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Title	Preoperative mechanical bowel preparation using conventional versus hyperosmolar polyethylene glycol-electrolyte lavage solution before laparoscopic resection for colorectal cancer (TLUMP test) : a phase III, multicenter randomized controlled non-inferiority trial
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1 **Original Article**

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7

8 **Preoperative mechanical bowel preparation using conventional versus hyperosmolar**  
9 **polyethylene glycol-electrolyte lavage solution before laparoscopic resection for colorectal**  
10 **cancer (TLUMP test): A phase III, multicenter randomized controlled non-inferiority trial**

11

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13 its contents.

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15

## 1 ABSTRACT

2 **Background:** A hyperosmolar ascorbic acid-enriched polyethylene glycol-electrolyte (ASC-  
3 PEG) lavage solution ensures excellent bowel preparation before colonoscopy; however, no  
4 study has demonstrated the efficacy of this lavage solution before surgery. This study aimed to  
5 establish the non-inferiority of ASC-PEG to the standard polyethylene glycol-electrolyte  
6 solution (PEG-ELS) in patients undergoing laparoscopic resection for colorectal cancer.

7 **Methods:** This was a prospective, single-blind, multicenter, randomized, controlled, non-  
8 inferiority clinical trial. Overall, 188 patients scheduled for laparoscopic colorectal resection  
9 for single colorectal adenocarcinomas were randomly assigned to undergo preparation with  
10 different PEG solutions between August 2017 and April 2020 at four hospitals in Japan.  
11 Participants received ASC-PEG (Group A) or PEG-ELS (Group B) preoperatively. The primary  
12 endpoint was the ratio of successful bowel preparations using the modified Aronchick scale,  
13 defined as “excellent” or “good.”

14 **Results:** After exclusion, 86 and 87 patients in Groups A and B, respectively, completed the  
15 study, and their data were analyzed. ASC-PEG was not inferior to PEG-ELS in terms of  
16 effective bowel preparation prior to laparoscopic colorectal resection (0.93 vs. 0.92; 95%  
17 confidence interval,  $-0.078$ – $0.099$ ,  $p = 0.007$ ). The total volume of cleansing solution intake  
18 was lower in Group A than in Group B (1757.0 vs. 1970.1 mL). Two and three severe  
19 postoperative adverse events occurred in Groups A and B, respectively. Patient tolerance of the  
20 two solutions was almost equal.

21 **Conclusions:** ASC-PEG is effective for preoperative bowel preparation in patients undergoing  
22 laparoscopic resection for colorectal cancer and is non-inferior to PEG-ELS.

23

24

- 1 **Keywords:** colorectal cancer, laparoscopy, bowel preparation, polyethylene glycol-electrolyte,
- 2 lavage solution
- 3
- 4

## 1 **Introduction**

2           Although surgical techniques and perioperative management have improved in recent  
3 decades, one of the greatest concerns of colorectal surgeons has been investigating strategies to  
4 prevent postoperative complications [1]. Infectious complications, including surgical site  
5 infection and anastomotic leakage, prolong the postoperative hospital stay of patients and  
6 worsen their quality of life. Mechanical bowel preparation (MBP) reduces stool burden and is  
7 performed to prevent infectious complications. Despite some negative opinions on the benefits  
8 of MBP in some clinical reports [2, 3], most surgeons use it before colorectal surgery [4-6]. The  
9 Society of American Gastrointestinal and Endoscopic Surgeons guidelines for laparoscopic  
10 resection of curable colon and rectal cancers suggest that preoperative MBP should be used to  
11 ease bowel manipulation and facilitate intraoperative colonoscopy [7]. An isotonic  
12 polyethylene glycol-electrolyte lavage solution (PEG-ELS) was first developed and used to  
13 irrigate the large intestine prior to colonoscopy in 1980 [8]. PEG-ELS is recognized as an  
14 effective and safe agent for MBP before colonoscopy and colorectal surgery [9, 10]. However,  
15 its use has some drawbacks, including an unpleasant taste and a large volume requirement.  
16 Furthermore, PEG-ELS administration often causes bowel distention due to edema of the  
17 intestine and swallowing of a large amount of air [11]. In laparoscopic colorectal surgery,  
18 intestinal distention is a particularly critical concern because distended intestines alter surgical  
19 visualization. Therefore, reducing or avoiding the use of standard PEG-ELS is necessary to  
20 mitigate these effects.

21           Recently, a new low-volume hyperosmolar PEG-ELS with a high dose of ascorbic acid  
22 (ASC-PEG, Moviprep, EA Pharma Co., Ltd., Tokyo, Japan) became available. A phase III  
23 randomized controlled trial (RCT) demonstrated that ASC-PEG was not inferior to PEG-ELS  
24 in the quality of colon preparation before colonoscopy [12]. The addition of ascorbic acid  
25 increased the osmotic pressure of the solution. Thus, ASC-PEG promotes the flow of water into

1 the bowel lumen. Therefore, a small volume of the solution exerts sufficient cleansing ability.  
2 In addition, the unpleasant taste of the solution was improved so that patients could easily drink  
3 it, thereby improving tolerability [12]. Several RCTs and meta-analyses have reported the  
4 adequate pre-colonoscopy bowel-cleansing effect, safety, and tolerability of ASC-PEG [13-15].  
5 Although ASC-PEG has been used in preparation for colonoscopy and colorectal surgery, there  
6 is a lack of evidence supporting its effectiveness and safety in bowel preparation prior to  
7 colorectal resection. If the safety and bowel cleansing is proven, the ASC-PEG preparation  
8 would be preferable for patients to receive the same MBP solution before colonoscopy and  
9 surgery. Therefore, it is essential to evaluate the efficacy, safety, and tolerability of ASC-PEG,  
10 compared to those of standard PEG-ELS, in bowel preparation before colorectal resection.

