (digestive tract disease, tumor history, metabolic diseases) and treatment history (surgery, radiotherapy, chemotherapy, antibiotic use);

(5) Disease diagnosis (tumor location, stage and pathological type);

(6) Physical examination (height, weight, BMI, abdominal palpation);

(7) Vital sign monitoring (blood pressure, heart rate, respiratory rate, body temperature);

(8) Imaging examination:

CT scan of upper and lower abdomen and pelvis with plain and enhanced (to evaluate the extent and metastasis of tumors);

Chest CT scan (excluding lung metastasis);

(9) Laboratory test:

Blood routine, blood biochemical (liver function, kidney function, electrolyte, blood sugar, blood lipid);

(10) Quality of life assessment: EORTC QLQ-C30 and QLQ-CR29 scales;

(11) Collect baseline biological specimens:

biological specimen	Method of collection	Collection volume	use	Method of preservation
Blood samples	Clinical	Fasting	Subsequent	Centrifuge and

	additional collection	venous blood 10mL	metabolites and molecular mechanism analysis	separate plasma/saliva for-80℃ storage
Stool samples	Clinical additional collection	5g	Fungal profiling	After sterile collection, it was directly frozen and stored at-80℃

2. Treatment

Time node: from intraoperative to 7 days after surgery

Research content and items to be collected/detected:

(1) Operation implementation:

In this study, the intervention group and the control group only differ in the digestive tract reconstruction method:

a. RISE anastomosis group (intervention group)

All procedures were performed under general anesthesia with the patient in lithotomy position. In accordance with established principles of laparoscopic right hemicolectomy, five cannulation needles were inserted to facilitate D2 lymph node dissection from inside out.

Step 1: Measurement and Dissection: Mark a 2 cm mark along the mesocolon at the terminal transverse colon, and mark the ileal distal end approximately 10 cm and 12 cm from the ileocecal junction. Use an endoscopic linear stapler to dissect the right half of the transverse colon. Perform mesenteric trimming on the ileal distal segment, ligate the ileum at marked points with 4-0 silk sutures, then dissect it using an ultrasonic scalpel. Carefully inspect both ends and disinfect with alcohol swabs.

Step 2: Intestinal End Inversion and Colon Insertion: Using an ultrasonic scalpel, make a horizontal incision 2 cm from the colon's distal end. Divide the proximal ileum into three equal segments, then suture them to the muscularis 浆膜 layer with 3-0 silk sutures, creating a 1.5 cm mucosal flap to form a simulated ileocecal valve. Perform an interrupted suture of three stitches at the midpoint of the inverted ileal segment using 3-0 silk sutures. Insert the intact ileal segment into the colon without

torsion, ensuring adjacent mesenteric vessels are free from torsion and tension.

Step 3: Intestinal Colon End-to-End Anastomosis. When there is no intestinal volvulus, fix three sutures at the transverse colon opening, one-third of the distance from the mid-point of the small bowel eversion line, to ensure precise fixation of the small intestine on the transverse colon. Close the anastomosis with 3-0 catgut suture (with barbs) using a tight stitch. If the closure is inadequate, perform interrupted suturing. After confirming no significant fistula formation, encase the anastomosis with seromuscular layer. Continuously suture the gap between the ileum and colonic mesentery with 3-0 catgut suture (with barbs). Finally, manually assess the anastomosis's size and patency.

