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Preoperative Hemoglobin Level as Predictor of the Development of High-output Stoma in Rectal Cancer Surgery

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Abstract. *Background/Aim: High-output stomas (HOSs) are a complication that can cause dehydration or renal dysfunction and affect the quality of life of patients, causing water, sodium, and magnesium depletion with malnutrition. Preoperative factors that are useful for predicting HOS are not well defined. Patients and Methods: A total of nine patients developed HOS among 31 patients who underwent rectal cancer surgery with ileostomies during 2014-2021. Clinicopathological and surgical parameters were also analyzed. HOS was defined as maximum output of ≥2,000 ml/day. Results: The clinicopathological features did not differ between the HOS and non-HOS groups. Lower Hemoglobin (Hb) levels (<12 mg/dl) and longer operation times (≥300 min) were shown to be risk factors in the development of HOS. Conclusion: Low Hb levels on preoperative blood tests were predictors of HOS development in patients who underwent rectal cancer surgery and ileostomies simultaneously in our data set. Further studies are required to improve the robustness of these findings.*

Colorectal cancer is the third most common cancer in males and the second most common in females, with approximately 1.9 million new cases and 0.9 million deaths in 2020 worldwide (1). Recent advances in rectal cancer surgical strategies and multidisciplinary treatments, including perioperative treatment, have greatly improved the recurrence and survival rates of rectal cancer (2). However, surgical resection with lymph node dissection still determines prognosis (3). While the primary objective of this intervention is the complete removal of cancerous tissue and regional lymph nodes, preservation of anorectal function has emerged as a key concern for patients. Thus, preserving the anus during low anterior resection has substantial clinical implications. In accordance with this trend, the number of patients in which temporary ileostomy is performed to avoid anastomotic leakage is increasing (4).

A newly constructed ileostomy begins to function approximately 24 h after surgery, initially producing approximately 1,200 ml/day of watery output, which gradually decreases over 2-3 months. The amount of fluid from the ileostomy output ranges from 500-2,000 ml/day, depending on the diet and gastrointestinal secretions (5). High-output stomas (HOSs) are a complication that can cause dehydration or renal dysfunction and affect patient quality of life. The effluent from an ileostomy is likely to be clinically significant when the output exceeds 2,000 ml/24 h, causing water, sodium, and magnesium depletion, with malnutrition occurring as a late complication (6). The reported risk factors for HOS include intra-abdominal infections, bowel obstruction, small intestine length less than 200 cm, enteritis caused by *Clostridium difficile* or Salmonella, and steroid use (7).

Most risk factors for HOSs identified to date include postoperative factors. Moreover, most studies included inflammatory bowel disease and malignant diseases in their analyses. This study aimed to clarify the perioperative risk factors for developing HOS in patients with ileostomies following rectal cancer surgery and their impact on the postoperative course.

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Table I. *Clinicopathological characteristics of HOS and non-HOS group.*

Characteristics		HOS group (n=9)	Non HOS group (n=22)	*p*-Value
Sex	Male (n, %)	7 (77.8)	17 (77.3)	
	Female (n, %)	2 (22.2)	5 (22.7)	0.976
Age	≥70 y/o (n, %)	3 (33.3)	13 (59.1)	
	<70 y/o (n, %)	6 (66.7)	9 (40.9)	0.193
Body mass index	≥24 kg/m^2 (n, %)	1 (11.1)	6 (27.3)	
	<24 kg/m^2 (n, %)	8 (88.9)	16 (72.7)	0.329
Diabetes Mellitus	Positive (n, %)	1 (11.1)	3 (13.6)	
	Negative (n, %)	8 (88.9)	19 (86.4)	0.849
pT	0-2 (n, %)	3 (33.3)	9 (40.9)	
	3-4 (n, %)	6 (66.7)	13 (59.1)	0.694
pStage	I, II (n, %)	6 (66.7)	13 (59.1)	
	III, IV (n, %)	3 (33.3)	9 (40.9)	0.694
Neoadjuvant therapy	Positive (n, %)	0 (0.0)	3 (13.6)	
	Negative (n, %)	9 (100.0)	19 (86.4)	0.244

HOS: High-output stoma.

Patients and Methods

Patient selection. Patients with rectal cancer who simultaneously underwent lower anterior resections or super lower anterior resections with curative intent and covering ileostomies at Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka, Japan between January 2014 and December 2021 were retrospectively reviewed. Patients who underwent emergency surgery were excluded. 31 patients were included in this study.

