



ORIGINAL ARTICLE

Cut-off value of ulcerative colitis endoscopic index of severity (UCEIS) score for predicting the need for pouch construction in ulcerative colitis: results of a multicenter study with long-term follow-up

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Abstract

Background Total proctocolectomy with ileal pouch–anal anastomosis (IPAA) was the first choice for the surgical treatment of the ulcerative colitis (UC) patients. The data on the predictive value of the ulcerative colitis endoscopic index of severity (UCEIS) for the need for IPAA in UC patients is scarce. We aimed to establish the UCEIS cut-off value to further analyse whether the UCEIS cut-off was suitable for predicting the need for IPAA in UC patients.

Methods The clinical data of UC patients from June 1986 to March 2020 at our institute were retrospectively assessed. The UCEIS scores recorded at the time of the first colonoscopy after hospitalization were used in the study. Receiver operating characteristic curve analysis was performed to determine the UCEIS cut-off value for predicting the need for IPAA.

Results A total of 283 UC patients were included in the study, with a median UCEIS of 4. During a median follow-up of 13 years, 80 patients (28.3%) received surgery invention, among whom 75 (93.8%) underwent IPAA surgery and 5 (6.2%) received subtotal colectomy with permanent ostomy. A UCEIS cut-off of 6 had the most significant area under the curve of 0.769 for predicting the need for IPAA ($P < 0.001$), with a sensitivity of 72.0% and specificity of 81.8%. UCEIS ≥ 6 was an independent predictive factor for the need for IPAA ($P < 0.001$) and malignant transformation ($P = 0.010$). Patients with UCEIS ≥ 6 had a significantly shorter IPAA-free survival time than those with UCEIS < 6 ($P < 0.001$).

Conclusions UCEIS ≥ 6 may be a threshold value for decision-making for IPAA and should be recommended for UC patients for reducing the incidence of malignant transformation.

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Key words: ulcerative colitis endoscopic index of severity; ileal pouch–anal anastomosis; ulcerative colitis

Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory disease that is characterized by alternating periods of activity and remission. Currently, the main treatment options for UC include administration of 5-aminosalicylic acid, corticosteroids, and immunomodulators [1]. Recently, biologics including targeted therapy with antitumor necrosis factor α (TNF- α) agents (infliximab, adalimumab) and subsequently anti-integrin (vedolizumab) therapies were both effective in inducing mucosal healing in UC [2]. However, remission is not achieved for all patients with these treatments and 10%–30% of UC patients need to undergo surgery owing to medically refractory disease, fulminant colitis, or colorectal neoplasia [3–5].

Subtotal colectomy with permanent ileostomy was performed for the patients who underwent emergency serious complications and did not receive pouch construction, which can improve long-term quality of life and also could contribute to psycho-social problems due to the permanent stoma [6, 7]. Total proctocolectomy (TPC) with ileal pouch–anal anastomosis (IPAA), proposed in 1978, was considered as the first choice for the radical surgical treatment of UC patients [8]. Although several surgical complications cannot be avoided, IPAA can improve a vast majority of patients and remains stable over time by restoring with a 'J' pouch as a reservoir for fecal continence and avoiding permanent ostomy [9–11]. Therefore, searching for a novel predictive factor to guide the need for IPAA that may aid clinicians in selecting the optimal treatment strategy to achieve an acceptable risk-to-benefit ratio for both surgeons and patients has become increasingly important and urgent.

The Mayo endoscopic score (MES) is the most commonly used index for estimating the disease activity of UC owing to its convenience and practicality [12]. Recently, the ulcerative colitis endoscopic index of severity (UCEIS) was proposed as a reliable tool for evaluating UC disease activity [13, 14]. Previous studies have reported that the UCEIS is better than the MES in reflecting the clinical outcomes and prognosis of patients with UC [15]. Moreover, some reports have suggested that the UCEIS may be useful for guiding the decisions for colectomy [16, 17]. However, the association between the UCEIS and the outcomes of pouch surgery and the predictive value of the UCEIS for the need for IPAA remain unclear. In this study, we aimed to establish the cut-off value for preoperative UCEIS to further analyse whether the UCEIS cut-off was suitable for predicting the need for IPAA in patients with UC.