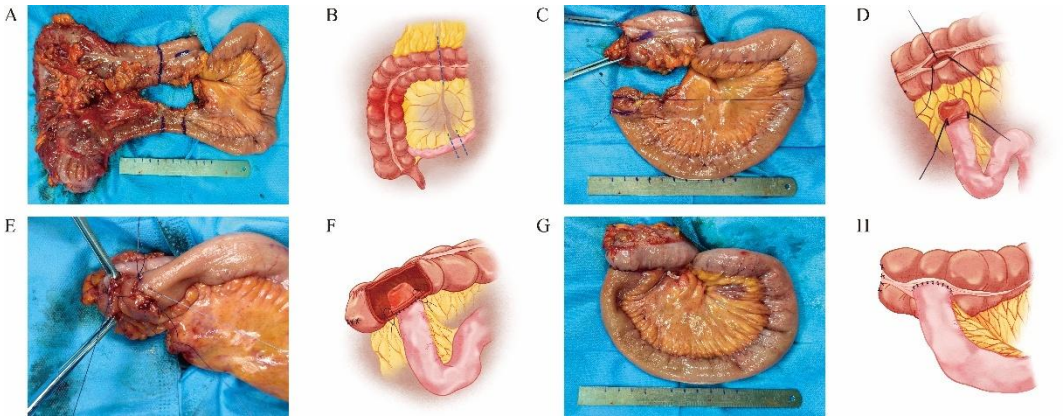

Figure 2 Schematic of RISE anastomosis steps. A-B: Identify and mark the transection sites on the transverse colon stump and terminal ileum. C-D: Evert the terminal ileum to mimic the anatomical structure of the ileocecal valve. E-F: Place fixation sutures at the transverse colon opening. G-H: Complete the RISE anastomosis of the terminal ileum with colon.

b. Conventional lateral side anastomosis group (control group)

After inserting the same cannula, ligating blood vessels, and making a 10 cm distal transection at the transverse colon mass along with a 15 cm proximal transection at the ileocecal valve, the specimen was extracted through a small midline incision. A linear stapler was used in vitro for the side-to-side ileocolonic anastomosis, followed by closure of the common intestinal incision with a second stapler. The anastomotic site was reinforced with 3-0 catgut sutures using reverse-staple technique.

(2) Intraoperative index recording:

- Total operation time (min);
- Surgical duration of anastomosis (min);
- Blood loss during operation (mL);
- Blood transfusion volume (mL);
-

(3) Immediate postoperative monitoring:

- Blood pressure, heart rate, respiration and body temperature at 24h,48h and 72h after surgery;
- Daily postoperative physical examination (abdominal signs, resumption of bowel sounds);
- Bristol stool score (recorded daily for 7 consecutive days);

(4) Laboratory test:

Blood routine and blood biochemistry (monitoring inflammatory indicators and metabolic status) at 24h and 72h after surgery;

(5) Postoperative complication records (according to Clavien-Dindo grading system):

Table 1. Clavien-Dindo grading system for surgical complications

I	**① Abnormal conditions that do not require medication or surgery, endoscopy and radiation therapy.** **② Antispasmodic, antipyretic, analgesic, diuretic, electrolyte and other drug therapy and physical therapy.** **③ Open infected wounds at the bedside**
II	① Complications requiring the use of medications other than those described above for treatment of grade I complications. ② Blood transfusion, total parenteral nutrition
III	Complications requiring surgery, endoscopy or radiation therapy
IIIa	No general anesthesia is required
IIIb	Need general anesthesia
IV	Life-threatening complications (including central nervous system complications, such as cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but not transient

	ischemic attack) require IC/ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiple organ dysfunction
V	die
"d"	If a patient has complications at discharge (see example in Table 2), the corresponding complication grade should be followed by the suffix "d". This label indicates that follow-up is required to fully assess the complication.

(6) Biological specimen collection:

biological specimen	Method of collection	Collection volume	use	Method of preservation
Organizing samples	Clinical additional collection	About 10g	Pathological analysis Molecular mechanism studies	Some were fixed in 10% formalin (for pathological analysis) and some were rapidly frozen in liquid nitrogen and transferred to-80 ℃ (for molecular mechanism studies)

3. Follow-up period

Time nodes: 1 month, 3 months, 6 months and 1 year after surgery

Research content and items to be collected/tested:

(1) 1 month (±1 week) after surgery:

- Intestinal function evaluation: barium contrast (observation of intestinal passage time and anastomosis morphology);
- Colonoscopy (to assess mucosal healing and inflammation at the anastomosis).
- Laboratory tests: blood routine, blood biochemistry, serum vitamin B12 test, tumor markers (CEA, CA19-9);
- Imaging examination: chest X-ray, abdominal CT enhancement (to assess anastomosis healing and tumor recurrence);

- Human body composition analysis (assessment of patient nutrition);
- Quality of life assessment: EORTC QLQ-C30 and QLQ-CR29 scales;
- Collection of biological specimens:

biological specimen	Method of collection	Collection volume	use	Method of preservation
Blood samples	Clinical additional collection	Fasting venous blood 10mL	Subsequent metabolites and molecular mechanism analysis	Centrifuge and separate plasma/saliva for-80℃ storage
Stool samples	Clinical additional collection	5g	Fungal profiling	After sterile collection, it was directly frozen and stored at-80℃

(2) 3 months, 6 months and 1 year (±1 week) after surgery:

