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Histopathology and post-operative complications in pediatric ulcerative colitis

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Keywords: child; colonic pouches; rectum; odds ratio; paneth cells; colectomy.

Abbreviations: UC: Ulcerative Colitis; J-pouch: Ileo-Anal Anastomosis Pouch Surgical Procedure; IPAA: Ileal Pouch Anal Anastomosis Procedure; BMI: Body Mass Index; PROTECT study score: Predicting Response To Standardized Pediatric Colitis Therapy; EPIC: Electronic Health Records; CHEO: Children's Hospital Of Eastern Ontario; REB: Research Ethics Board; HPF: High Powered Field; REDCap: Research Electronic Data Capture; PUCAI: Pediatric Ulcerative Colitis Activity Index Score; IQR: Interquartile Range; CI: Confidence Intervals; IBD: Inflammatory Bowel Disease.

Abstract

Introduction: Few studies have explored the influence of uniquely histopathologic factors, and correlated them to post-operative J-pouch procedure complications in pediatric ulcerative colitis. The objective of this study was to evaluate the predictive capacity of histological parameters for post-operative complications of J-pouch procedure in pediatric patients with ulcerative colitis.

Methods: A retrospective chart review was conducted for all patients with refractory ulcerative colitis who underwent J-pouch procedure between January 2012 and June 2019. Tissue sections generated from colectomy and surgical rectum resection at J-pouch procedure were graded using histological parameters described in a modified version of the Geboes et al. score and the PROTECT study score. A total of 22 parameters assessed at four anatomical sites in the intestine were analyzed.

Discussion: Thirty-one patients were included in this study, 17 (54.8%) of whom developed post-operative complications. Paneth cell metaplasia in the rectum length (modified Geboes et al. score), as well as Paneth cell metaplasia in crypt epithelium (PROTECT study score) in the rectum length at J-pouch procedure were significantly associated with decreased odds of post-operative complication following J-pouch [odds ratio (95% confidence interval): 0.0 (0.0, 0.6) for both].

Conclusion: Our study found that Paneth cell metaplasia in the rectum length may lead to decreased odds of post-operative complications following the J-pouch procedure, while the remaining histological parameters did not show evidence of predicting post-operative complications. This knowledge is clinically important and relevant for pathologists and gastroenterologists who may consider using the Geboes et al. score or PROTECT score to identify histopathological parameters that could predict the presence of post-operative complications. Consequently, they can communicate relevant findings to surgeons during post-operative treatment planning.

Introduction

Ulcerative colitis (UC) is first treated with drug therapy, including corticosteroids and immunosuppressants [1]. However, patients who do not present with successful remission of clinical or histological findings, are characterized as refractory UC necessitating surgery [2]. Pediatric-onset UC, in particular, is often more severe at diagnosis and less responsive to drug therapy, when compared to adult-onset UC [1,3]. The ileo-anal anastomosis pouch (J-pouch) surgical procedure is the most commonly used option for surgical management of refractory UC in pediatric patients [2,4,5]. Yet, the surgical outcome of the J-pouch procedure consists of various post-operative complications, such as anastomotic leak, pouchitis, bowel stricture, and bowel obstruction [6-8]. Currently, several peri-operative risk factors for post-operative J-pouch complications in adult populations have been reported in the literature, including patient comorbidity, prolonged and high-dosage steroid use, and obesity [9-11]. Studies present mixed results regarding clinical factors associated with pouchitis after the ileal pouch anal anastomosis (IPAA) procedure in pediatric UC. In particular, sex, BMI (body mass index), age at UC diagnosis, age at colectomy, IPAA stage, colitis extent, exposure to biologics, extraintestinal manifestations, and time from colectomy to pouch formation, were not predictive of pouchitis [12-15]. In contrast, older age at colectomy was found to be protective [14], while patients who had preoperative vitamin-D deficiency [14], received a preoperative steroid dose of >10 000 mg, and had a blood count neutrophil percentage of >65% were more likely to develop pouchitis [16].

