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ORIGINAL ARTICLE

Colectomy risk score predicts pouchitis in patients with ulcerative colitis

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Abstract

Risk stratification is required to improve the management of pouchitis with ulcerative colitis (UC) patients who undergo ileal pouch-anal anastomosis (IPAA). Recently, the colectomy risk score (CRS) has been used to assess UC severity and predict the need for surgery. We explored whether the CRS predicted pouchitis in patients with UC who underwent IPAA. This retrospective study included 168 UC patients who underwent IPAA. Pouchitis was diagnosed according to the pouchitis disease activity index. The primary endpoint was the cumulative incidence of pouchitis. The risk factors for pouchitis using preoperatively obtained data, including the CRS, were investigated. Based on their CRS, patients were assigned to low- (scores 0–3), intermediate- (scores 4–6), and high-risk (scores 7–9) groups. The incidence of pouchitis was estimated using the Kaplan–Meier curve. CRS validity was assessed using the Cox proportional hazards model. During the median 7.2 (interquartile range [IQR] 2.8–11.1) years' follow-up, 37 (28.5%) patients were diagnosed with pouchitis. Patients with pouchitis had significantly higher CRS than patients without pouchitis (median 7.0; IQR, 4.0–7.0 vs median 5.0; IQR, 3.0–7.0). The cumulative incidences of pouchitis in the low-, intermediate-, and high-risk groups were 10.3%, 18.3%, and 36.1% at 5 years, respectively. Thus, the incidence trended to increase significantly as CRS increased. Multivariate analysis revealed high-risk CRS status was an independent predictor of pouchitis (hazard ratio: 18.03; 95% confidence interval 1.55–210.05). CRS is useful in risk stratification for the development of subsequent pouchitis in patients with UC undergoing IPAA.

Keywords Ulcerative colitis · Pouchitis · Ileal pouch-anal anastomosis · Risk score

Introduction

Restorative proctocolectomy (RPC) and ileal pouch-anal anastomosis (IPAA) is now the standard surgical treatment for ulcerative colitis (UC) [1, 2]. Most patients report a good functional outcome after IPAA, and the quality of life after IPAA is largely satisfactory [3, 4]. However, a substantial proportion of patients still develop pouchitis. Pouchitis occurs in 23–46% of patients following IPAA and is a major late postoperative complication after IPAA in patients with UC [4–6]. Although the etiology of pouchitis remains unclear, the underlying cause of pouchitis is attributable to an abnormal immune response of UC [7]. When patients with UC develop pouchitis, they may be hospitalized repeatedly, which lowers their quality of life, and eventually develop pouch failure.

Previous studies have reported several risk factors for pouchitis. Specifically, the presence of extensive UC, backwash ileitis, preoperative thrombocytosis, corticosteroid use, extraintestinal manifestations, especially PSC, the presence of p-ANCA, non-smoking status, and the use of NSAIDs is associated with pouchitis. Also, gene polymorphisms of IL-1ra and NOD2/ CARD15 are related with pouchitis [8]. Despite many reported risk factors, no preoperative prediction model for pouchitis has been developed. If patients who are at a high risk of developing pouchitis can be identified, perioperative management and surgical approaches might be reconsidered. Moreover, these risks can be assessed with

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postoperative surveillance and the introduction of maintenance therapy. Therefore, there is a growing demand for preoperative risk stratification in pouchitis of patients with UC requiring IPAA.

Recently, Ananthakrishnan et al. [9] confirmed the utility of a Colectomy Risk Score (CRS) in assessing UC severity and predicting the need for operation. The CRS distinguishes low-, intermediate-, and high-risk patients; it usefully predicted the need for colectomy and the length of hospital stay. The CRS' usefulness in other aspects of perioperative management of patients with UC has not been validated. CRS may be better able to predict pouchitis since patients with severe UC are expected to have a risk of pouchitis. This study's objective is to clarify the CRS' usefulness for predicting pouchitis.

Materials and methods

Study design and population

This study used a retrospective design and data obtained from patient records. All study patients were adults who underwent IPAA to treat UC in Keio University Hospital between April 2002 and April 2018. The exclusion criteria were: (1) no diverting ileostomy closure after IPAA, (2) no undergone pouchoscopy for the functioning pouch after IPAA, and (3) missing clinical data.