- Laboratory tests: blood routine, blood biochemistry, serum vitamin B12 test; tumor markers (CEA, CA19-9);
- Imaging examination: chest X-ray, abdominal enhanced CT (to assess anastomosis healing and tumor recurrence);
- Human body composition analysis (assessment of patient nutrition);
- Collection of biological specimens:

biological specimen	Method of collection	Collection volume	use	Method of preservation
Blood samples	Clinical additional collection	Fasting venous blood 10mL	Subsequent metabolites and molecular mechanism analysis	Centrifuge and separate plasma/serum for-80℃ storage
Stool samples	Clinical additional collection	5g	Fungal profiling	After sterile collection, it was directly frozen and stored at-80℃

Research process table

search procedure	Screening period	stage of therapy			follow-up period			
		Postoperative 24h	Postoperative 48h	Postoperative 72h	Postoperative 1 month	Postoperative 3 months	Postoperative 6 months	Postoperative 1 year
Sign the informed consent form	√							
Review selection/exclusion criteria	√							
General information	√							
medical history	√							
check-up	√	√	√	√				
vital sign	√	√	√	√				
Full abdominal scan with enhanced CT	√				√	√	√	√
Chest X-ray	√				√	√	√	√
routine blood test	√	√		√	√	√	√	√
Blood Biochemistry 1	√	√		√	√	√	√	√
Surgery time		√						
amount of bleeding		√						
mRS grade		√						
NIHSS grade		√						
Therapeutic medication		√	√	√				
complication		√	√	√	√	√	√	√
adverse event		√	√	√	√	√	√	√
enteroscopy					√			
Barium contrast					√			
Bristol Fecal Score	√	√	√	√	√	√	√	√
Stool samples	√				√	√	√	√
Blood samples	√				√	√	√	√
Organizing samples		√						
remarks ： 1: Blood biochemistry includes liver function, kidney function, blood electrolyte, blood sugar, blood lipid								

5. End-point indicators

Key endpoint indicator: Time to first stool formation post-surgery (Bristol Stool Score <4): The Bristol Stool Scale categorizes stool into seven grades. As stool shape correlates with retention time in the colon, this score helps assess both intestinal transit time and anastomotic function. Scoring criteria:>5 indicates diarrhea, 6 represents mild diarrhea, and 7 signifies severe diarrhea. (Detailed scoring guidelines are provided in the appendix)

Secondary endpoints:

a. Surgical safety:

The operation was successful and the treatment effect was accurate, without anastomosis fistula, bleeding, stenosis-related symptoms; no serious complications occurred.

Indicators during operation: operation time, anastomosis time, intraoperative blood loss;

Postoperative indicators: complications within 30 days after surgery and postoperative inflammatory indicators.

Follow-up indicators: anastomosis healing, gastrointestinal iodine water radiography, upper gastrointestinal barium meal, colonoscopy, blood glucose, blood lipid and glycosylated hemoglobin and physiological related indicators.

b. Nutrient metabolism disorder:

Due to the corresponding nutritional complications such as bile acid malabsorption (BAM) after right hemicolectomy, the patients' albumin level, total protein, VitB12, bile acid and body composition analysis were tested on 3 days, 1 month, 3 months, 6 months and 1 year after surgery.

c. Improvement of quality of life after surgery:

The EORTCQLQ-C30 and EORTCQLQ-CR2930 scales were completed one month before and after surgery.

d. Total survival and tumor-free survival:

The total survival and tumor-free survival of patients after surgery. One year after surgery, imaging examination, endoscopy and tumor marker detection were used to

evaluate the recurrence and distant metastasis of tumors.

e. Changes in gut microbiota and metabolites:

Following diarrhea onset, significant taxonomic shifts occur in the gut microbiota, favoring the proliferation of fast-growing facultative anaerobes. Proteus species (primarily Enterobacteriaceae/Escherichia coli) and Streptococcus species (mainly Streptococcus salivarius and Streptococcus gallolyticus) show the most pronounced enrichment during early stages, with relative abundance potentially reaching 80% in fecal microbiota. The dramatic decline of obligate anaerobic gut symbionts and the oxidative changes in intestinal environment during diarrhea further promote their proliferation, as evidenced by elevated expression of genes encoding low-affinity cytochrome oxidases. This abundance increase coincides with the abrupt disappearance of obligate anaerobic gut symbionts (Blautia, Prevotella, Faecalibacterium, Lachnospiraceae, Ruminococcaceae, etc.), leading to depletion of related metabolites such as short-chain fatty acids. Differential analysis was conducted by detecting changes in abundance and metabolites of these associated bacterial groups.