Despite these findings, few studies have explored the influence of uniquely histopathologic factors, and correlated them to post-operative J-pouch procedure complications in pediatric UC. El Demellawy et al. assessed the value of histopathology for predicting post-operative complications of the J-pouch procedure [2], using a modified version of the Geboes et al. grading system to evaluate UC disease activity and chronicity [2,17]. Another histological grading system that accurately evaluates UC disease activity and chronicity is The PROTECT (Predicting Response to Standardized Pediatric Colitis Therapy) study score [18]. The advantage of these scoring systems is that they are standardized, and reproducible (objective), unlike the Geboes et al. score, which has subjectively defined terms [17,19,20]. The aim of this current study is to evaluate the ability of the histological parameters described in the modified Geboes et al. score [2,17] and the PROTECT study score [18] to predict post-operative complications of the J-pouch procedure in cases of pediatric UC.

Material and methods

Case selection

A retrospective chart review in EPIC Hyperspace [21] was conducted to identify all pediatric patients (<18 years) with UC who underwent a J-pouch procedure at the Children's Hospital of Eastern Ontario (CHEO) between January 1st, 2012 and June 1st, 2019. Histological slides previously generated from colectomy specimens at subtotal colectomy and surgical rectum resection specimens at J-pouch procedure were collected from CHEO archives. Using an Open Epi calculator and consulting the pathologist for UC cases at our institution for each year, our estimated total sample size was 52 (of which 26 UC children who underwent IPAA would experience a post-operative complication) [22]. Tissue sections from the colectomy for each de-identified case were reviewed by an experienced pediatric pathologist (DED) in a blinded manner to verify the diagnosis of UC. The pathologist sampled extensively from the full length of the colon and rectum to minimize sampling error, and assessed the whole circumference of the rectal margin. Cases that did not have slides of the complete rectum resection available, or patients diagnosed with Crohn's disease were excluded, since this was not our disease of interest. This study was approved by the CHEO Research Ethics Board (CHEOREB#19/71X).

Data collection

The Tissue sections of the colon from the colectomy and the rectum specimen resected during the J-pouch procedure were reviewed by two experienced pediatric pathologists (DED, JDN) and one undergraduate research student (NI) under HPF (high powered field). Reviewers were blinded to post-operative outcomes. The two pediatric gastrointestinal pathologists (DED, JDN) only disagreed on 3 cases (9.7%). If discrepancies occurred, both pathologists reviewed the histopathological criteria on a multi-head microscope and came to a consensus. For all tissue sections, the intestinal mucosa was evaluated based on 22 parameters:

1. The ten parameters described in the modified version of the Geboes et al. score (i.e., Grades 0, 1, 2A, 2B, 3, 4, 5, 6, 7, and 8) along with three dichotomous parameters of interest added by the current study authors (i.e., Grades 9, 10 and 11).

2. The nine histological parameters described in the PROTECT study score [18].

The tables in the Supplementary Material files (Tables S1 and S2) display detailed explanations of the modified version of the Geboes et al. score [2,17] and the PROTECT study score [18] respectively. Higher scores indicate more severe disease activity and/or chronicity.

A score was assigned for each of the 22 parameters at four specific anatomical sites for each patient case: (1) colon margin; (2) colon length; (3) rectum margin; and (4) rectum length. For each of the colon margin and the rectal margin, the assigned scores were based on the assessment of the entire margin. For each of the colon length and the rectal length, one cross-sectional sample was selected to represent the entire specimen from which it was taken; the selection of the representative section was standardized by visualizing all slide sections composing one specimen and selecting that which displayed the most severe histological findings (i.e., findings that would be assigned the greatest score, based on the scoring systems used). When scoring specimen sections, regions of ulceration were avoided, because ulcers would have destroyed the presence of all other histological features of interest [23] and thus could have yielded an inaccurate scoring on various histological parameters. If a non-ulcerated section of a specimen did not exist, all histological parameters, other than those pertaining to ulceration, were scored as 'not applicable'.