Study data

Clinical characteristics were collected from medical records and included follow-up time after IPAA, age during the operation, sex, duration of UC, smoking history, extent of UC, medical treatments 1 month before surgery, the presence or absence of preoperative extraintestinal manifestations (EIM), indications for operation, type of operation (hand-sewn versus stapled IPAA), and Lichtiger index score. The Lichtiger index [10] is used widely to characterize disease severity. Based on that index, the cohort was stratified into three groups: clinical remission (scores 0–3), mild-to-moderate disease (4–9), and severe disease (10–21) [11]. The CRS was calculated using seven variables: anemia, requirement for blood transfusion, malnutrition, requirement for total parenteral nutrition (TPN), ulcerative pancolitis status, transfer from another hospital, and admission to a teaching hospital. Anemia and malnutrition were defined as preoperative hemoglobin < 10 g/dL and albumin [Alb] < 3.0 g/dL. Malnutrition and ulcerative pancolitis were each worth 2 points, and the other criteria were worth 1 point each. Thus, the risk scores ranged from 0 to 9. The cohort was then stratified into three groups as follows: low risk, intermediate risk, and high risk; the cutoffs were selected to maximize discrimination between groups as described by Ananthakrishnan et al. [9]. The intermediate risk was defined as a CRS score < 7 points and the low risk was defined as a CRS score ≤ 3 points. The CRS and the Lichtiger index were calculated using data recorded immediately before surgery.

Outcomes of interest

The primary endpoint was the overall and cumulative incidence of pouchitis. The risk factors for pouchitis were investigated using preoperatively obtained data, including the CRS, to predict the development of subsequent pouchitis. Thus, we confined variables to preoperative clinical and demographic characteristics.

Diagnosis of pouchitis

The duration between the date of the operation and that of pouchoscopic diagnosis for pouchitis or final pouchoscopy date for patients without pouchitis was used. After IPAA, the patients were followed up every 3–6 months after stoma closure at our hospital. Pouchoscopy was performed when patients reported any symptom that led a physician to suspect pouchitis. Moreover, pouchoscopy was also performed annual surveillance pouchoscopy regardless of symptoms. Pouchitis was diagnosed according to the Pouchitis Disease Activity Index (PDAI) and defined as a total PDAI score of 7 or greater [12]. All endoscopic reports and biopsy specimens were reviewed in a blinded fashion by expert endoscopists and pathologists. Pouchitis, including mucosal inflammation caused by nonsteroidal anti-inflammatory drugs, CMV infection, ischemia, and Crohn's disease, was excluded from the present study. Patients with ulcers confined to the staple line or the rectal remnant (strip pouchitis) were also excluded from the present study [13, 14].

Statistical analyses

Fisher's exact test, Mann–Whitney *U* test, and one-way analysis of variance (ANOVA) were used to compare the distributions of categorical variables. Kaplan–Meier curves, with log-rank comparison, were used to estimate the incidence of pouchitis after IPAA. The Cox proportional hazards model was used for multivariate analysis to identify risk factors for pouchitis development. The contribution rate was a ratio of the sum of the absolute values of the standardized regression coefficients (%), as generated by multiple Cox regression analysis. *P* values < 0.05 were considered to reflect statistical significance. All analyses were performed with Stata software (ver. 11.2; Stata Corporation, College Station, TX, USA).

Ethics statement

The study was approved by our university's ethics committee (20150051). All authors had access to all study data and reviewed and approved the final manuscript.

Results

Study population

We included 168 adults who underwent IPAA at Keio University Hospital between April 2002 and April 2018. Thirty-eight patients were excluded because of absent diverting ileostomy closure (nine cases), they did not undergo pouchoscopy for the functioning pouch (six cases), or had missing data (23 cases). Ultimately, 130 patients were included. Demographic and clinical characteristics of the 130 patients (78 male/52 female; median age at surgery 40 (interquartile range [IQR] 31–51) years; median duration of UC 7.4 (IQR 3.0–15.8) years) are summarized in Table 1. Overall, extensive colitis was present in 99 (76.2%) patients and EIM was present in 13 (10.0%) patients.