11 We hypothesized that ASC-PEG would be non-inferior to standard PEG-ELS in terms  
12 of its bowel-cleansing effect prior to laparoscopic colorectal resection. This comparative study  
13 evaluated the efficacy of ASC-PEG and standard PEG-ELS bowel preparation in patients with  
14 colorectal cancer undergoing laparoscopic colorectal resection in a randomized trial of MBP in  
15 laparoscopic colorectal surgery using the Moviprep: TLUMP test.

16

## 17 **Methods**

### 18 *Study design*

19 Between August 2017 and April 2020, we conducted a multicenter, prospective,  
20 randomized, controlled, single-blind, parallel-group, non-inferiority trial to compare the ASC-  
21 PEG and PEG-ELS bowel preparations in patients who were scheduled to undergo elective  
22 laparoscopic colorectal resection. The participants were enrolled from four different hospitals  
23 in Japan and were diagnosed with histologically confirmed single colorectal adenocarcinoma.  
24 Additional eligibility criteria were age between 20 and 85 years, Eastern Cooperative Oncology  
25 Group performance status between 0 and 2, and expected primary lesion resection. The

1 exclusion criteria included gastrointestinal obstruction, intestinal perforation, delayed gastric  
2 emptying, toxic megacolon, glucose-6-phosphate dehydrogenase deficiency, renal dysfunction,  
3 severe acute colitis, vomiting reflex dysfunction, dehydration, severe heart disease, liver  
4 dysfunction, severe anemia, receiving intravenous hyperalimentation, preoperative  
5 chemotherapy/radiotherapy/immunotherapy, uncontrollable diabetes mellitus, severe  
6 interstitial pneumonia/pulmonary emphysema, drug allergy, and pregnancy. The extent of  
7 lymph node dissection and cancer stage were classified according to the 2014 Japanese Society  
8 for Colon and Rectum Cancer guidelines [16].

9 All patients provided written informed consent to participate in the study. This trial  
10 was registered with the Japan Registry of Clinical Trials: jRCTs011180005 and adhered to the  
11 CONSORT 2010 criteria for RCTs. This study was performed in accordance with the ethical  
12 standards of the Helsinki Declaration of 1975, and the experimental protocols were approved  
13 by the Committee on Human Experimentation of Hokkaido University Hospital (Approval No.  
14 018-006) and met the guidelines of the responsible governmental agency.

15

### 16 ***Randomization***

17 Random allocation was performed by stratified block randomization. The patients  
18 were stratified according to the surgical hospital and tumor location (colon/rectum). The  
19 allocation ratio was 1:1. Treatment allocation was not masked; this process was performed  
20 using the electronic data capture system.

21

### 22 ***Perioperative management and surgical intervention***

23 All patients were admitted to the hospital and instructed to follow a normal diet.  
24 Patients fasted after lunch the day before surgery. Three hours after lunch, participants received  
25 ASC-PEG or PEG-ELS (Niflec: EA Pharma Co., Ltd., Tokyo, Japan). The PEG-ELS group was

1 instructed to drink 2 L at a rate of 1 L per hour. The ASC-PEG group was instructed to drink  
2 the first 1 L of solution, followed by 0.5 L of water within 1 hour. If the defecated feces  
3 remained unclear, they were instructed to drink the remaining 1 L of the solution followed by  
4 0.5 L of water within the second hour until the defecated feces became clear. Additional use of  
5 laxatives, drugs for digestive hyperperistalsis, and enema was prohibited. However, the use of  
6 preoperative oral antibiotics was not restricted. The vital signs of the patients were examined  
7 before and after consuming the cleansing solution. All patients responded to questionnaires on  
8 stool consistency and frequency of defecation, taste/quantity/acceptability of the cleansing  
9 solution, and symptoms.

10           Laparoscopic colorectal resection was performed in accordance with current practice  
11 guidelines and by the Japan Society for Endoscopic Surgery Endoscopic Surgical Skill  
12 Qualification System-certified surgeons [17, 18]. The small and large bowels were observed at  
13 the beginning of laparoscopic surgery to evaluate distention. After resection of the specimen,  
14 the surgeon held the cut end of the oral side, and the oral side bowel lumen of the anastomosis  
15 was recorded for more than 10 seconds using laparoscopy to evaluate the effectiveness of the  
16 bowel preparation/cleaning solution. In cases without anastomosis, the oral side bowel lumen  
17 of the stoma was observed. Conversion to laparotomy was defined as the need for an incision  
18 longer or different from what was planned without needing a preoperative statement of the  
19 length and location of the incisions. Follow-up visits were made on postoperative days 1 and 3.  
20 Vital signs, blood tests, and radiographs were assessed at each follow-up. Postoperative  
21 complications were monitored until hospital discharge.