Data on patient demographics, clinical presentations, medical therapies, and post-operative outcomes were retrieved from

CHEO electronic medical records and/or paper-based patient files, and entered into the Research Electronic Data Capture (REDCap), a secure web application for building and managing databases [24]. Data on sex, age at diagnosis (years), Pediatric Ulcerative Colitis Activity Index (PUCAI) score, Bristol Stool Scale score, Mayo grade at initial endoscopy, colectomy indications, duration of medicinal treatment, type of initial treatment (steroids, immunosuppressants, amino salicylates), time between procedures (months), and type of pouch complications were extracted. There is clinical relevance in examining the effect of time interval between colectomy and ileo anal anastomosis, in relation to histopathology. Surgeons can identify the impact of length of time between procedures and potential changes in histopathological features, and subsequently use this information for operative planning. All included patient cases were separated into two comparative groups: (1) those who experienced at least one of the six common post-operative complications of anastomotic leak, pouchitis, bowel stricture, pelvic abscess, fistula, or bowel obstruction; and (2) those who did not experience any of these six post-operative complications. Although histopathology could best predict pouchitis, we could not statistically examine this complication in isolation, and thus supplemented with other complications, regardless of known pathological risk.

Statistical analysis

Patient characteristics were summarized using frequencies for categorical variables, and median, interquartile range (IQR) for continuous variables. The scores of the 22 discrete histological parameters that compose the modified Geboes et al. score [2,17] and PROTECT study score [18] were analyzed for association with post-operative complications. Fisher's exact test was used to compute odds ratios (OR) and 95% confidence intervals (CI) to determine the likelihood of developing at least one post-operative complication given varying histological parameters at four anatomical sites: (1) colon margin; (2) colon length; (3) rectal margin; and (4) rectal length. In accordance with expert statistical advice, false discovery corrections are not required, since this is an exploratory study of modest sample size, and dichotomized p-values are not presented. To examine if time

Table 1: Patient characteristics of the study sample.

	Study sample (n=31)	Complicated group (n=17)	Uncomplicated group (n=14)
Male; n (%)	16 (51.6%)	8 (47.1%)	8 (57.1%)
Age at diagnosis (years); median (IQR)	12.9 (11.5, 14.6)	12.8 (11.6, 14.6)	12.9 (11.6, 15.4)
PUCAI score; median (IQR)	50.0 (45.0, 60.0) (n=23)	55.0 (45.0, 60.0) (n=11)	50.0 (48.8, 60.0) (n=12)
Bristol Stool Scale score; n (%)	(n=23)	(n=11)	(n=12)
Types 1-4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Type 5	1 (4.3%)	0 (0.0%)	1 (8.3%)
Type 6	12 (52.2%)	5 (45.5%)	7 (58.3%)
Type 7	10 (43.5%)	6 (54.5%)	4 (33.3%)
Mayo grade at initial endoscopy; n (%)	(n=23)	(n=11)	(n=12)
Mayo 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mayo 2	4 (17.4%)	2 (18.2%)	2 (16.7%)
Mayo 3	19 (82.6%)	9 (81.8%)	10 (83.3%)
Indication for colectomy; n (%)			
Failed response to medicinal therapy	30 (96.8%)	16 (94.1%)	14 (100.0%)
Urgent case	1 (3.2%)	1 (5.9%)	0 (0.0%)
Duration of medicinal treatment (months); median (IQR)	9.4 (2.7, 25.5)	9.0 (1.6, 13.0)	10.6 (4.0, 31.5)
Steroids as initial treatment (n,%)	25 (80.6%)	14 (82.4%)	11 (78.6%)
Immunosuppressants as initial treatment (n,%)	5 (16.1%)	2 (11.8%)	3 (21.4%)
Amino salicylates as initial treatment (n,%)**	11 (35.5%)	6 (35.3%)	5 (35.7%)
Age at J-pouch procedure (years); median (IQR)	15.2 (13.2, 17.1)	14.8 (12.8, 17.1)	15.5 (14.4, 17.1)
Time between procedures (months); median (IQR)	12.7 (8.1, 15.2)	13.3 (10.0, 20.5)	9.3 (7.3, 13.2)
Type of pouch complication (n=17); n complications (% of patients)*			
Pouchitis	N/A	5 (29.4%)	N/A
Bowel stricture	N/A	5 (29.4%)	N/A
Bowel obstruction	N/A	5 (29.4%)	N/A
Intra-abdominal abscess/infection	N/A	3 (17.6%)	N/A
Anastomotic leak	N/A	2 (11.8%)	N/A
Fistula	N/A	0 (0.0%)	N/A