Pouchitis

During the median 7.2 (IQR 2.8–11.1) years' follow-up, 37 (28.5%) of the 130 IPAA patients were diagnosed with pouchitis. Compared to patients who did not develop pouchitis, patients with pouchitis had significantly higher preoperative biological therapy in medical treatment (45.9% vs 22.6%; $P=0.01$) and higher Lichtiger index scores (median 11.0; IQR, 7.0–14.0 vs median 8.0; IQR, 3.0–10.0; $P<0.01$). There was no difference between patients with and without pouchitis in terms of surgical characteristics, including operation indication and anastomosis. Patients with pouchitis had significant higher CRS in comparison with patients without pouchitis (median 7.0; IQR, 4.0–7.0 vs median 5.0; IQR, 3.0–7.0; $P<0.01$; Table 1).

The cumulative incidences of pouchitis

The cumulative incidences of overall pouchitis were 1.5%, 23.2%, and 40.4% at 1, 5, and 10 years, respectively, after the pouch operation (Fig. 1a). 35 (26.9%), 50 (38.5%), and 45 (34.6%) patients were assigned to the low-, intermediate-, and high-risk groups, respectively, by the CRS. The cumulative incidences of pouchitis by CRS stratum is shown in

Table 1 Patient characteristics

	All Patients $n=130$ (%)	Pouchitis $n=37$ (%)	Non pouchitis $n=93$ (%)	P value
Age at surgery[a]	40 (31–51)	35 (28–53)	40 (33–51)	0.29
Sex				
Male	78 (60.0)	22 (59.5)	56 (60.2)	1.00
Female	52 (40.0)	15 (40.5)	37 (39.8)	
Duration of UC, years[a]	7.4 (3.0–15.8)	5.9 (2.4–15.8)	8.4 (3.2–15.6)	0.64
Smoking history	25 (19.2)	9 (24.3)	16 (17.2)	0.45
Extent of UC				
Extensive colitis	99 (76.2)	32 (86.5)	67 (72.0)	0.11
Medical treatment[b]				
Steroid	111 (85.4)	34 (91.9)	77 (82.8)	0.27
Immunomodulators	56 (43.1)	19 (51.4)	37 (39.8)	0.25
Biological therapy	38 (29.2)	17 (45.9)	21 (22.6)	0.01
Preoperative EIM	13 (10.0)	5 (13.5)	8 (8.6)	0.52
Operation indication				
Inflammation	87 (66.9)	28 (75.7)	59 (63.4)	0.22
Neoplasm	43 (33.1)	9 (24.3)	34 (36.6)	
Anastomosis				
Stapled	99 (76.2)	26 (70.3)	73 (78.5)	0.36
Handsewn	31 (23.8)	11 (29.7)	20 (21.5)	
Lichtiger index[a]	9.0 (5.0–12.0)	11.0 (7.0–14.0)	8.0 (3.0–10.0)	<0.01
Colectomy risk score[a]	5.5 (3.0–7.0)	7.0 (4.0–7.0)	5.0 (3.0–7.0)	<0.01

[a]Median (IQR)