22

### 23 ***Outcomes***

24           The primary endpoint was the effectiveness of preoperative bowel preparation using  
25 the cleansing solution, evaluated by an independent review committee (IRC). The IRC

1 consisted of three gastrointestinal surgeons who were blinded to allocation from different  
2 facilities. IRC members independently reviewed the intraoperative video. Because the  
3 intraoperative evaluation of bowel preparation is not identical to that in colonoscopy, the  
4 primary endpoint was evaluated using a five-point scale based on the Aronchick scale: 0,  
5 unevaluable situation; 1, completely cleansed with >80% of mucosa visible (excellent); 2,  
6 incompletely cleansed with 50%–80% of mucosa visible (good); 3, incompletely cleansed with  
7 <50% of mucosa visible (not good); and 4, incomplete cleansing and mucosa could not be  
8 visualized (poor) (Online Resource 1, Figure S1) [19, 20]. Grades 1 and 2 were considered  
9 “effective bowel preparation,” and grades 3, 4, and 0 were considered “ineffective bowel  
10 preparation.” The judgment made by two or three members of the IRC was the final judgment  
11 in each case.

12 The secondary outcomes were the volume of intake of the cleansing solution, degree  
13 of bowel distention, postoperative bowel function, occurrence of adverse events, and  
14 tolerability of the solution. The degree of bowel distention was evaluated on a three-point scale:  
15 0, collapse; 1, mild distention; and 2, remarkable distention [21]. The average of the score  
16 assigned by the IRC members was considered the distention score of the bowel section in each  
17 case. Data were collected, and patients were observed at follow-up according to a protocol  
18 based on individual case report forms using the electronic data capture system.

19

### 20 ***Sample size and statistical analysis***

21 For the sample size calculation, we assumed an expected effectiveness of 93% for  
22 ASC-PEG and 90% for PEG-ELS. This was based on the results of a phase III trial evaluating  
23 the use of ASC-PEG for pre-colonoscopy intestinal preparation and a phase II trial evaluating  
24 the use of PEG-ELS for preoperative intestinal preparation [12, 22]. Using the Farrington–  
25 Manning test with a one-sided alpha of 0.025, power of 0.80, assuming a 10% dropout rate, and

1 a non-inferiority margin of 0.10, the total sample size required was estimated to be 188 patients.  
2 The primary and secondary endpoints were evaluated in a population composed of all  
3 randomized cases, except participants whose primary endpoint could not be evaluated for any  
4 reason. Patients who could not complete the consumption of the bowel preparation were also  
5 included in the analysis. The inter-rater reliabilities among IRC surgeons for the primary and  
6 secondary endpoints were evaluated using Fleiss' kappa. The safety of the solution was  
7 evaluated in a population composed of all randomized cases to whom the cleansing solution  
8 was administered. All adverse events that occurred during the test period were recorded. Severe  
9 adverse events were defined as imminent death, hospital admission requirement or prolongation  
10 of hospital stay, imminent disability, and congenital disorder of the next generation. Subgroup  
11 analyses for the primary endpoint were performed for tumor location, clinical stage,  
12 performance status, age, sex, stool frequency within a week, regular administration of laxative,  
13 and tumor size. The questionnaires on the taste, quantity, and acceptability of the cleansing  
14 solutions were analyzed using the Wilcoxon rank sum test. Results are presented as mean  $\pm$   
15 standard deviation. A one-sided  $p$ -value of  $<0.025$  in the primary endpoint and a two-sided  $p$ -  
16 value of  $<0.05$  in the secondary endpoints were considered statistically significant. All  
17 statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North  
18 Carolina, USA).

19

## 20 **Results**

### 21 *Study participants*

22 Between August 2017 and April 2020, 188 patients were consecutively enrolled in this  
23 study. Of these patients, 92 and 96 were randomized to the ASC-PEG and PEG-ELS groups,  
24 respectively. After randomization, two and four patients in the ASC-PEG and PEG-ELS groups,  
25 respectively, were excluded before administering the cleansing solution. After administration

1 of the cleansing solution, before the operation, three patients in each group were excluded. After  
2 surgery, one and two patients in the ASC-PEG and PEG-ELS groups, respectively, were  
3 excluded. Therefore, the data of 86 and 87 patients in the ASC-PEG and PEG-ELS groups,  
4 respectively, were analyzed (Fig. 1).

5 Patients and disease characteristics were generally balanced between the two groups,  
6 except age (Table 1). The incidence of comorbidities was 77.9% and 71.3% in the ASC-PEG  
7 and PEG-ELS groups, respectively, and 15.1% and 10.3% of patients in the ASC-PEG and  
8 PEG-ELS groups, respectively, used laxatives regularly (Online Resource 2, Table S1).

9

### 10 ***Primary outcomes***

11 ASC-PEG was not inferior to PEG-ELS in the effectiveness of preoperative bowel  
12 preparation before laparoscopic colorectal resection (0.930 vs 0.920; 95% confidence interval  
13 [CI],  $-0.078$ – $-0.099$ ,  $p = 0.007$ ; Fig. 2). Fleiss' kappa was 0.761 (CI, 0.679–0.842), which  
14 reinforced inter-rater reliability among the IRC surgeons. Prespecified subgroup analyses for  
15 the primary endpoint were conducted to estimate the efficiency of the cleansing solutions. ASC-  
16 PEG was not considered inferior to PEG-ELS in populations such as patients with rectal tumors,  
17 those aged  $\geq 75$  years, those who defecated more than seven times per week, and those who  
18 used laxatives regularly.