*14 patients experienced 1 complication each, while 3 patients experienced 2 complications each (1 patient had pouchitis and anastomotic leak, 1 patient had pouchitis and bowel obstruction, and 1 patient had abscess and anastomotic leak).

** Patients may have received a combination of amino salicylates and steroids at initial treatment.

Table 2: Odds of having a post-operative complication following J-pouch procedure for each histological parameter of the modified Geboes et al. score.

Odds ratio (95% CI)				
Histological parameter	Anatomical site			
	Colon margin	Colon length	Rectum margin	Rectum length
Architectural changes	0.0 (0.0-inf)	0.0 (0.0-inf)	0.0 (0.0-inf)	0.0 (0.0-inf)
Mononuclear inflammatory infiltrate	0.0 (0.0-inf)	0.0 (0.0-inf)	Inf (0.0-inf)	Inf (0.2-inf)
Lamina propria infiltration by diffuse neutrophils	4.4 (0.7-35.1)	1.1 (0.2-5.6)	0.6 (0.1-3.7)	1.9 (0.2-26.1)
Lamina propria infiltration by diffuse eosinophils	2.7 (0.5-17.0)	1.5 (0.3-7.9)	1.5 (0.1-100.9)	1.0 (0.2-5.6)
Neutrophils in epithelium	0.0 (0.0-47.3)	0.0 (0.0-inf)	0.6 (0.1-3.7)	5.7 (0.5-314.1)
Crypt destruction	0.0 (0.0-47.3)	0.0 (0.0-inf)	0.6 (0.1-3.7)	5.7 (0.5-314.1)
Erosion or ulceration	0.3 (0.0-1.9)	1.3 (0.2-7.8)	0.5 (0.0-4.4)	2.9 (0.3-37.8)
Muscularis propria inflammation	2.7 (0.2-157.1)	0.5 (0.1-4.0)	0.5 (0.0-5.6)	2.7 (0.2-157.1)
Lymphoid follicles	2.2 (0.4-13.5)	1.3 (0.2-7.8)	0.6 (0.1-3.3)	2.9 (0.3-37.8)
Crypt epithelial apoptosis	1.8 (0.2-23.5)	1.8 (0.2-23.5)	1.6 (0.2-21.7)	0.8 (0.1-4.9)
Paneth cell metaplasia	0.4 (0.1-2.4)	2.5 (0.4-20.4)	0.3 (0.0-7.5)	0.0 (0.0-0.6)*
Crypt atrophy	0.0 (0.0-4.3)	0.8 (0.0-68.6)	0.9 (0.1-9.2)	0.9 (0.2-5.2)
Crypt shortening	1.8 (0.2-23.5)	0.5 (0.0-5.2)	0.7 (0.0-15.4)	2.4 (0.1-157.0)

CI – confidence interval, Inf – infinity. *Statistically significant odds

Table 3: Odds of having a post-operative complication following J-pouch procedure for each histological parameter of the PROTECT study score.