Tumor stage classification and assessment were performed in accordance with the 8th American Joint Committee on Cancer/Union for International Cancer Control tumor-node-metastasis (TNM) classification (8). Mechanical bowel preparation was implemented in all patients, using magnesium citrate and sodium picosulfate the day prior to the surgery, except in patients with bowel obstruction. No chemical preparations such as kanamycin or metronidazole were administered preoperatively. All patients received intravenous cefmetazole every three hours during the surgery.

Output measurements. The amount of output from the ileostomy was measured routinely for seven days postoperatively. HOS was defined as a maximum output of ≥2,000 ml/day (9). Blood laboratory tests, including white blood cell (WBC) count, hemoglobin (Hb), albumin (Alb), blood urea nitrogen (BUN), creatinine (Cr), sodium, potassium, chloride, and C-reactive protein (CRP) levels, were routinely performed before surgery and one and three days postoperatively. Patients with a high postoperative stoma output or signs of dehydration received additional fluid infusions at the discretion of the respective surgeon. Postoperative complications were assessed according to the Clavien-Dindo classification (10).

Statistical analysis. All statistical analyses were performed using GraphPad Prism 8.0. Single-factor analysis was performed using the chi-squared and Fischer's exact tests.

Ethical considerations. This study was approved by the Institutional Review Board of our institution (Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers).

Approval. The Ethics Committee of Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers waived the need for written informed consent due to the retrospective nature of this study. Participants had the option to opt-out through the Kyushu Central Hospital website. The authors declare that this study was performed in accordance with the ethical standard as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable standards.

Results

Patient characteristics. The highest median stoma output before hospital discharge was 1,200 ml/day. Among the 31 patients, nine patients developed HOS in this study. The clinicopathological characteristics of the 31 patients, 24 (77.4%) males and 7 (22.6%) females, are summarized in Table I. The median patient age was 70 years (range=51-82 years). Neoadjuvant therapy was administered to 3 (9.7%) patients. There were no significant differences in sex, age, body mass index, diabetes mellitus, tumor depth, pathological stage, or neoadjuvant therapy between the HOS and non-HOS groups.

Preoperative and surgical factors. Clinical and surgical factors associated with HOS are summarized in Table II. In univariate analyses, lower Hb levels (<12 mg/dl) and longer operative times (≥300 min) were shown to be risk factors in the development of HOS (p=0.005).

Postoperative courses. Table III shows a comparison of the postoperative blood test results, complications, and length of postoperative hospital stay. In the HOS group, BUN and BUN/Cr were significantly higher on postoperative day three, and CRP levels were also higher on postoperative day three.

Table II. *Univariate analyses of preoperative laboratory data and surgical findings associated with HOS.*

Variables	HOS group (n=9)	Non HOS group (n=22)	*p*-Value
Hb (<12.0 mg/dl) (n, %)	5 (55.6)	2 (9.1)	0.005
Alb (<4.0 g/dl) (n, %)	4 (44.4)	11 (50.0)	0.779
CRP (≥0.3 mg/dl) (n, %)	2 (22.2)	5 (22.7)	0.976
Operation time (≥300 min) (n, %)	8 (88.9)	11 (50.0)	0.044
Blood loss (≥100 ml) (n, %)	2 (22.2)	8 (36.4)	0.445
Intraoperative blood transfusion (n, %)	1 (11.1)	0 (0.0)	0.112
Laparoscopic surgery (n, %)	8 (88.9)	17 (77.3)	0.779
Distance from Bauhin valve (≥25 cm) (n, %)	8 (88.9)	13 (59.1)	0.107

Alb: Albumin; CRP: C-reactive protein; Hb: hemoglobin; HOS: high-output stoma.