19

### 20 ***Secondary outcomes***

21 The total cleansing solution intake volume was lower in the ASC-PEG group than in  
22 the PEG-ELS group (ASC-PEG vs. PEG-ELS:  $1757.0 \pm 383.4$  vs.  $1970.1 \pm 137.3$  mL; 95% CI,  
23  $1674.8$ – $1839.2$  vs.  $1940.8$ – $1999.4$  mL; Table 2). Seventy-five patients (87.2%) were required  
24 to drink more than 1000 mL of ASC-PEG. Furthermore, 56 patients (65.1%) drank 2000 mL of  
25 ASC-PEG (data not shown). In the ASC-PEG group, the patients drank an additional  $892.4 \pm$

1 330.8 mL of water. The time to first defecation was almost equivalent between the two groups  
2 ( $1.70 \pm 0.94$  vs.  $1.82 \pm 1.59$  hours; 95% CI, 1.50–1.90 vs. 1.48–2.16 hours). The required time  
3 for bowel preparation was longer in the ASC-PEG group than in the PEG-ELS group ( $3.15 \pm$   
4  $1.45$  vs.  $2.38 \pm 0.82$  hours; 95% CI, 2.84–3.47 vs. 2.20–2.55 hours).

5 Although the operative outcome was similar in both groups, the conversion rate to  
6 laparotomy was lower in the ASC-PEG group than in the PEG-ELS group (2.33 vs. 6.90%;  
7 Online Resource 2, Table S2). The distention scores of the small ( $0.398 \pm 0.431$  vs.  $0.376 \pm$   
8  $0.392$ ) and large ( $1.008 \pm 0.831$  vs.  $0.837 \pm 0.702$ ) bowels were comparable between the two  
9 groups (Online Resource 2, Table S3). However, the Fleiss' kappa was very low (data not  
10 shown).

11 Recovery of intestinal function based on the passage of flatus or feces and the  
12 commencement of eating was earlier in the ASC-PEG group than in the PEG-ELS group. The  
13 duration of postoperative hospital stay was shorter in the ASC-PEG group ( $12.87 \pm 5.41$  vs.  
14  $13.1 \pm 5.46$  days; 95% CI, 11.71–14.03 vs. 11.94–14.27 days; Table 3).

15 The total number of adverse events was 110 in 47 patients (52.2%) in the ASC-PEG  
16 group and 90 in 46 patients (51.1%) in the PEG-ELS group (Table 4). There was no mortality.  
17 Five and three patients in the ASC-PEG and PEG-ELS groups, respectively, stopped taking the  
18 cleansing solution. One patient in the PEG-ELS group who stopped taking PEG-ELS because  
19 of abdominal distension was administered an additional laxative and was excluded from the  
20 analysis of the primary endpoint. The surgical site infection (SSI) rate was low in both groups  
21 (8.89% vs. 5.43%). However, two and three severe postoperative adverse events occurred in  
22 the ASC-PEG and PEG-ELS groups, respectively. Except a patient who had intestinal  
23 obstruction in the PEG-ELS group, four of the five patients with severe adverse events required  
24 reoperation (Online Resource 2, Table S4).

25 Ancillary analyses of the taste, quantity, and acceptability of the cleansing solutions

1 reported by the patient are shown in Fig. 3. All patients in both groups had already experienced  
2 the taste and mode of administration of alternative cleansing solutions during a previous  
3 endoscopy screening or colorectal intervention. Taste, quantity, and acceptability were not  
4 significantly different between the two groups (taste,  $p = 0.17$ ; quantity,  $p = 0.31$ ; acceptability,  
5  $p = 0.05$ ).

## 7 **Discussion**

8 This study (the TLUMP test) demonstrated the non-inferiority in terms of effectiveness  
9 of ASC-PEG to PEG-ELS, in bowel preparation for patients undergoing laparoscopic colorectal  
10 resection for colorectal cancer. Inadequate bowel preparation can lead to contamination of the  
11 surgical field and an increased risk of SSI. Therefore, the bowel-cleansing effect was designated  
12 as the primary endpoint in this study, which was the same as that used in the previous phase III  
13 trial before colonoscopy [12]. Subgroup analysis revealed that the efficacy of both solutions in  
14 cleansing the bowel was equally high. However, it is possible that the non-inferiority of ASC-  
15 PEG to PEG-ELS is not definitively demonstrated in some populations. First, in the subgroup  
16 that underwent rectal resection, we speculated that higher residual food in the rectum among  
17 patients in the ASC-PEG group was due to the administration of a larger amount of liquid. A  
18 previous animal experiment showed that fecal water in the intestinal contents was significantly  
19 higher in the ASC-PEG group than in the PEG-ELS group [23]. Unlike colonoscopy, the  
20 effectiveness of bowel cleansing was evaluated in only one part of the bowel (i.e., the rectum),  
21 and non-inferiority was not observed in the rectal resection subgroup. Second, it is unclear why  
22 the ASC-PEG did not meet the inferiority criteria in older adult patients. The phase III trial that  
23 evaluated the use of ASC-PEG for pre-colonoscopy bowel preparation included only one  
24 patient (0.5%) aged  $\geq 75$  years [12]. Thus, the effectiveness of bowel cleansing in older adult  
25 patients was unknown. In our study, the ratio of the total volume of water to that of the ASC-

1 PEG solution was lower in older patients (48%) than in younger patients (52%). Although there  
2 was a small difference, reduced water intake in older adult patients could negatively affect the  
3 bowel-cleansing effect of ASC-PEG. We believe that a sufficient volume of water intake is  
4 necessary when using ASC-PEG in older adults. Third, intraluminal water is absorbed by the  
5 mucosa of the large bowel according to the concentration gradient of osmotic pressure.  
6 Intraluminal osmotic pressure is generally lower than that in blood vessels. If the intraluminal  
7 osmotic pressure increases, water absorption in the large bowel is disturbed, and the frequency  
8 of stool increases. We believe that the large bowel of patients experiencing a high frequency of  
9 stools is exposed to high osmotic pressure. Thus, it is challenging to recommend ASC-PEG,  
10 which has high osmotic pressure, in patients with a high stool frequency. Forth, we believe that  
11 the limited number of patients does affect the results in the subgroup with routine laxative use.