Odds ratio (95% CI)				
Histological parameter	Anatomical site			
	Colon margin	Colon length	Rectum margin	Rectum length
Acute and chronic inflammation grades	0.0 (0.0-inf)	0.0 (0.0-inf)	0.0 (0.0-inf)	Inf (0.0-inf)
Eosinophilic inflammation grades	2.5 (0.5-14.3)	1.9 (0.4-10.1)	1.5 (0.1-100.9)	1.4 (0.3-7.9)
Ulcer/erosion	0.5 (0.1-2.5)	1.3 (0.2-7.8)	0.5 (0.0-4.4)	2.9 (0.3-37.8)
Crypt distortion/atrophy	1.2 (0.0-102.5)	0.0 (0.0-inf)	0.0 (0.0-52.0)	0.0 (0.0-inf)
Surface villiform changes	3.4 (0.6-21.7)	1.4 (0.3-7.4)	0.8 (0.0-67.9)	0.4 (0.0-3.2)
Basal plasmacytosis	0.3 (0.0-3.1)	2.0 (0.2-27.8)	0.9 (0.1-6.8)	7.8 (0.7-418.6)
Basal lymphoid aggregates	0.0 (0.0-47.3)	0.0 (0.0-inf)	0.6 (0.0-12.8)	0.6 (0.0-12.5)
Paneth cell metaplasia in crypt epithelium	0.0 (0.0-inf)	2.5 (0.4-20.4)	0.3 (0.0-7.5)	0.0 (0.0-0.6)*
Granuloma	0.0 (0.0-inf)	0.0 (0.0-inf)	Inf (0.0-inf)	Inf (0.0-inf)

CI – confidence interval, Inf – infinity. *Statistically significant odds

Table 4: Change in score of each histological parameter of the modified Geboes et al. and PROTECT study score between colectomy and J-pouch procedure.

Spearman correlation coefficient		
Geboes histological parameters	Anatomical site	
	Colon margin and rectum margin	Colon length and rectum length
Architectural changes	0.37	0.49
Mononuclear inflammatory infiltrate	0.01	0.45
Lamina propria infiltration by diffuse neutrophils	-0.23	0.05
Lamina propria infiltration by diffuse eosinophils	0.35	0.10
Neutrophils in epithelium	-0.12	0.33

Crypt destruction	-0.34	0.42
Erosion or ulceration	0.26	0.03
Muscularis propria inflammation	-0.06	0.26
Lymphoid follicles	-0.21	0.14
Crypt epithelial apoptosis	-0.22	0.02
Paneth cell metaplasia	0.47	-0.36
Crypt atrophy	0.44	0.41
Crypt shortening	0.35	0.51
PROTECT Histological parameters		
Acute and chronic inflammation grades	-0.37	0.26
Eosinophilic inflammation grades	-0.37	0.26
Ulcer/erosion	0.21	-0.02
Crypt distortion/atrophy	0.19	N/A*
Surface villiform changes	-0.36	-0.25
Basal plasmacytosis	-0.07	0.35
Basal lymphoid aggregates	0.04	0.12
Paneth cell metaplasia in crypt epithelium	0.49	-0.36
Granuloma	-0.07	-0.05

*The Spearman correlation coefficient for the change in crypt distortion/atrophy grade in the length and time between procedures cannot be calculated as all patients had score 0 at both colectomy and J-pouch.

between subtotal colectomy and J-pouch procedure predicted intestinal health or post-operative complications, a Spearman correlation test was performed. The Spearman correlation test seemed most appropriate in order to accommodate nonlinear ranked difference. Change in intestinal health was determined by comparing the score for a given histological parameter during the J-pouch procedure relative to the score for the same parameter during the colectomy; a higher score indicated worse intestinal health. A positive correlation coefficient indicated an association between increasing time interval and a higher histological score (i.e., worse intestinal health). The correlation was considered strong if $r > \pm 0.70$, moderate if $\pm 0.7 \geq r \geq \pm 0.5$, fair if $\pm 0.5 \geq r \geq \pm 0.3$, or poor $r < \pm 0.3$ [25]. The Kruskal-Wallis test was used to determine if the time interval between surgeries affected the presence of post-operative complications. All statistical analyses were performed using R version 3.6.2 [26].

Results

Study sample characteristics

Thirty-one pediatric patients who underwent J-pouch procedure met the inclusion criteria. This cohort was composed of cases with and without surgical complications, 17 (54.8%) and 14 (45.2%) respectively. Patient characteristics of the study sample are shown in (Table 1). The majority of patients received steroids as initial treatment in the total cohort (n=25), and complicated vs uncomplicated groups.