[b]There is some overlapping

EIM extraintestinal manifestations

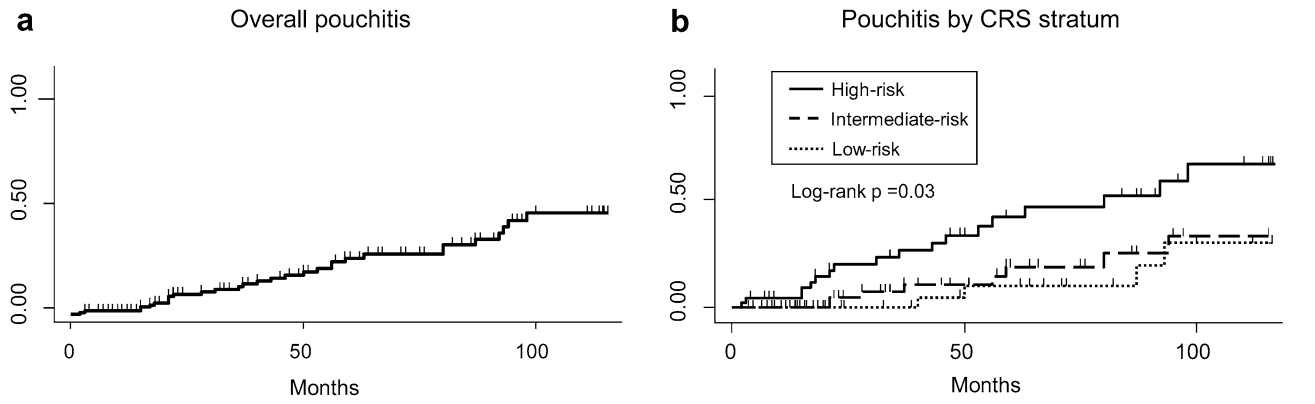

Fig. 1 **a** Cumulative incidence of overall pouchitis. **b** Cumulative incidence of pouchitis using the CRS

Fig. 1b. The cumulative incidences of pouchitis in the low-, intermediate-, and high-risk groups were 10.3% vs 18.3% vs 36.1% at five years, in proportion to the grade of CRS (log-rank test $P = 0.03$).

Influence of CRS on pouchitis

Univariable analysis revealed that the preoperative biological therapy in medical treatment, a severe Lichtiger index and a high-risk CRS were significant risk factors for the development of overall pouchitis (hazard ratio [HR]: 8.80, 95% confidence interval [CI], 4.07–19.00, $P < 0.01$ for biological therapy in medical treatment, HR: 2.53, 95% CI, 1.01–6.37, $P = 0.04$ for a severe Lichtiger index and HR: 2.87, 95% CI, 1.07–7.68, $P = 0.03$ for a high-risk CRS; Supplementary Table 1). In a multivariate analysis including the above factors, high-risk CRS status was an independent predictor of pouchitis (HR: 18.03; 95% CI 1.55–210.05; $P = 0.01$; Table 2). Compared with low-risk CRS status, the hazard ratio of intermediate-risk CRS status was 5.76 (95% CI, 0.6–56.7) and that of high-risk CRS status was 18.03 (95% CI, 1.6–210.1) revealing dose-responsibility. On the other hand, the hazard ratios of the severe group of Lichtiger index were similar compared with the remission group of Lichtiger index, revealing no dose-responsibility. Moreover, to evaluate high-risk CRS status, the CRS and Lichtiger index were classified into two groups and compared. As in the three-group analysis, high-risk CRS status was found to be an independent predictor of pouchitis (HR: 2.52; 95% CI: 1.19–5.31; $P = 0.02$; Table 3).

The relationship between the PDAI score at the diagnosis of pouchitis and the CRS stratum is shown in Fig. 2. The mean PDAI score was 2.9 (standard deviation [SD], 0.6) in the low-risk group, median 4.2 (SD, 0.5) in the intermediate-risk group, and median 6.2 (SD, 0.8) in the high-risk group. The high-risk group had significantly higher PDAI scores than the low-risk group ($P < 0.01$). The high-risk group's PDAI scores were twice as high as the low- and intermediate-risk groups. This result indicates that the high-risk group had been diagnosed with more severe pouchitis.

The contribution of each item of the CRS was evaluated in multivariate analysis among the items of the CRS were investigated. The individual factors in CRS are not an independent predictor of pouchitis, but ulcerative pancolitis was

Table 2 Univariate and multivariate analyses using the Cox proportional hazard ratio model to evaluate the reliability of pouchitis prediction in three CRS groups

	Univariate			Multivariate		
	Hazard ratio	95%CI	*P*	Hazard ratio	95%CI	*P*
Lichtiger index						
Remission		ref			ref	
Mild to moderate	0.70	0.26, 1.87	0.48	0.18	0.02, 1.43	0.11
Severe	2.53	1.01, 6.37	0.04	2.04	0.26, 16.08	0.50
CRS						
Low		ref			ref	
Intermediate	1.38	0.48, 3.97	0.56	5.76	0.58, 56.69	0.10
High	2.87	1.07, 7.68	0.03	18.03	1.55, 210.05	0.01