12         The incidence of postoperative complications was very low, including anastomotic  
13 leakage (2.33% vs. 1.15%) and SSI (8.89% vs. 5.43%), in both groups compared to previous  
14 reports [24-26]. Although administration of a cleaning solution can result in electrolyte  
15 imbalances or renal dysfunction, the postoperative incidence of these adverse effects was very  
16 low in both groups. It is considered that intraoperative fluid replacement can compensate for  
17 these adverse events if they occur. Furthermore, perioperative vital signs and blood tests did not  
18 show substantial differences between the two groups (data not shown). Our data showed that  
19 the use of ASC-PEG effectively and safely reduced the stool burden and suppressed the  
20 appearance of SSI and anastomotic leakage. These results were comparable with those of PEG-  
21 ELS.

22         In addition to a decrease in infectious complications, we speculated that ASC-PEG has  
23 other benefits in laparoscopic colorectal surgery owing to its characteristics: ASC-PEG contains  
24 a high amount of ascorbic acid. After administering ASC-PEG, residual ascorbic acid in the  
25 intestine functions as an osmotic laxative, increasing the activity of PEG-ELS. The cleansing

1 effect of ASC-PEG is exerted by residual ascorbic acid in the bowel lumen [27]. A previous  
2 report showed that the more ascorbic acid ingested, the less ascorbic acid was absorbed [28].  
3 Based on their findings, the rate of ascorbic acid absorption by ASC-PEG was estimated to be  
4 <20%. The large amount of ascorbic acid remaining in the bowel elevates osmotic pressure,  
5 increases intraluminal water and promotes peristaltic motion of the intestines. Although no data  
6 published so far indicate the dwell time of ascorbic acid in the bowel, most of the ascorbic acid  
7 is rapidly evacuated with water stool. We believe that residual ascorbic acid in the bowel  
8 restrictively contributes to postoperative bowel function. Based on its characteristics, ASC-PEG  
9 is thought to prevent bowel distention due to increased fluid inflow into the bowel lumen and  
10 decreased intestinal wall edema. In addition, we expected that the operative time would be  
11 shortened with better visualization of the operative field. Contrary to our expectations, although  
12 Fleiss' kappa was very low, the degree of intestinal distention (~~data not shown~~) and operative  
13 time in the ASC-PEG group were nearly equal to those in the PEG-ELS group. The additional  
14 water intake is considered to negate the expected benefits of ASC-PEG due to a decrease in the  
15 osmotic pressure in the bowel lumen and an increase in the amount of air swallowed during the  
16 intake of the cleansing solution, even if ASC-PEG improved intestinal edema.

17 To maximize the potential of ASC-PEG, it is very important to understand the  
18 properties of the product and improve the tolerability of patients for better compliance. The  
19 patient tolerability of ASC-PEG was not high in this study. This finding is inconsistent with  
20 previous reports on the use of ASC-PEG before colonoscopy [29, 30]. In this study, the  
21 preparation time before laparoscopic colorectal resection was much longer in the ASC-PEG  
22 group than in the PEG-ELS group ( $3.15 \pm 1.45$  vs.  $2.38 \pm 0.82$  hours). This result was contrary  
23 to the previous RCT before colonoscopy ( $2.67 \pm 0.84$  vs.  $3.19 \pm 1.02$  hours) [12]. We believe  
24 that older age negatively affects the time of preparation. In the present study, patient age was  
25 significantly higher in the ASC-PEG group than in the PEG-ELS group ( $69.8 \pm 10.0$  vs.  $65.7 \pm$

1 12.1 years). In contrast, in the previous RCT before colonoscopy, the patients were younger in  
2 the ASC-PEG group than in the PEG-ELS group ( $50.7 \pm 11.6$  vs.  $53.5 \pm 12.0$  years) [12].  
3 Furthermore, the frequency of adverse events during the administration of cleansing solutions,  
4 such as nausea, vomiting, and abdominal distention, was higher in the ASC-PEG group than in  
5 the PEG-ELS group in this study. These findings indicate that older adults are likely to spend  
6 more time consuming the cleansing solution because of the high frequency of adverse effects.  
7 We believe these contradictory results between the two studies are linked to the differences in  
8 patient age. Despite the efficacy and safety of PEG-ELS, the large volume and unpleasant taste  
9 may negatively affect patient acceptance and compliance [31-34]. To improve tolerability, some  
10 clinical trials have examined and demonstrated that a reduced volume of PEG-ELS could  
11 effectively cleanse the bowel lumen [14, 30]. The patients in this study ingested the cleansing  
12 solution according to the drug information. However, patients in the ASC-PEG group had to  
13 ingest a significantly larger amount of cleansing and water (approximately 2.5 L in total) than  
14 those in the PEG-ELS group because the time to the first defecation was longer than 1.5 hours  
15 during the intake of the cleansing solution. To improve patient tolerability and reduce the total  
16 amount of liquid intake, we recommend that patients should rest for approximately 1 hour after  
17 consuming 1 L of ASC-PEG and ingest additional solution and water thereafter, if necessary.  
18 We believe our results will help improve patient compliance and tolerability before surgery and  
19 before colonoscopy. It is important to note that additional water intake in the PEG-ELS group  
20 was not recorded. Some patients might consume additional water at their discretion for reasons  
21 such as thirst. We believe that such additional water intake should be recorded in future studies.