Patients and methods

Study design and study subjects

A diagnostic study was conducted. We enrolled a total of 283 UC patients who had received standardized treatment or surgery (including IPAA and subtotal colectomy with ileostomy) between June 1986 and March 2020 at two centers in Shanghai, China (Xinhua Hospital and Ruijin Hospital). Clinical data of consecutive UC patients were retrospectively collected from a prospectively maintained, institutional-review-board-approved database (Chinese Database System for IBD) [18, 19]. The study protocol was reviewed and approved by the Ethics Committee of Xinhua Hospital (approval No. XHEC-D-2020-083).

The inclusion criteria were patients with an age at diagnosis of >18 years and complete clinical and follow-up data. Exclusion criteria were as follows: (i) patients who were diagnosed with Crohn's disease, indeterminate colitis, or familial adenomatous polyposis (FAP); (2) poor treatment compliance.

Evaluation of the UCEIS

The UCEIS score was assessed by two independent endoscopists who were blinded to our research. The UCEIS scores recorded at the time of the first colonoscopy after hospitalization were used in the study. In the past 15 years, the UCEIS was assessed through electronic photographs of the medical record system and earlier endoscopic data were according to the printed colonoscopy report. The UCEIS scoring system includes the following three items: vascular pattern (0–2 points), bleeding (0–3 points), and erosions and ulcers (0–3 points) [14]. The scores for each item were added to obtain the final UCEIS score, which ranged from 0 to 8. When there was inconsistency in a patient's UCEIS scores recorded by the two evaluators, the higher value was chosen for our analysis.

Indications for IPAA

In our institutions, indications for surgery were as follows: (i) persistent symptoms despite the administration of appropriate medical treatment; (ii) request for surgical treatment owing to the inability to afford high drug-related expenses; (iii) medication intolerance because of serious side effects; (iv) complications requiring surgical management; and (v) malignant transformation. While in this cohort, most patients (93.8%) received IPAA surgery and only a fraction of patients (6.2%) underwent permanent stoma. Therefore, we specifically defined the above conditions as the indications for IPAA to further research the relationship between the UCEIS and IPAA.

Clinical evaluation and definition

The extent of UC was classified as E1 (proctitis), E2 (left-sided colitis), and E3 (pancolitis) according to the Montreal classification system [20]. The extra-intestinal manifestation (EIM) referred to secondary EIM in UC duration, while primary EIM before diagnosis was excluded. Malignant transformation was defined as the development of confirmed UC-associated dysplasia or colorectal cancer (CRC). UC and UC-associated dysplasia or CRC were diagnosed based on the final pathological results. Surgery in this study included IPAA that maintained bowel continuity by creating a continent fecal reservoir with the 'J' pouch and subtotal colectomy with ileostomy. Previous use of medical therapies, such as mesalamine, biologics, steroids, and immunomodulators, was recorded. In the current study, all patients treated with a biological agent (infliximab) were performed on after 2008. The hemoglobin and albumin levels after hospitalization were also recorded. In addition, weight loss was defined as a weight loss of >5 kg during the course of the disease. The development of serious complications, such as serious gastrointestinal bleeding, intestinal obstruction, and colon perforation, was recorded.