*Adjusted for the following variables: age, sex, smoking, EIM, medical treatment, operation indication, and anastomosis

Table 3 Univariate and multivariate analyses using the Cox proportional hazard ratio model to evaluate the reliability of pouchitis prediction in two CRS groups

	Univariate			Multivariate		
	Hazard ratio	95%CI	*P*	Hazard ratio	95%CI	*P*
Lichtiger index						
Remission and Mild to moderate		ref			ref	
Severe	2.40	1.20, 4.79	0.01	1.92	0.66, 5.61	0.23
CRS						
Low and Intermediate		ref			ref	
High	2.33	1.20, 4.53	0.01	2.52	1.19, 5.31	0.02

*Adjusted for the following variables: age, sex, smoking, EIM, medical treatment, operation indication, and anastomosis

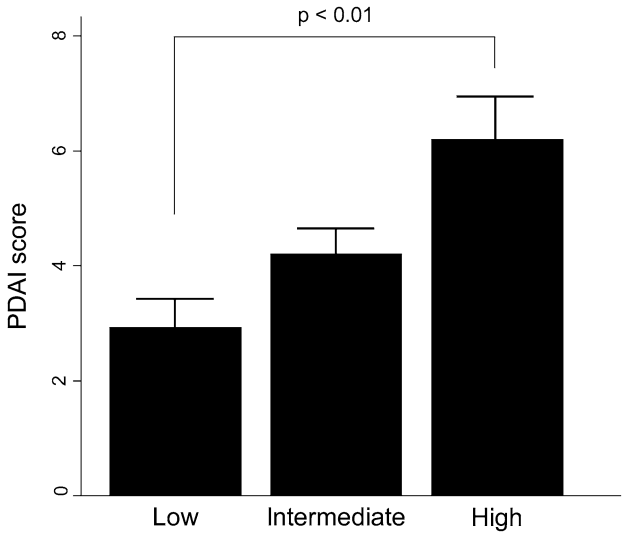

Fig. 2 The relationship between the PDAI score at the first diagnosis of pouchitis and CRS stratum

Table 4 Multivariate Cox regression analyses evaluating the reliability and contribution ratios of pouchitis predicted by the CRS

	Multivariate			Contribution ratio
	HR	95%CI	*P*	%
CRS				
Ulcerative pancolitis	2.43	0.90, 6.57	0.08	30.04
Anemia	1.68	0.75, 3.75	0.21	20.77
Total parenteral nutrition	1.28	0.59, 2.78	0.53	15.82
Malnutrition	1.23	0.46, 3.28	0.68	15.20
Requirement for blood transfusion	1.06	0.50, 2.328	0.88	13.10
Transfer from outside hospital	0.41	0.16, 1.06	0.07	5.07
Admission to a teaching hospital	–	–	–	–

the most contributing factor in predicting pouchitis in CRS items (contribution ratio 30.04%; Table 4).

Discussion

We explored whether the CRS could predict pouchitis in patients with UC undergoing RPC and IPAA. CRS is a scoring system developed to assess the severity of UC and predict the need for surgery. Patients with pouchitis had significantly higher CRS than patients without pouchitis. The cumulative incidence of pouchitis was significantly greater in the high-risk than in the low-risk group. In particular, high-risk status in CRS was an independent predictor of pouchitis. Moreover, this study showed a strong correlation between CRS and PDAI score. The high-risk group had been diagnosed with more severe pouchitis. Although individual factor in CRS is not an independent predictor of pouchitis, ulcerative pancolitis may be the best predictor of pouchitis in the CRS items. Those findings support the usefulness of CRS in predicting pouchitis in patients with UC undergoing RPC and IPAA.