22         This study has several limitations. First, this study was not blinded. Second, the  
23 evaluation of the bowel-cleansing effect could have been affected by the variation in the time  
24 interval between the intake of the cleansing solution and the intervention [25, 35]. Third, unlike  
25 colonoscopy, the bowel-cleansing effect was evaluated in only one part of the bowel.

1           In summary, this prospective multicenter randomized trial demonstrated that ASC-  
2 PEG had efficacy comparable to that of standard PEG-ELS for preoperative bowel preparation  
3 in patients undergoing laparoscopic colorectal resection for colorectal cancer. To directly  
4 demonstrate whether ASC-PEG reduces postoperative complications, a superiority trial will be  
5 required after understanding the special characteristics of ASC-PEG, as shown in this study.

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6

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## 1 **Figure Legends**

2 **Fig. 1** Flowchart of the patient selection process

3 ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; PEG-ELS,  
4 polyethylene glycol-electrolyte lavage solution

5

6 **Fig. 2** Forest plot showing that ASC-PEG was non-inferior to PEG-ELS in terms of effective  
7 bowel preparation before laparoscopic colorectal resection

8 ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; CI,  
9 confidence interval; PEG-ELS, polyethylene glycol-electrolyte lavage solution; PS,  
10 performance status

11

12 **Fig. 3** Box plot showing patients' evaluation of ASC-PEG and PEG-ELS

13 The taste, quantity, and acceptability of the solutions are shown (a score of 0 being the worst  
14 and 10 being the best). ○, average of the ASC-PEG group; +, average of the PEG-ELS group;  
15 Red, ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; blue,  
16 PEG-ELS, polyethylene glycol-electrolyte lavage solution

17

18 **Online Resource 1**

19 **Supplementary Figure**

20 **Figure S1.** Representative intraluminal images

21

22 **Online Resource 2**

23 **Supplementary Tables**

24 **Table S1.** Patients' medical history and concomitant drug use

25 **Table S2.** Operative outcomes

1

2 **Table S3.** Severe adverse events

**Table 1. Patient characteristics**

<b>Variables</b>		<b>ASC-PEG (n = 86)</b>	<b>PEG-ELS (n = 87)</b>	<b>P-value</b>
<b>Sex</b>	<b>Male/Female</b>	48/38 (55.8/44.2)	52/35 (59.8/40.2)	0.60
<b>Age (years)</b>		69.8 ± 10.0	65.7 ± 12.1	0.01
<b>BMI (kg/m<sup>2</sup>)</b>		23.3 ± 3.8	23.1 ± 3.2	0.62
<b>PS</b>	<b>≤I/≥II</b>	86/0 (100.0/0.0)	86/1 (98.9/1.1)	0.32
<b>Tumor location</b>	<b>Colon/rectum</b>	53/33 (61.6/38.4)	51/36 (58.6/41.4)	0.69
<b>Clinical stage</b>	<b>≤I/≥II</b>	50/36 (58.1/41.9)	51/36 (58.6/41.4)	0.95

Data are presented as mean ± standard deviation or number (percentage)

ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; BMI, body mass index; PEG-ELS, polyethylene glycol-electrolyte lavage solution; PS, performance status

**Table 2. Bowel preparation**

Variables	ASC-PEG (n = 86)		PEG-ELS (n= 87)		Difference	
		95% CI		95% CI		95% CI
<b>Total volume of cleansing solution (mL)</b>	1757.0 ± 383.4	(1674.8–1839.2)	1970.1 ± 137.3	(1940.8–1999.4)	-213.1	(-299.4 to -126.9)
<b>Water intake (mL)</b>	892.4 ± 330.8	(821.5–963.4)				
<b>Time to first defecation (hour)</b>	1.70 ± 0.94	(1.50–1.90)	1.82 ± 1.59	(1.48–2.16)	-0.12	(-0.51–0.28)
<b>Time of preparation (hour)</b>	3.15 ± 1.45	(2.84–3.47)	2.38 ± 0.82	(2.20–2.55)	0.78	(0.42–1.13)
<b>Fluid infusion (yes)</b>	20 (23.3)		23 (26.4)			
<b>Preoperative oral antibiotics (yes)</b>	13 (15.1)		19 (21.8)			
<b>Stool consistency within 1 week*</b>	15/45/23/3		9/55/21/2			
<b>(Hard/normal/loose/diarrhea)</b>	(17.4/52.3/26.7/3.5)		(10.3/63.2/24.1/2.3)			

<b>Frequency of defecation within 1 week*</b>	26/60	37/50
<b>(&lt;7/≥7)</b>	(30.2/69.8)	(42.5/57.5)

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Data are presented as mean ± standard deviation or number (percentage). \*Data were collected from patient questionnaires.

ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; CI, confidence interval; PEG-ELS, polyethylene glycol-electrolyte lavage

**Table 3. Postoperative outcomes**

<b>Variables</b>	<b>ASC-PEG (n = 86)</b>		<b>PEG-ELS (n = 87)</b>		<b>Difference</b>	
		<b>95% CI</b>		<b>95% CI</b>		<b>95% CI</b>
<b>Time to leave the bed (day)</b>	1.00 ± 0.15	(0.97–1.03)	0.98 ± 0.21	(0.93–1.02)	0.02	(–0.03–0.08)
<b>Time to first flatus (day)</b>	1.67 ± 1.00	(1.46–1.89)	1.69 ± 0.93	(1.49–1.89)	–0.02	(–0.31–0.27)
<b>Time to first defecation (day)</b>	2.56 ± 1.63	(2.21–2.91)	2.62 ± 1.75	(2.25–2.99)	–0.06	(–0.57–0.45)
<b>Time to commencement of drinking (day)</b>	1.06 ± 0.28	(1.00–1.12)	0.99 ± 0.19	(0.95–1.03)	0.07	(0.00–0.14)
<b>Time to commencement of eating (day)</b>	4.23 ± 1.85	(3.84–4.63)	4.91 ± 3.09	(4.25–5.57)	–0.68	(–1.44–0.09)
<b>Length of postoperative hospital stay (day)</b>	12.87 ± 5.41	(11.71–14.03)	13.1 ± 5.46	(11.94–14.27)	–0.23	(–1.86–1.40)

Data are presented as mean ± standard deviation or number (percentage)

ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; CI, confidence interval; PEG-ELS, polyethylene

glycol-electrolyte lavage solution

**Table 4. Adverse events**

Events	ASC-PEG (n = 90)			PEG-ELS (n = 92)	
	Preoperative		Post-operative	Preoperative	
	Total	Stopped administration	Total	Preoperative	
		Stopped administration		Total	Stopped administration
Abdominal distension	19		20	1	2
Nausea	15	3	8		2
Abdominal pain	9		5		3
Fatigue	4		4		
Vomiting	4	1	2	2	
Vertigo	4		2		1
Headache	4				
Thirst	3		7		
Chills	3		3		
Insomnia	2		1		
Discomfort of the ear	1	1			
Elevated blood pressure	4		1		1
Decreased blood pressure	1		1		
Tachycardia	1		1		
Bradycardia				1	1
Liver dysfunction				4	6
Renal dysfunction					1
Electrolyte imbalance					

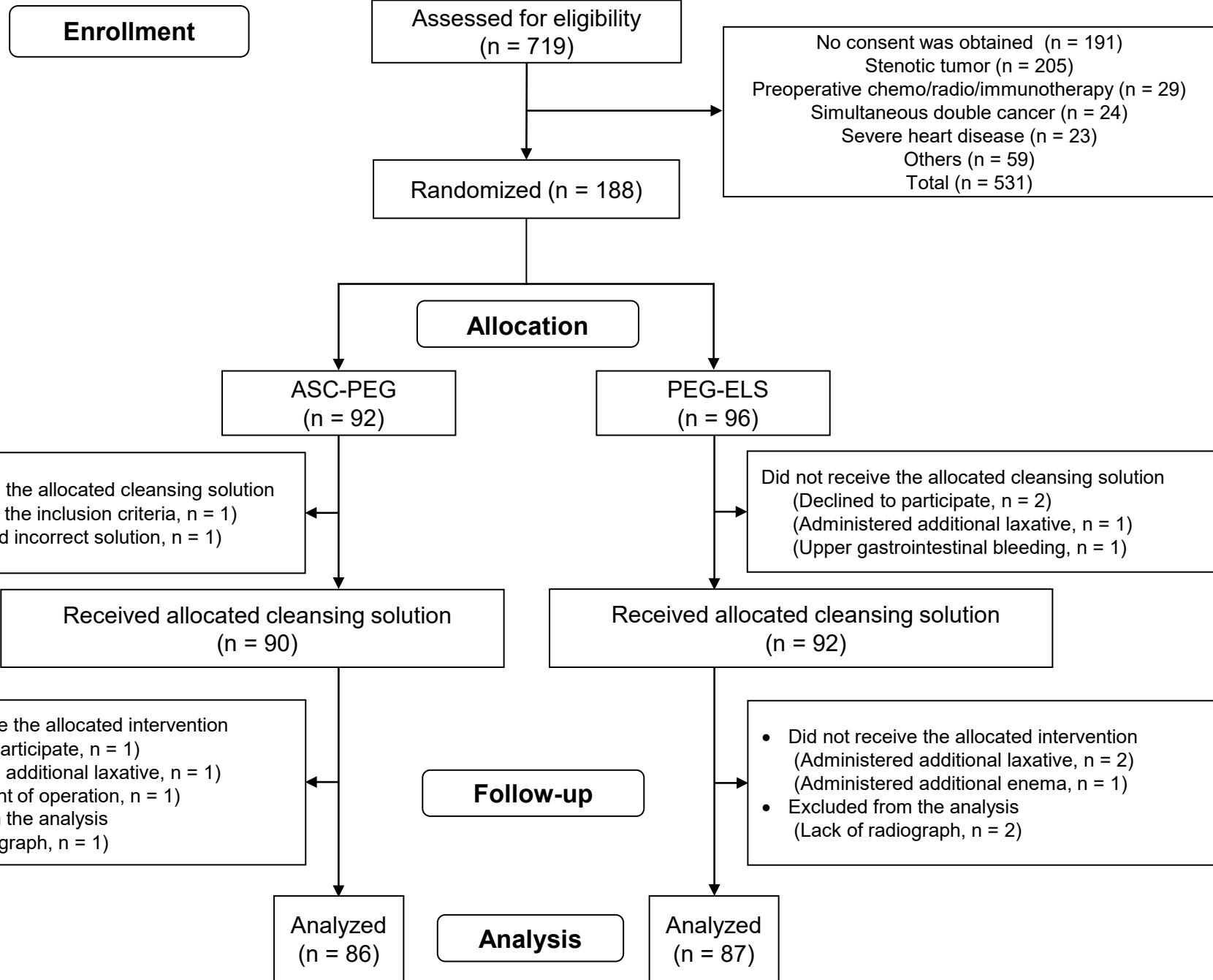
Hyponatremia			1			
Hypochloremia			1			
Hyperkalemia			1			
<b>Bowel obstruction</b>			3			5 (1)
<b>Anastomotic bleeding</b>			4			
<b>Intra-abdominal bleeding</b>			2 (1)			
<b>Colitis</b>			3			3
<b>Diverticulitis</b>			1			
<b>Small bowel perforation</b>						1 (1)
<b>Delirium</b>			1			
<b>Pneumonia</b>			1			
<b>Pulmonary atelectasis</b>						1
<b>SSI</b>						
Wound infection			5			4
Intra-abdominal abscess			1			
Anastomotic leakage*			2 (1)			1 (1)
<b>Others</b>			3			4
<b>Total</b>	74	5	36	55	3	35
<b>Severe events</b>	0		2	0		3
<b>Mortality</b>	0		0	0		0

