

Title:

NCT number:

2024/1/08

Study Protocol

Title: Drainage Fluid Biomarkers and Postoperative Gastrointestinal Dysfunction in Laparoscopic Colorectal Surgery. A Monocentric Prospective Observational Study

NCT number: NA yet

Study data: 2024.01.08

1. Study background

Postoperative gastrointestinal dysfunction (POGD), often referred to as postoperative ileus (POI), is a common gastrointestinal issue that frequently occurs after colorectal surgery. It is characterized by symptoms such as nausea and vomiting, abdominal distension, and delayed defecation and evacuation. The incidence of POI is not clearly defined due to the varying definitions across healthcare institutions, but it is estimated to be approximately 10-30% and is one of the most common complications after colorectal surgery (1,2). The occurrence of POI increases the nutritional risk of patients (e.g., malnutrition, myasthenia gravis, malignant morbidity), prolongs the length of hospital stay, increases hospital costs, and significantly adds to the health economic burden (3,4).

In 2018, the American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement considered abandoning the traditional definition of POI and proposed a scoring system based on intake, sensation of nausea, vomiting, physical examination, and duration of symptoms (I-FEED). They also introduced a definition of postoperative gastrointestinal dysfunction (POGD) based on scores classifying postoperative gastrointestinal function as normal (0-2), postoperative gastrointestinal intolerance (POGI) (3-5), and postoperative gastrointestinal dysfunction (POGD) (>6) (5).

The complex pathogenesis of POGD involves a brief neurogenic phase (within 3 hours) and a more prolonged inflammatory phase (beginning at 3-4 hours and lasting for days). The inflammatory phase is crucial and is recognized as initiated by mast cells and damage-associated molecular patterns that activate macrophages in the intestinal muscle layer. Subsequently, it triggers a series of cascading inflammation reactions through the release of inflammatory factors and recruitment of inflammatory cells, which contributes to the development and exacerbation of POGD.(6-13)

Levels of inflammatory cells and factors in the peritoneal fluid are changed following abdominal surgery in both rodents and humans (14,15). Many previous studies have confirmed that the use of drainage fluids also reduces the incidence of elevated inflammatory

markers, such as CRP, in the presence of unrelated inflammatory stimuli, such as concurrent infections and systemic diseases (16,17). For instance, in other diseases like meningitis, blood IL-6 is less specific than IL-6 in the drainage fluid (18). In addition, abdominal drainage fluid is more effective and efficient than routinely collected blood for detecting anastomotic leakage (AL) following colorectal cancer surgery. However, fewer studies have been conducted to predict the recovery of postoperative gastrointestinal function by analyzing drainage fluid. We believe that analyzing postoperative gastrointestinal drainage fluid is of greater clinical importance in predicting postoperative gastrointestinal function.

In our study, we collected abdominal drainage fluid near the anastomosis on the first and third day after laparoscopic colorectal cancer surgery for biochemical and cytological tests. These tests included lactate dehydrogenase (LDH), adenosine deaminase (ADA) and albumin. We also performed conventional cytological tests for neutrophils, lymphocytes, monocytes, etc. In addition, we calculated inflammatory indices such as neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and prognostic nutrition index (PNI). We also collected peripheral blood for the same cytological indices and evaluated the outcome of the patients' gastrointestinal function recovery using the I-FEED score. In addition, we analyzed the correlation between the above indices and PODG, and combined the inflammation indices of peritoneal drainage and serum to predict the outcome of gastrointestinal function recovery after laparoscopic colorectal cancer surgery, aiming to improve the accuracy and effectiveness of prediction and accelerate patient recovery.

2. Purpose of the study

Primary purpose: The study aims to examine the role of markers lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR) as markers of inflammation, in the prediction of postoperative gastrointestinal dysfunction (POGD) in drainage fluids on day 1 following laparoscopic colorectal cancer surgery.

Secondary objective: 1. The study aims to examine the role of markers lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR) as markers of inflammation, in the

prediction of POGD in drainage fluids on day 3 following laparoscopic colorectal cancer surgery.

2. The study aims to explore the correlation between albumin, adenosine deaminase (ADA), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI) and other inflammation indicators in drainage fluids on day 1 and day 3 following colorectal cancer surgery, and the occurrence of POGD.

3. The study aims to explore the correlation between neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), and other inflammation indicators in peripheral blood on day 1 and day 3 following colorectal cancer surgery, and the occurrence of POGD.

4. Combined inflammatory markers in peritoneal fluid and peripheral blood to predict POGD.

5. To evaluate the practical application of the I-FEED score in clinical practice.

3. Study endpoints

Primary endpoint:

Grading of postoperative gastrointestinal function (according to the scoring system based on intake, sensation of nausea, vomiting, physical examination, and duration of symptoms (I-FEED). normal (0-2), postoperative gastrointestinal intolerance (POGI) (3-5), and postoperative gastrointestinal dysfunction (POGD) (>6).