Table III. *Association between HOS and postoperative courses.*

Variables		HOS	Non HOS	*p*-Value
WBC (/μl) (mean±SD)	1POD	10.467±1,895	9,165±708	0.4300
	3POD	9,156±1,407	6,990±416	0.0576
BUN (mg/dl) (mean±SD)	1POD	10.0±0.88	9.905±0.54	0.3313
	3POD	14.9±1.73	10.1±1.10	0.0257
Cr (mg/dl) (mean±SD)	1POD	0.85±0.068	0.86±0.039	0.9484
	3POD	1.07±0.13	0.98±0.05	0.4553
BUN/Cr (mean±SD)	1POD	13.2±1.19	11.8±0.62	0.2417
	3POD	14.3±1.09	10.1±0.85	0.0093
Sodium (mEq/l) (mean±SD)	1POD	141.8±0.57	140.9±0.50	0.3215
	3POD	136.6±1.16	138.6±0.64	0.1108
Potassium (mEq/l) (mean±SD)	1POD	3.74±0.11	3.79±0.77	0.7661
	3POD	4.24±0.09	4.20±0.10	0.7942
Chloride (mEq/l) (mean±SD)	1POD	110.1±1.15	107.5±0.60	0.3641
	3POD	103.4±1.58	103.8±0.66	0.7964
CRP (mg/dl) (mean±SD)	1POD	5.82±0.77	6.49±0.50	0.4778
	3POD	13.3±2.22	9.15±0.92	0.0457
Postoperative complications (Clavien-Dindo ≥2) (%)		5 (55.5)	8 (36.4)	0.3256
Postoperative hospital stay (days) (mean±SD)		33.6±7.1	24.7±2.8	0.1617

BUN: Blood urea nitrogen; Cr: creatinine; CRP: C-reactive protein; HOS: high-output stoma; SD: standard deviation; WBC: white blood cell; POD: postoperative day.

The HOS group also showed a trend toward a higher WBC count on postoperative day three; however, the difference was not statistically significant. There were five patients in the HOS group and eight patients in the non-HOS group regarding the development of postoperative complications of Clavien-Dindo ≥2 other than HOS. Still, there was no significant difference between the two groups. Postoperative hospital stays tended to be longer in the HOS group (33.6±7.1 days in the HOS group and 24.7±2.8 days in the non-HOS group), but the difference was not significant.

Detail of nine HOS cases. Details of the HOS patients are summarized in Table IV. In all patients, oral fluid intake was initiated the day after surgery. The timing of oral food intake

Table IV. *Details of nine HOS cases.*

No.	Age	Sex	Food intake (POD)	Maximum output day (POD)	Amount of stoma output on the maximum output day (ml)	Postoperative hospital stay (days)	Postoperative complication	Drug administration
1	51	Male	7	12	4480	59	Intraabdominal abscess	Miya-BM, polycarbophil calcium
2	59	Male	8	4	2170	34	Ileus	Miya-BM
3	70	Male	1	2	2250	19	-	
4	62	Male	2	1	2290	79	Intraabdominal abscess	Miya-BM, polycarbophil calcium
5	68	Male	2	2	2100	27	Anastomotic leakage	Miya-BM
6	78	Female	2	2	2030	28	-	Miya-BM, polycarbophil calcium
7	62	Female	2	5	2890	21	-	Miya-BM, polycarbophil calcium, loperamide
8	78	Female	3	4	3600	19	Renal dysfunction	Polycarbophil calcium
9	65	Female	3	2	3030	17	-	Miya-BM, polycarbophil calcium, loperamide

HOS: High-output stoma; POD: postoperative day.

initiation was determined at the discretion of each clinician. In most patients, the highest stoma output occurred within the first five postoperative days, but in one patient, the highest stoma output volume occurred on the 12th postoperative day. Regarding complications, two cases of intra-abdominal abscess, one case of anastomotic leakage, one case of ileus, and one case of renal dysfunction were observed, all of which were Clavien-Dindo 2, and no complications of Clavien-Dindo ≥3 were observed. The treatment interventions for HOS were implemented at the discretion of each clinician. Miya-BM, which contains Clostridium butyricum M588, was administered to seven patients. Polycarbophil calcium and loperamide were used in six and two patients, respectively. One patient required unscheduled readmission to correct electrolyte abnormalities before stoma closure was performed.

Discussion

Various complications including ischemia, retraction, small bowel obstruction, transstomal decompression, and HOS, can occur with ileostomies (11-13). Among these postoperative complications, HOS triggers dehydration, renal dysfunction, and electrolyte abnormalities, leading to rehospitalization (14). The output from an ileostomy is usually estimated to be 600-1,200 ml depending on oral intake; however, HOS is considered when the output exceeds 1,500-2,000 ml (15).