Statistical analysis

SPSS version 19.0 (IBM 2010, Chicago, IL, USA) and GraphPad Prism 5 (San Diego, CA, USA) were used for statistical analysis. The Chi-square test or Fisher's exact test was used for the comparison of the categorical variables, and the Wilcoxon's rank-sum test was used for the comparison of the ranked variables. Multivariate logistic regression was used to analyse the factors associated with malignant transformation and the need for IPAA. Receiver operating characteristic (ROC) curve analysis was performed to determine the UCEIS cut-off value that aided in decision-making regarding the requirement for IPAA. The Kaplan-Meier method and log-rank test were used to assess the IPAA-free survival time and determine statistical significance. All tests were two-sided, with confidence intervals (CIs) set at 95%. A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Figure 1 presents the schematic flow diagram of this study. Overall, 283 UC patients were included. There were 136 males and 147 females with a median age at diagnosis of 42.0 years. The median UCEIS was 4 [interquartile range (IQR): 2–6]. During a median follow-up of 13 years (IQR: 8–17), 80 patients (28.3%) received surgery invention. Among these, 75 (93.8%) underwent IPAA surgery and 5 (6.2%) received subtotal colectomy with permanent ostomy (Table 1).

In patients with IPAA, 50 patients (66.7%) did so because of unresponsiveness to medical treatment, 3 (4%) due to the inability to afford the high cost of medications, 7 (9.3%) due to serious side effects, 10 (13.3%) due to serious complications, and 5 (6.7%) due to malignant transformation, whereas, in five patients with permanent stoma, all of them received emergency subtotal colectomy with ileostomy and the reasons that they rejected IPAA were high cost ($n=4$) and satisfaction with the status of the stoma ($n=1$). Given that only a small fraction of patients had a permanent stoma, we mainly focused on the

Table 1. Baseline characteristics of patients with ulcerative colitis

Characteristic	Total (n = 283)
Sex (male/female)	136/147
Age at diagnosis (years)	42 (29–52)
Disease duration (years)	6 (4–10)
Follow-up time (years)	13 (8–17)
UCEIS score	4 (2–6)
Conditions of relapse	
First occurrence	57 (20.1%)
First recurrence	53 (18.7%)
Multiple recurrences	173 (61.1%)
Weight loss	102 (36.0%)
Extra-intestinal manifestations	11 (11.7%)
Family history	
No	266 (94.0%)
Family history of CRC or IBD	8 (2.8%)
Family history of other cancer	9 (3.2%)
History of surgery	42 (14.8%)
Extent of disease	
E1	7 (2.5%)
E2	139 (49.1%)
E3	137 (48.4%)
Hemoglobin (g/L)	114.5 ± 24.6
Albumin (g/L)	28.4 ± 21.5
Surgery	
No	203 (71.7%)
Ileal pouch–anal anastomosis	75 (26.5%)
Subtotal colectomy with permanent stoma	5 (1.8%)
Medications	
Mesalamine	178 (62.9%)
Biologics	94 (33.2%)
Steroids	173 (61.1%)
Immunomodulators	38 (13.4%)

Values presented as median (interquartile range), mean ± standard deviation, or *n* (%).

UCEIS, ulcerative colitis endoscopic index of severity; CRC, colorectal cancer; IBD, inflammatory bowel disease.