Secondary endpoints:

- a. Time to first postoperative deflation.
- b. Time to first postoperative bowel movement.
- c. Time to first postoperative food tolerance.
- d. Morbidity and mortality from 30-day postoperative complications .

4. Outcome Measures

Primary Outcome Measure:

Measurement of drainage fluid lactate dehydrogenase (LDH) and neutrophil to lymphocyte ratio (NLR) on postoperative day 1

Secondary Outcome Measure :

- a. Measurement of drainage fluid LDH and neutrophil to lymphocyte ratio (NLR) on postoperative day 3.
- b. Measurement of drainage fluid albumin, adenosine deaminase (ADA), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI) on postoperative day 1.
- c. Measurement of drainage fluid albumin, adenosine deaminase (ADA), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI) on postoperative day 3
- d. Measurement of blood serum neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII) on postoperative day 1.
- e. Measurement of blood serum neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII) on postoperative day 3.

4.Sample collection

Patient drainage fluid was collected on the first and third postoperative days. All samples were transferred to the laboratory for analysis within 30 minutes, and collected samples were aliquoted into 2 ml cryotubes and stored at -80 degrees Celsius until further use. Cytological analyses for neutrophils, lymphocytes, monocytes, etc. were performed using a Sysmex XN 1500 (Sysmex, Shanghai). Biochemical assays were performed using an AU480 chemistry analyzer (Beckman Coulter, USA) with enzyme kinetic assay for lactate dehydrogenase, peroxidase assay for adenosine deaminase and bromocresol green assay for albumin.

5.Follow-up plan

Content	Cytology (drainage fluid)	Biochemical (drainage fluid)	Biochemistry (peripheral blood)	Cytology (peripheral blood)	Consultation	medical examination	pathological results
preoperative			√	√			√
POD.1	√	√		√	√	√	
POD.2					√	√	
POD.3	√	√		√	√	√	
POD.4					√	√	
POD.5					√	√	
postoperative							√

POD: Post-operative day

6. Study Design

Study Type: Prospective single-central observational study

Observational Study Model: Case-Only

Study Start: February 18, 2024

Estimated completion date: October 1, 2024

7. Study population

7.1 Inclusion Criteria:

- Preoperative diagnosis of colorectal cancer through colonoscopy biopsy.
- Patients aged 18-80 years.
- Underwent laparoscopic radical resection for colorectal cancer with confirmed postoperative pathology.
- No prior radiotherapy, chemotherapy, or immunotherapy before surgery.
- Voluntary participation in the study and signing of a written informed consent form.

7.2 Exclusion Criteria:

- Pregnant or lactating women.
- Severe liver dysfunction (Child-Pugh class B or above); severe renal dysfunction

(serum creatinine level greater than 177).

- Patients with severe heart failure, chronic obstructive pulmonary disease, and other underlying diseases.
- Patients with pre-existing severe infections (developing sepsis or not improving after antibiotic treatment) before surgery.
- Patients with postoperative fistulas or those requiring a two-stage anastomosis.
- Intraoperative and postoperative intraperitoneal chemotherapy.
- Blood disorders (leukemia, lymphoma, aplastic anemia, etc.).
- Patient or family member withdraws midway;
- Intraoperative or postoperative instability of vital signs requires admission to the intensive care unit.
- Those with serious post-operative infections (e.g., incisional, lung, and urinary tract infections)
- Intraoperative conversion to open laparotomy.

8. Peri-operative procedures

The surgery was performed by an experienced surgeon (deputy head physician or above). The patient fasted for 6 hours and prohibited drinking water for 2 hours before the operation. General anesthesia was administered using static aspiration combined with endotracheal intubation under predominantly long-acting intravenous opioids (e.g. sufentanil). Anastomosis was performed using routine linear or circular techniques for resection of the left half of the colon, right half of the colon, sigmoid colon, and rectum, without the routine use of manual suture reinforcement. Drains were routinely placed in the post-operative period and removed after approximately 3 days post-operatively, once anastomotic fistulae and peritoneal effusion were excluded. Post-operative analgesia was provided. The patient utilized a patient-controlled intravenous paroxysmal pain regimen consisting of sufentanil (0.2ug/kg), tolstanesetron (5mg), and dizocin (20mg). Within 48 hours after surgery, the patient is allowed to consume fluids and enteral nutrition is gradually resumed as tolerated by the

patient. Patients were encouraged to mobilize early and were assisted in getting out of bed as they desired.

9. Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chaoyang Central Hospital of China Medical University (2024 No. 02). Each subject was informed and signed an informed consent form prior to enrolment.

10. Reference

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