Histologic parameters predicting post-operative complications

Paneth cell metaplasia (Grade 9 of the modified Geboes et al. score [2,17]) scored in the rectum length was significantly associated with decreased odds of post-operative complication following J-pouch [OR (95% CI): 0.0 (0.0, 0.6)]. Paneth cell metaplasia in the crypt epithelium (Grade H of the PROTECT study score [18]) scored in the rectum length was also significantly associated with decreased odds of post-operative complication [0.0 (0.0, 0.6)]. All other combinations of histological parameters and anatomical sites of assessment (i.e., colon margin, colon length, rectum margin, and rectum length) were not significantly associated with increased or decreased odds of post-operative complications. (Tables 2 and 3) summarize the ORs and 95% CIs for the 13 parameters of the modified Geboes et al. score [2,17] and the 9 parameters of the PROTECT study score [18], respectively.

Effect of time interval

Table 4 summarizes the Spearman correlation coefficients (i.e., the strength and direction of an association between two ranked variables, and not a measure of statistical significance) for the 13 parameters of the modified Geboes et al. score and the nine parameters of the PROTECT study score, respectively.

There was a fair relationship between increasing time interval between colectomy and J-pouch procedure and decreasing histological score (i.e., improved intestinal health) for the following parameters: Crypt destruction (Grade 4 of the modified Geboes et al. score) in the colon margin, Paneth cell metaplasia (Grade 9 of the modified Geboes et al. score) in the colon length, Acute and chronic inflammation (Grade A of the PROTECT study score) in the colon margin, Eosinophilic inflammation (Grade B of the PROTECT study score) in the colon margin, Surface villiform changes (Grade E of the PROTECT study score) in the colon margin, and Paneth cell metaplasia in crypt epithelium (Grade H of the PROTECT study score) in the colon length.

There was a moderate relationship observed between increasing time between colectomy and J-pouch procedure and increasing score (i.e., worse intestinal health) for crypt shortening (Grade 11 of the modified Geboes et al. score) in the colon length. A fair relationship was observed between increasing time interval between colectomy and J-pouch procedure and increasing histological score for the following parameters: Architectural changes (Grade 0 of the modified Geboes et al. score) in the colon margin, and colon length; Mononuclear inflammatory infiltrate (Grade 1 of the modified Geboes et al. score) in the colon length; Lamina propria infiltration by diffuse

eosinophils (Grade 2B of the modified Geboes et al. score) in the colon margin; Crypt destruction (Grade 4 of the modified Geboes et al. score) in the colon length; Paneth cell metaplasia (Grade 9 of the modified Geboes et al. score) in the colon margin; Crypt atrophy (Grade 10 of the modified Geboes et al. score) in the colon margin and colon length; Crypt shortening (Grade 11 of the modified Geboes et al. score) in the colon margin; and Basal plasmacytosis (Grade F of the PROTECT study score) in the colon length. The time interval between surgeries was not significantly different between the complicated and uncomplicated group (p=0.52).

Discussion

Our objective was to determine if histopathological parameters from the two scoring systems could predict any post-operative complications after the IPAA procedure. The 2007 PROTECT study core has recently been applied to assess UC disease activity. Although certain parameters overlap with the 2000 Geboes et al. system (e.g., Paneth cell metaplasia), we wanted to discern if there was any additional benefit of using the PROTECT versus the Geboes system, given that the PROTECT score also captures eosinophilic inflammation. The presence of Paneth cell metaplasia (from the Geboes et al. score) in the rectum length, as well as the presence of Paneth cell metaplasia in crypt epithelium (from the PROTECT study score) in the rectum length were each found to be significantly associated with decreased odds of developing a post-operative complication.

Due to multiple, independent tests performed, there is substantial likelihood that this finding is a false positive – occurring from random chance alone rather than representing a true statistical difference. However, these findings might loosely indicate that Paneth cell metaplasia in the rectum length, has a protective effect following the J-pouch procedure. In the complications group, the time elapsed between the initial disease diagnosis and time of J-pouch procedure was only two years. If the timing of the surgical intervention had been delayed, then the condition of the children might have worsened, and Paneth cell metaplasia may have been detected later during the UC disease course. Therefore, we may have detected a protective effect of Paneth cell metaplasia, since the timing of intervention was swift and the likelihood of chronicity potentially lower. In contrast, Simmonds et al. determined that a high proportion of UC patients showed Paneth cell metaplasia in the distal colon, and this feature presents early in the disease, but is not correlated with chronicity [27].