The etiology of pouchitis remains unclear, but there are two major mechanisms associated with pouchitis: abnormal autoimmune responses and dysbiosis. UC is considered an autoimmune disease. An abnormal autoimmune response is also suspected to be the key factor for pouchitis. Pouchitis is less frequently observed in patients with FAP than in those with UC [15, 16]. Additionally, pouchitis is treated effectively with corticosteroids, immunosuppressants, or biologic therapy [17–19]. Dysbiosis or altered microflora is suspected to be the key pathogenic factor for pouchitis. The use of antibiotics in the treatment of pouchitis and the use of probiotics in the prophylaxis of pouchitis have suggested a strong relationship with dysbiosis in pouchitis [20–23]. The previous study has shown the persistence of Fusobacter and Enteric species associated with the disease state and the absence of specific bacteria such as Streptococcus species in the inflamed pouch [24]. These findings suggested that abnormal autoimmune responses and dysbiosis are associated with pouchitis.

Abnormal autoimmune responses and dysbiosis may be helpful for understanding the etiology of pouchitis.

The study showed that CRS is a simpler, less expensive method for predicting pouchitis development because it is a scoring system using a convenient clinical database. Moreover, the composite scale based on clinical data has never been reported before. A previous study has reported that the risk for pouchitis after IPAA can be predicted based on the fecal microbial composition before colectomy [25]. Moreover, elevated fecal calprotectin and lactoferrin levels have appeared to be significant predictors of pouchitis for UC [26]. These tests are more expensive and take longer to examine. This study indicates that CRS is the first composite scale to predict the development of pouchitis and is a simple preoperative predictive system. Furthermore, the usefulness of the CRS should be validated with patient data from other institutions in the future.

This study's results have found three new clinical possibilities. First, surgical procedures including operation indication and anastomosis may not affect pouchitis. Without mucosectomy in patients with severe UC, leaving a diseased mucosa exposes the patient to the risk of residual proctitis and possibly pouchitis due to backwash. However, mucosectomy with handsewn did not prevent pouchitis in this study. Second, preoperative risk stratification can affect postoperative surveillance. Diagnosing pouchitis requires a combined evaluation of the endoscopic assessment of the pouch and histopathology from pouch biopsies, which is a great burden on patients with UC. Patients at low risk of pouchitis by CRS may require fewer examinations and, as a result, lower medical expenses. Third, perioperative management is important for the preventing pouchitis. Patients with a high CRS may need to use 5-Aminosalicylic acid or biologics for prevention soon after surgery. This study showed that CRS had a significant correlation with PDAI score. Patients with severe status before surgery can develop severe pouchitis, which is clinically important. From the above, CRS may help identify patients at risk before surgery and foster prevention and management of pouchitis after IPAA.

This study has several limitations. First, it was a retrospective design and conducted in a single institution, so several biases may have arisen. Preoperative backgrounds were based on medical records, so we could not exclude selection biases completely. Moreover, we could not evaluate admission to a teaching hospital's influence on the risk of pouchitis because our study was conducted in a single institution (a teaching hospital). Second, it is unknown whether clinical or endoscopic findings matter in the diagnosis of pouchitis. Assessment of pouchitis is various and not constant. Thus, this study was not investigated by classifying into two distinct entities: acute pouchitis and chronic relapsing pouchitis. Third, the small sample size precludes any definitive conclusions about the efficacy of CRS, and further multicenter studies are required.

Conclusions

The CRS usefully stratified the risk of pouchitis in patients with UC undergoing RPC and IPAA. The CRS reliably evaluated UC severity and general preoperative condition at risk for subsequent pouchitis development and will be valuable when obtaining informed patient consent and during surgical decision making.

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Author contributions AI: conceptualization, methodology, software, writing-original draft. KO: conceptualization, methodology, data curation, supervision, writing—review & editing. MT: supervision. KS: data curation, supervision. RS: data curation, supervision. MS: formal analysis, data curation, visualization. MN: investigation, formal analysis, data curation. YK: project administration. All authors read and approved the final manuscript.

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Availability of data and material Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

Code availability Not applicable.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval The study was approved by Keio university's ethics committee (20150051).

Informed consent All patients signed the institution informed consent for colorectal surgery. No specific consent for this type of study is required.

Consent for publication Consent to submit the present paper has been received explicitly from all co-authors, as well as from Keio university's ethics committee.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

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