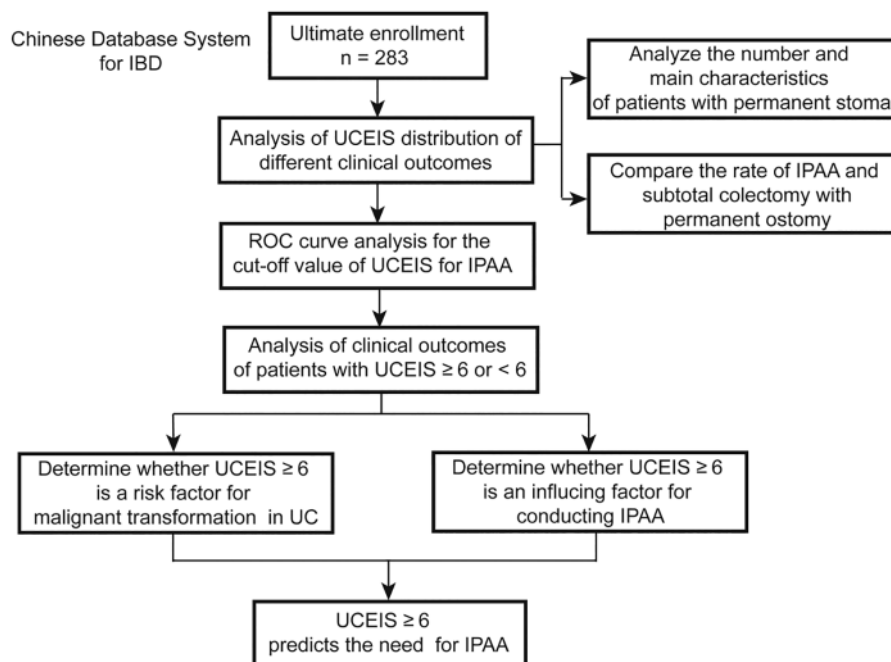


Figure 1. Schematic flow diagram of the present study. IBD, inflammatory bowel disease; UCEIS, ulcerative colitis endoscopic index of severity; IPAA, ileal pouch–anal anastomosis; ROC, receiver operating characteristic; UC, ulcerative colitis.

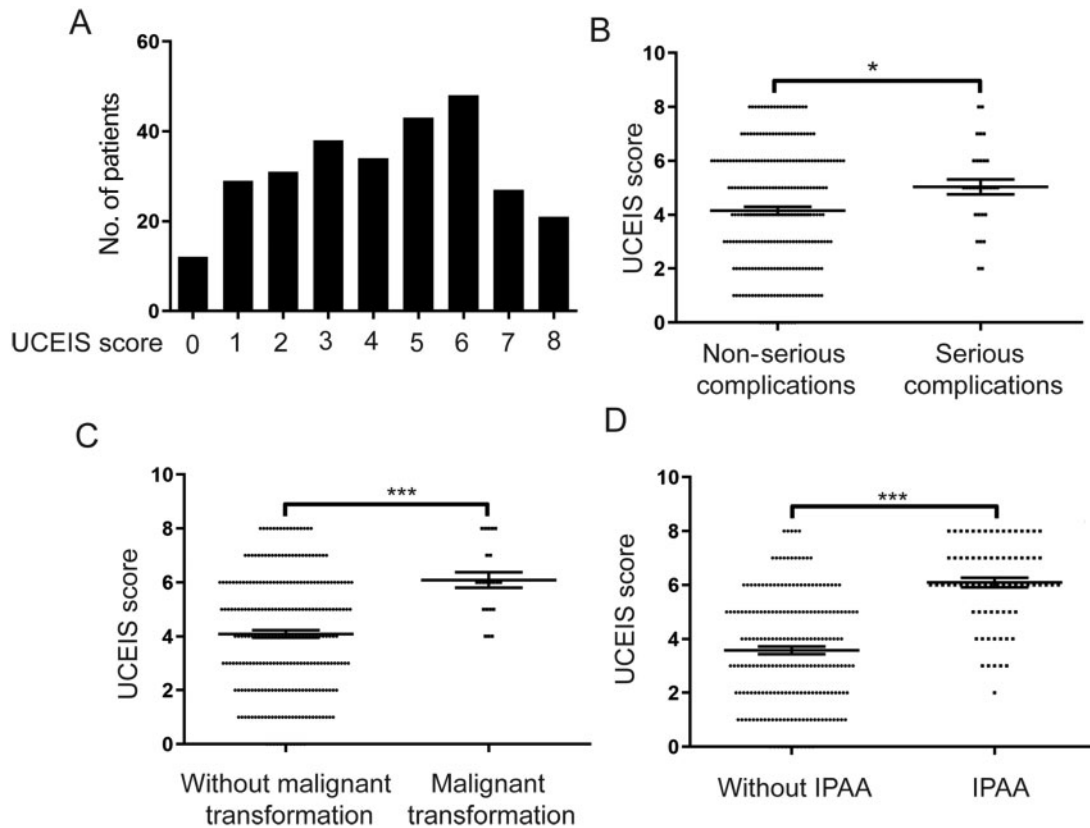


Figure 2. The distribution of the ulcerative colitis endoscopic index of severity (UCEIS) based on different clinical outcomes. (A) UCEIS in the cohort of patients ($n = 283$). (B) Comparison of median UCEIS between patients with ($n = 30$) and without serious complications ($n = 253$). (C) Comparison of median UCEIS between patients with ($n = 22$) and without malignant transformation ($n = 261$). (D) Comparison of median UCEIS between patients with ileal pouch–anal anastomosis (IPAA, $n = 75$) and without surgery ($n = 203$). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

patients with IPAA and discovered whether preoperative UCEIS could have predicted the need for IPAA.