\*Anastomotic leakage was defined as a defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extraluminal compartments, regardless of whether it was locally, generally, or radiologically diagnosed.

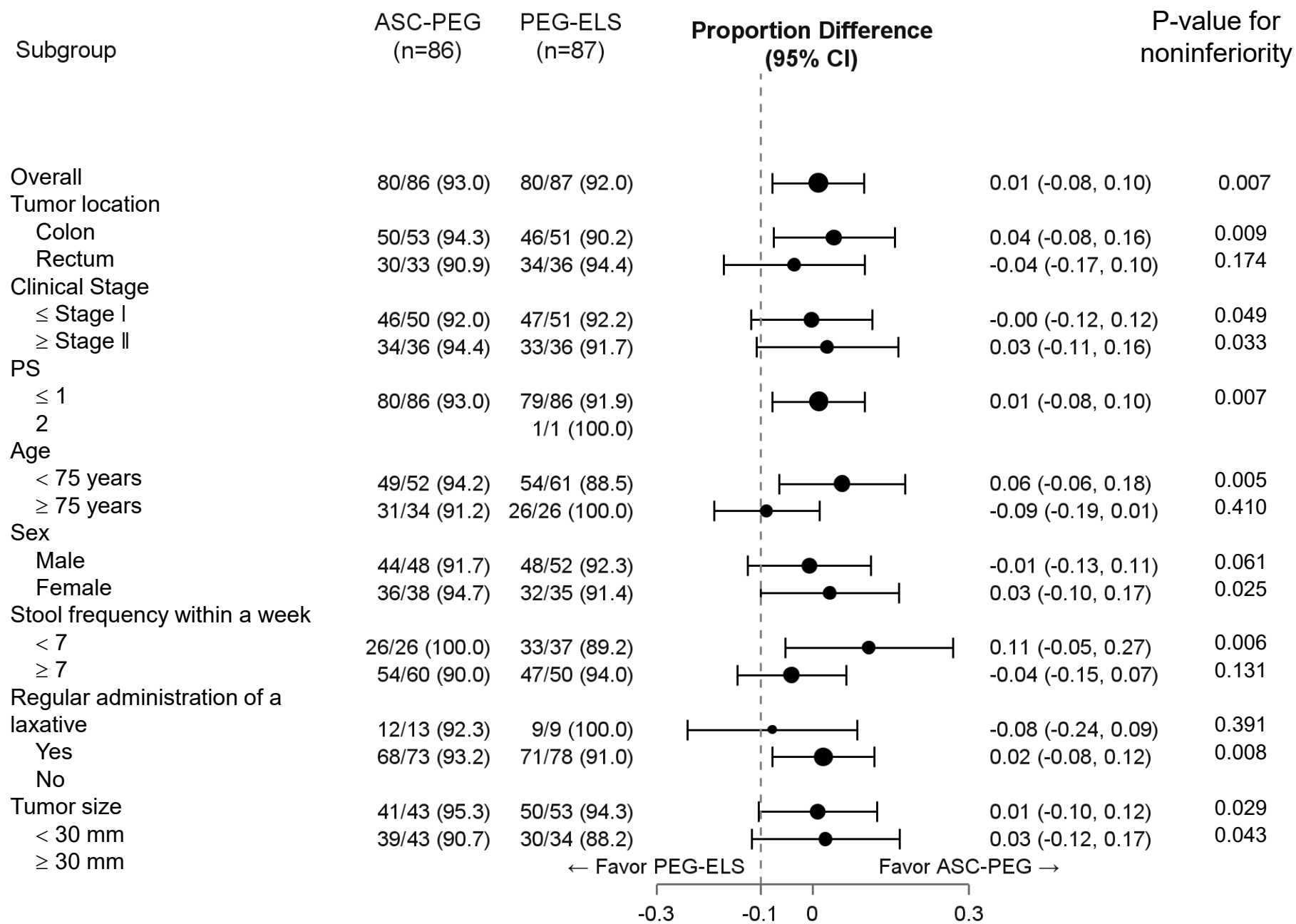
( ), number of severe adverse events

ASC-PEG, ascorbic acid-enriched polyethylene glycol-electrolyte lavage solution; PEG-ELS, polyethylene glycol-electrolyte lavage solution; SSI, surgical site infection

# Figure 1



# Figure 2



**Figure 3**