Exploratory endpoints:

Potential organ cross-talk and molecular mechanisms of nutritional and metabolic disorders caused by RISE anastomosis. Based on the changes in patients' postoperative metabolism and stool habits, the corresponding metabolites and molecular changes in blood, stool and bile were detected to speculate the potential mechanism.

6. Data management and statistical analysis

The clinical departments utilize the institution's electronic medical record system to compile relevant patient data. Clinical outcomes are systematically analyzed by designated personnel using SPSS 22.0 statistical software. Categorical data are presented as [count (%)], analyzed through $\chi 2$-tests. Quantitative data, validated by S-W method testing for normal distribution, are expressed as ($x \pm s$) and evaluated using t-tests. Statistical significance is defined as $P < 0.05$.

Follow-up processing: The lost cases were included in the intention-to-treat (ITT) analysis, and multiple interpolation was used to fill in the missing data.

IV. Observation, recording and disposal of adverse events

Safety was evaluated by detecting or observing various vital signs, adverse events and laboratory indicators. Adverse event evaluation was based on the Clavien-Dindo Complication Scoring System (score details are shown in the appendix).

All adverse events, whether reported by patients or identified through physical examinations, laboratory tests, or other methods by investigators, will be documented in the original medical records with appropriate follow-up. Postoperative anastomotic leakage occurs when intestinal wall defects at the anastomosis site create a communication between the intestinal lumen and external environment. The presence of bleeding near the anastomosis or pelvic abscesses — even without obvious connection to the intestinal lumen — should raise suspicion for leakage. Clinical manifestations include sudden severe abdominal pain, high fever, chills, significantly elevated inflammatory markers, and changes in drainage fluid characteristics (cloudiness or bloody discharge). Immediate symptomatic treatment including fasting, anti-infective therapy, and hemostasis should be initiated upon symptom onset. Close monitoring of vital signs is required, with potential consideration for endoscopic hemostasis or repair. Emergency surgery may be considered if endoscopic treatment proves ineffective. The research team assigns dedicated personnel to document all adverse events during the trial period (from informed consent to 30 days post-surgery) in original medical records. Adverse events will be reported in detail using standardized medical record forms, with thorough evaluation of their correlation to study interventions. When necessary, senior physicians will provide guidance to ensure effective medical care and minimize adverse reaction risks.

V. Quality control

1. Development of study protocol and standard operating procedures (SOPs)

Unified research plan: clarify the research design, inclusion and exclusion criteria, intervention measures, evaluation indicators, data collection methods, etc.

Operation manual: covers sample collection, testing methods, equipment calibration, adverse event recording, etc.

Data entry specification: unified filling rules of electronic case report form (eCRF).

2. Personnel training and qualification certification

Unified training: Researchers, coordinators and data administrators are required to pass centralized training (online/offline) and pass the assessment and certification.

Training content: research protocol, SOPs, ethics, use of data entry system.

Regular retraining: retraining for process updates or problem feedback.

Authorization list: records the qualifications and operation rights of personnel in each center.

3. Data management

Use a unified EDC system (e.g., REDCap, Medidata) to set up logical checks (e.g., numerical ranges, required items).

Real-time monitoring of data entry progress and quality.

Data verification and cleanup:

Centralized data monitoring: periodic sampling of data and source documents (Source Data Verification, SDV).

Abnormal value automatic alarm (such as laboratory indicators beyond the normal range).

Central Laboratory and Imaging Center:

Biological samples are sent to the central laboratory for testing to avoid differences in testing between different laboratories.

The images were evaluated by an independent central laboratory in a blind manner.

4. Monitoring and auditing (Monitoring & Auditing)

Centralized monitoring: An independent monitoring team will check the

implementation of each center on a regular basis (frequency: once a month in the initial stage and once a quarter later).

Key inspection: subject informed consent, consistency of original data with eCRF, adverse event records.

Risk-based monitoring (RBM): Strengthen monitoring of high-risk centers or critical data points (e.g., primary endpoints).

Third-party audit: Invite an independent audit team to conduct surprise inspection on randomly selected centers to ensure compliance.

5. Equipment and materials management

Equipment standardization: all centers use the same brand and model of key equipment (such as blood pressure monitors, centrifuges); regular calibration and record calibration certificates.