Association between the UCEIS and clinical outcomes

In the whole cohort of 283 patients, 156 patients (55.6%) achieved clinical remission, 87 (30.7%) developed active disease, 30 (10.6%) developed serious complications, and 75 (26.5%) underwent IPAA. In addition, 22 (7.8%) patients were diagnosed with malignant transformation and 6 (2.1%) patients died during the study period. As shown in **Figure 2A**, 96 patients (33.9%) had UCEIS ≥ 6 . We found that a higher UCEIS was associated with serious complications ($P = 0.048$; **Figure 2B**), malignant transformation ($P < 0.001$; **Figure 2C**), and need for IPAA ($P < 0.001$; **Figure 2D**).

UCEIS cut-off score for predicting the need for IPAA

To further evaluate the performance of the early evaluated UCEIS to guide the need for IPAA in UC, we excluded the five patients with permanent stoma and performed the ROC curve analysis. As shown in **Figure 3**, a UCEIS cut-off value of 6 was the most efficacious for predicting the need for IPAA, with an area under the ROC curve (AUC) of 0.769 ($P < 0.001$; sensitivity 72.0% and specificity 81.8%).

UCEIS ≥ 6 is an independent factor for predicting IPAA requirement and malignant transformation

Based on the results of the ROC analysis, the UCEIS score of 6 was chosen as the cut-off value for further research. Our

analysis showed that patients with UCEIS ≥ 6 had a higher likelihood of requiring IPAA and developing malignant transformation than those with UCEIS scores < 6 (**Table 2**). Multivariate logistic regression analysis testified that UCEIS ≥ 6 (odds ratio 13.777, 95% CI 6.481–29.285; $P < 0.001$) was an independent factor for predicting the need for IPAA (**Table 3**). Then we performed a Kaplan–Meier analysis to compare the IPAA-free survival between patients with UCEIS ≥ 6 and those with UCEIS scores < 6 . As shown in **Figure 4**, patients with UCEIS ≥ 6 had a significantly shorter IPAA-free survival time than those with UCEIS < 6 ($P < 0.001$).

In addition, we determined whether UCEIS ≥ 6 is a contributing factor for malignant transformation. Multivariate analysis demonstrated that UCEIS ≥ 6 was an independent risk factor for malignant transformation (**Table 4**).

Discussion

IPAA can restore intestinal continuity by pouch construction compared to a permanent ostomy and has been recognized as the first surgery treatment for UC. In our institute, 80 patients received surgery invention with a high rate of IPAA (93.8%) and only 5 patients (6.2%) had subtotal colectomy with permanent stoma. Therefore, searching for a novel predictive factor to guide the need for IPAA has become increasingly important and urgent. To our knowledge, this study is the first to report that a UCEIS score ≥ 6 is an independent risk factor for malignant transformation and the need for IPAA in patients with UC.