In our study, we defined HOS as stoma output exceeding 2,000 ml/day, referring to previous reports (16). In this retrospective observational study, we found that low preoperative serum Hb levels and long operative times were risk factors for the development of HOS. Blood tests on the third postoperative day showed higher BUN levels and BUN/Cr ratios in the HOS group, suggesting that HOS was the cause of dehydration. CRP levels were also higher in the HOS group on the third postoperative day. However, no significant differences were observed in the incidence of postoperative complications. There was a trend toward a longer postoperative hospital stay in the HOS group; however, the difference was not significant.

Causes of HOS include residual small bowel less than 200 cm, intra-abdominal infections, bowel obstruction, enteritis (*Clostridium difficile* or Salmonella), and steroid withdrawal. Previous studies have included patients with rectal cancer as well as surgical cases of benign disease (7, 17). We believe that patients with inflammatory bowel disease and those with rectal cancer differ greatly in terms of age, nutritional status, and surgical manipulation. Therefore, a distinction needs to be made regarding the factors that contribute to the development of HOS after surgery for inflammatory bowel disease and rectal cancer.

Younger age, high WBC counts on the first postoperative day, outlet obstruction, diabetes mellitus, total proctocolectomy, and preoperative chemoradiotherapy have been identified as HOS in previous studies (18-20). It was not clear whether elevated WBC counts resulted in HOSs or whether HOSs resulted in an elevated inflammatory response. Previous studies reported limited analysis of risk factors based on preoperative blood tests, and this is the first report of low preoperative Hb levels as a predictor of HOS development to our knowledge.

Early therapeutic intervention may prevent irreversible renal dysfunction in patients who develop HOSs and present with electrolyte abnormalities and renal dysfunction. Although renal impairment and dialysis can be avoided by correcting dehydration with intravenous infusions containing appropriate amounts of sodium, care should be taken not to give too much amount of fluids (7, 15). Oral intake of soluble fiber has also been shown to be effective in reducing stoma output (6). Regarding drug therapy, the efficacy of proton pump inhibitors, histamine inhibitors, antisecretory drugs such as somatostatin and octreotide, and high-capacity loperamide has been reported (21-23). It has been reported that Clostridium species infections are involved in the pathogenesis of HOSs (17), and Matsuzawa et al. reported that Miya-BM containing Clostridium butyricum M588 may be a useful treatment for altering the gut microbiota in HOSs (24). In the present study, seven of nine patients who developed HOSs were treated with Miya-BM, although the effectiveness of the therapeutic intervention with Miya-BM was unclear.

The strength of the study was that preoperative blood test results may predict the development of HOSs. Interventions for HOSs at an earlier stage may provide positive results. The mechanism by which low Hb levels cause HOSs may involve various complex factors. However, one of the reasons may be that low Hb levels reduce oxygen delivery to the intestinal tract, resulting in inadequate absorption of nutrients in the intestinal tract and subsequent diarrhea and increased stool output. The evidence for this mechanism is insufficient and requires further experimental investigation.

In recent years, various innovations have been made regarding the construction of diverting stomas in rectal cancer surgery. Hernández et al. has reported the efficacy of ghost ileostomy, the surgical procedure of tunneling the small bowel meso with silicone loop, which was then externalized and fixed at the trocar site (25). Eto et al. has reported that umbilical defunctioning ileostomy resulted in fewer incisional hernias than conventional ileostomies after the stoma closure (26). In our study, conventional loop ileostomy was placed in the right lower abdomen in all cases, and further investigation is required for the surgical procedure of ileostomy.

This study had certain limitations. Firstly, it was a retrospective observational study conducted at a single institution with a small sample size. There are only few reports on preoperative blood tests predicting HOSs and further studies are needed to strengthen the results of the present study. Secondly, we did not assess the volume of intravenous infusions or oral intake. Therefore, it is necessary to accumulate data on oral intake and perioperative infusion volumes for further detailed studies.

Conclusion

We found that low Hb levels on preoperative blood tests may be a predictor of HOS development in patients who underwent rectal cancer surgery and ileostomy simultaneously. Further prospective studies are needed to validate this evidence. However, it is our opinion that early intervention for HOSs may be possible if preoperative blood tests are used to predict the onset of HOS.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

TK and KO designed the study. TK collected the clinical data, and performed the statistical analysis. TK, KO, YF. HW, and KM wrote and edited the manuscript. RN revised the article. YI supervised the article. All the Authors have read and approved the final manuscript.

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