Unified supply of materials: Research drugs/instruments are uniformly packaged, coded and distributed by the central pharmacy to avoid label errors.

6. Communication and coordination mechanisms

Regular meetings: kick-off meeting, mid-term analysis meeting and summary meeting to ensure that all centers update progress and problems simultaneously; establish a steering committee to resolve disputes.

Problem feedback and correction: set up a central mailbox or online platform to report problems (such as plan deviation, equipment failure) in real time; formulate the "plan deviation processing process" to record and analyze the root cause.

7. Statistical analysis and central effect adjustment

Preset statistical plans: How to handle center effects (e.g., stratified analysis, mixed effects model) is predefined in the Statistical Analysis Plan (SAP).

Sensitivity analysis: compare the consistency of results in different central subgroups and evaluate the robustness of results.

VI. Ethical principles and requirements for clinical research

Clinical research will adhere to the Helsinki Declaration of the World Medical Assembly and China's "Measures for Ethical Review of Human Life Science and

Medical Research", implementing principles including informed consent, privacy protection, compensation for free participation, risk control, special subject protection, and liability for related damages. Clinical trials may only commence after obtaining approval from the ethics committee for the study protocol. Prior to enrollment, investigators must provide participants or their legal representatives with a comprehensive explanation of the study's purpose, procedures, and potential risks, followed by signing written informed consent forms. Participants must be fully aware that their decision to join is entirely voluntary, and they retain the right to withdraw at any stage without facing discrimination or retaliation, while maintaining their medical rights. Investigators shall strictly safeguard participants' personal privacy and data confidentiality. All research materials will be stored at the Second Affiliated Hospital of the Army Medical University. Exceptions to privacy protection and personal information confidentiality may occur under legal/regulatory circumstances, allowing investigators, research supervisors, and ethics committees to access such materials.

The research team hereby commits: We will make every effort to protect participants 'personal privacy and information within the bounds of the law. Security measures include concealing identifiable participant information during data reporting, restricting access to such information, implementing data anonymization, and ensuring that all public reports regarding this study's findings will not disclose participants' personal identities.

VII. PROJECT TEAM MEMBERS

surname and personal name	unit	administrative or technical offices	professional ranks and titles	Year and month of GCP training	Division of project work
Xiao Weidong	Newbridge Hospital	forensic sursery	botanic physician	April 2017	Project Overall Manager
Jiang Enlai	Newbridge Hospital	forensic sursery	associate chief physician	May 2017	project implementation
Du Guangsheng	Newbridge Hospital	forensic sursery	associate chief physician	February 2022	project implementation

Qiu Yuan	Newbridge Hospital	forensic sursery	associate chief physician	March 2023	Head of the Subcentres
Zheng Daofeng	Newbridge Hospital	forensic sursery	physician	May 2025	data statistics
Zihan Wang	Newbridge Hospital	forensic sursery	chief physician	March 2017	project implementation

VIII. PARTICIPATING ORGANIZATIONS

1. List of sub-centres

name of organization	**Department/office**	**leading official**	**divide the work**	**cell-phone number**
The First Affiliated Hospital of Chongqing Medical University	Hong-yu zhang	Medical team leader	Patient enrollment at the sub-center	13983055038
Affiliated Hospital of North Sichuan Medical College	Wei Shoujiang	head of department	Patient enrollment at the sub-center	13990898624
Department of Gastrointestinal Hernia, Guang 'an People's Hospital, Sichuan Province	Li Yang	head of department	Patient enrollment at the sub-center	13551950216
Third People's Hospital of Yibin City, Sichuan Province	Liu Shicheng	head of department	Patient enrollment at the sub-center	18683120314

2. Other units

name of organization	Department/office	leading official	divide the work	cell-phone number
not have				

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ANNOTATIONS

Bristol defecation classification criteria

grade	expression
1	Hard small particles are difficult to pass and may be accompanied by constipation.
2	Irregularly shaped, chunky stools are difficult to pass and may be accompanied by constipation.
3	The stool is similar to a lump but smooth on the outside and easy to pass.
4	A banana-shaped stool is the standard form of normal bowel movements.
5	Soft and mushy stool, easy to pass, is a normal range of changes.
6	Fusel stools, relatively loose, may be accompanied by diarrhea.
7	Complete liquid stool is a sign of diarrhea.

Adverse event evaluation was based on the Clavien-Dindo complication scoring system.

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.