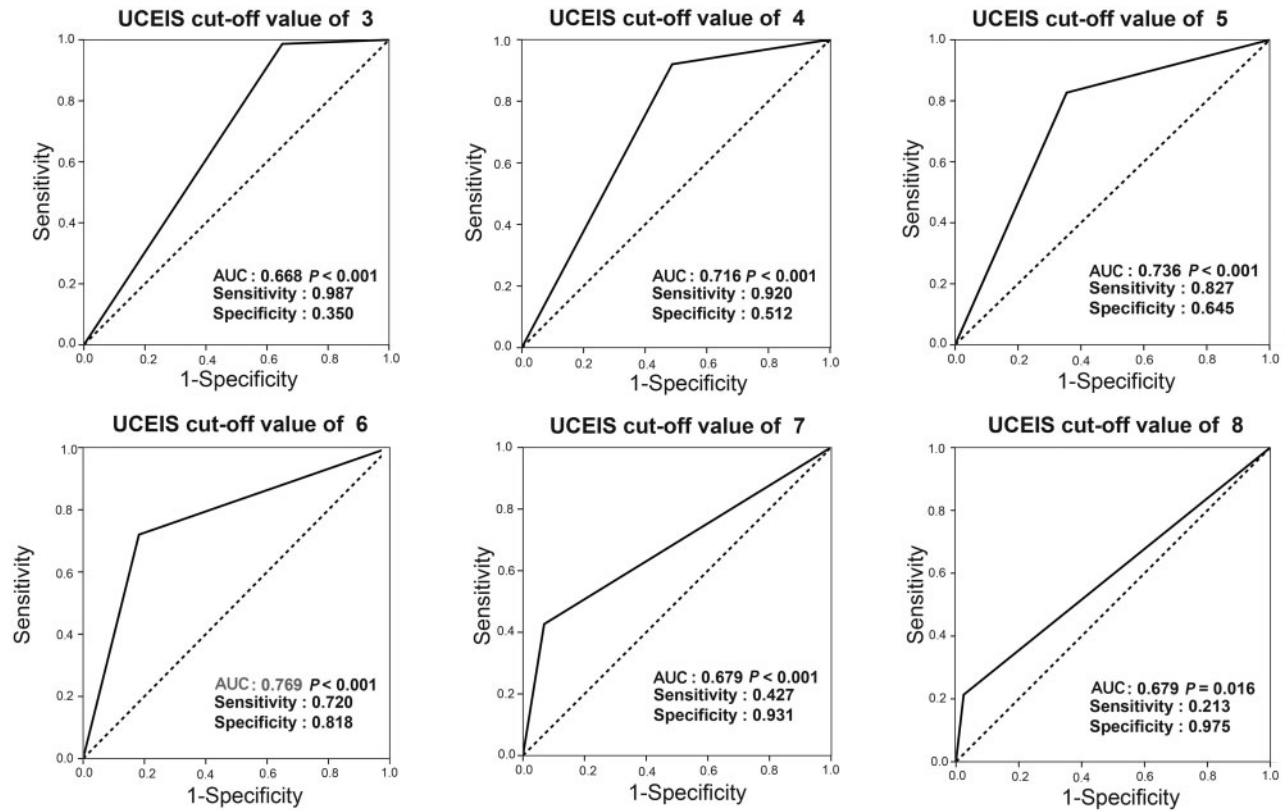


Figure 3. Receiver operating characteristic (ROC) curves of the ulcerative colitis endoscopic index of severity (UCEIS) in predicting the need for ileal pouch–anal anastomosis (IPAA). The UCEIS had the most significant area under the curve (AUC) of 0.769 with a sensitivity of 72.0% and specificity of 81.8% with the cut-off value of 6.

Table 2. Clinical outcomes of patients with ulcerative colitis based on the ulcerative colitis endoscopic index of severity (UCEIS)

Outcome	UCEIS <6 (n = 187)	UCEIS ≥6 (n = 96)	P-value
Clinical remission [n (%)]	99 (52.9)	57 (59.4)	0.303
Alternate or continuous disease activity [n (%)]	62 (33.2)	25 (26.0)	0.220
Serious complications [n (%)]	20 (10.7)	10 (10.4)	0.943
Ileal pouch–anal anastomosis [n (%)]	21 (11.2)	54 (59.3) ^a	<0.001
Malignant transformation [n (%)]	7 (3.7)	15 (15.6)	<0.001
Death [n (%)]	2 (1.1)	4 (4.2)	0.185

^aAmong 96 patients with UCEIS ≥6, five with permanent stoma were excluded from the calculation.

Formulating appropriate treatment plans and surgical options based on a timely UCEIS assessment is an important issue in UC management. In the present study, we found that UCEIS ≥6 was a risk factor for the development of malignant transformation. It is well known that patients with UC are prone to developing chronic and inflammatory polyps, both of which are reported to be independent risk factors for malignant transformation [18, 21, 22].

IPAA has the major advantage of avoiding a permanent stoma by creating a pouch as a reservoir for fecal continence that remains stable over time in the vast majority of patients; this feature has a considerable positive impact on the QOL [9–11]. It remains a challenge for clinicians to choose the appropriate predictor to guide the need for IPAA in UC patients. Corte *et al.* [16] have reported that a third of patients with UCEIS ≥5 require colectomy and that almost all patients with UCEIS ≥7

should receive treatment with infliximab or cyclosporine. Furthermore, Xie *et al.* [17] showed that severe UC patients with UCEIS ≥7 frequently need colectomy. However, these studies did not specify whether the required surgical method was subtotal colectomy with ileostomy or TPC with IPAA; additionally, small patient numbers precluded an accurate estimation of the association between UCEIS and clinical outcomes. Although Saigusa *et al.* [23] reported that UCEIS scores are able to predict outcomes in UC patients treated with infliximab, the association with surgical outcomes, especially the need for IPAA, was unclear. In our study, we identified that UCEIS ≥6 was independently associated with the need for IPAA, which was consistent with the fact that we further proposed that UCEIS ≥6 was a significant indicator for guiding the need for IPAA. Permanent stomas can contribute to psycho-social problems to some extent and have a low proportion in the present research. Thus, IPAA

Table 3. Univariable and multivariate logistic regression analysis for predicting the need for IPAA in patients with ulcerative colitis (n = 278)

Variables	No. of patients	IPAA (n = 75)	P-value	Multivariate analysis		
				Odds ratio	95% CI	P-value
Sex			0.053			
Male	134	29 (21.6)				
Female	144	46 (31.9)				
Age at diagnosis (years)			0.335			
<40	124	37 (29.8)				
≥40	154	38 (24.7)				
Disease duration (years)			<0.001	4.306	2.018–9.187	<0.001
<5	93	39 (41.9)				
≥5	185	36 (19.5)				
UCEIS score			<0.001	13.777	6.481–29.285	<0.001
<6	187	21 (11.2)				
≥6	91	54 (59.3)				
Conditions of relapse			0.178			
First occurrence	57	4 (7.0)				
First recurrence	48	36 (75.0)				
Multiple recurrences	173	35 (20.2)				
Extra-intestinal manifestation			0.489			
No	245	68 (27.6)				
Yes	32	7 (21.9)				
Extent of disease			<0.001	6.222	3.008–12.867	<0.001
E1	7	1 (14.3)				
E2	138	12 (8.7)				
E3	133	62 (46.6)				
Mesalamine			0.734			
No	103	29 (28.2)				
Yes	175	46 (26.3)				
Steroids			0.753			
No	107	30 (28.0)				
Yes	171	45 (26.3)				
Immunomodulators			0.005	1.804	0.728–4.470	0.202
No	241	58 (24.1)				
Yes	37	17 (45.9)				
Hemoglobin (g/L)			0.852			
≥90	236	63 (26.7)				
<90	42	12 (28.6)				
Albumin (g/L)			0.761			
≥35	206	54 (26.2)				
<35	72	21 (29.2)				
Colorectal stricture			0.563			
No	246	65 (26.4)				
Yes	32	10 (31.2)				
Malignant transformation			0.864			
No	257	69 (26.8)				
Yes	21	6 (28.6)				

CI, confidence interval; UCEIS, ulcerative colitis endoscopic index of severity.

should be positively taken into full consideration in patients with preoperative UCEIS ≥ 6 to prevent malignant transformation for UC patients.

Limitations to the study mainly included its retrospective nature and the relatively small sample size. Larger prospective multicenter studies should be conducted to determine whether UCEIS stratification is useful to guide the surgical selection process and prognosis evaluation. Due to the extremely low proportion of subtotal colectomies with permanent ostomy in our institute, we cannot precisely and statistically compare the differences in clinical outcomes between patients with IPAA and

those with permanent stomas. More samples of permanent stomas should be included for further research to determine whether it is better for patients with preoperative UCEIS ≥ 6 to receive IPAA rather than subtotal colectomy with permanent ostomy.

Conclusion

This current research reported that UCEIS ≥ 6 was an independent risk factor for malignant transformation and the need for IPAA in UC patients. Therefore, we suggest that UCEIS

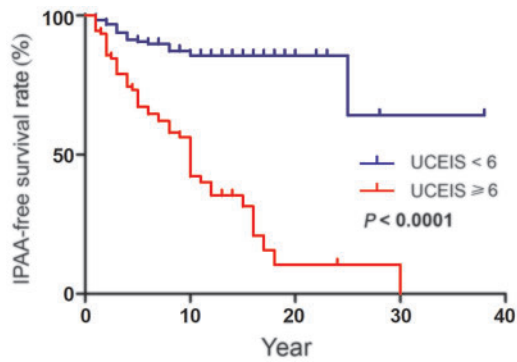


Figure 4. Ileal pouch–anal anastomosis (IPAA)-free survival rates in patients with ulcerative colitis endoscopic index of severity (UCEIS) ≥ 6 vs UCEIS < 6 .

assessment should be included in the decision-making process for determining the need for IPAA in UC patients. IPAA should be discussed and recommended in patients with preoperative UCEIS ≥ 6 for reducing the incidence of malignant transformation.

Authors' Contributions

P.D. was the guarantor of the article. P.D. and Y.G. conceived of and designed the study. W.X. performed analyses of the data and wrote the manuscript. W.O. and J.F. helped to collect the clinical data and follow-up information. J.Z. and L.C. supervised the work and data analyses. All authors participated in revising the manuscript and approved the final version.

Table 4. Univariable and multivariate logistic regression analysis for predicting malignant transformation in patients with ulcerative colitis ($n = 283$)

Variable	No. of patients	Malignant ($n = 22$)	P-value	Multivariate		
				Odds ratio	95% CI	P-value
Sex			0.799			
Male	136	10 (7.4)				
Female	147	12 (8.2)				
Age at diagnosis (years)			0.012	4.527	1.315–15.589	0.017
< 40	124	4 (3.2)				
≥ 40	159	18 (11.3)				
Disease duration (years)			0.046	1.158	0.407–3.297	0.783
< 10	195	11 (5.7)				
≥ 10	88	11 (12.5)				
UCEIS score			< 0.001	3.821	1.377–10.063	0.010
< 6	187	7 (3.7)				
≥ 6	96	15 (15.6)				
Conditions of relapse			0.794			
First occurrence	57	5 (8.8)				
First recurrence	53	3 (5.7)				
Multiple recurrences	163	14 (8.1)				
Extra-intestinal manifestation			0.303			
No	250	18 (7.2)				
Yes	33	4 (12.1)				
Colorectal stricture			< 0.001	11.072	3.693–33.190	< 0.001
No	251	11 (4.4)				
Yes	32	11 (34.4)				
Weight loss			1.000			
No	181	14 (7.7)				
Yes	102	8 (7.8)				
Family history			< 0.001	1.667	0.658–4.223	0.281
No	266	17 (7.1)				
CRC or IBD	8	5 (62.5)				
Other cancer	9	0 (0.0)				
Extent of disease			0.636			
E1	7	1 (14.3)				
E2	139	9 (6.5)				
E3	137	12 (8.8)				
Hemoglobin (g/L)			0.756			
≥ 90	240	18 (7.5)				
< 90	43	4 (9.3)				
Albumin (g/L)			0.800			
≥ 35	97	7 (7.2)				
< 35	186	15 (8.1)				

CI, confidence interval; UCEIS, ulcerative colitis endoscopic index of severity; CRC, colorectal cancer; IBD, inflammatory bowel disease.

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None.

Conflict of Interest

None declared.

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