Paneth cell metaplasia may be a targeted response to inflammatory bowel disease (IBD) inflammatory differences, or arises due to changes in the bacterial flora [28]. Typically, heightened colonic Paneth cells in IBD adapt in response to alpha defensins and antimicrobial proteins, as a protective barrier is formed to prevent mucosal infection in an inflamed bowel [29-31]. Paneth cell-derived antimicrobial agents and defensins are responsible for immune homeostasis of the intestine [30]. Specifically, changes in the expression of defensins and Paneth cells can directly or indirectly affect the host, and contribute to innate and adaptive responses to microbial infection and thus, tissue damage. Moreover, an increase in Paneth cells usually occurs in response to the intestinal luminal environment, and can possibly improve the mucosal innate immunity [30]. Therefore, Paneth cell metaplasia may actually be beneficial to the mucosa within the intestine, which could possibly explain the protective effect following the J-pouch procedure in our study. However, the pathogenesis of Paneth cells in UC remains to be elucidated. Alternatively, Paneth cell metaplasia may not be a protective factor; rather, it is possible that a factor not accounted for in this study may explain the decreased odds of post-operative complication observed.

Previous studies have reported inconclusive findings regarding the association between histopathology and post-operative complications of the J-pouch procedure. Arashiro et al. did not identify a correlation between the presence of metaplasia and pouchitis, possibly because paneth cell metaplasia presents early in the disease process (p = 0.17) [27,32]. In contrast, Fruin et al. found that both the degree of colonic metaplasia and inflammation were higher in patients who experienced pouchitis following the J-pouch procedure, compared to those without pouchitis [33,34]. Similarly, Gawad et al. identified that histologic inflammation in the rectum margin was significantly associated with pouchits. Lastly, El Demellawy et al. found that patients with post-operative complications had a significantly higher summed activity score at the rectum margin compared to patients without post-operative complications (mean 7.3 ± 3.1 versus 4.8 ± 3.1; p = 0.04) [2].

One potential explanation for discrepant findings between our current study and the previous study by El Demellawy et al. [2] is the two time periods when patients were recruited. Patients from 2000 to 2013 may have had variable characteristics and underwent different treatment plans than those in 2019. Therefore, our more recent cohort of patients may have had less severe histological features at colectomy and J-pouch, due to new drug therapies for UC that have been administered more often in the past decade, such as Tofacitinib and Ustekinumab [35]. Thus, the decreased severity of histological features in more recent UC cases may be due to newly prescribed medications. Despite this, the percentage of complications in our current study (54.8%, 17/31) is higher than the percentage reported in El Demellawy et al. (35.7%, 10/28). Our current cohort of patients has changed over time, particularly with respect to ethnic diversity, and refractory status. We captured patients who did not initially respond well to treatment. In fact, nearly 100% of the entire cohort did not respond to medical therapy. As such, we may expect heighted post-operative complications due to failure to react to current treatment strategies. Of note, the same group of four surgeons at our institution have performed the J-pouch procedure for over a decade; therefore, there is no effect of surgical technique on post-operative complications. The frequency of complications is unlikely to differ by surgeon, since identical protocols are followed and surgical results are comparable.

Although we did not identify increased odds of post-operative complication in our study, the residual presence of active disease following J-pouch procedure can potentially compromise the successful closure of the ileo-anal anastomosis site, and lead to septic complications such as anastomotic leak, fistula or pelvic abscess [36]. Furthermore, pouchitis and small bowel obstruction have been previously identified as long-term complications stemming from residual active UC disease in the recto-anal transitional zone, as the presence of histological activity in UC patients is a known marker of disease persistence [37]. We rationalize that the frequency of pouchitis (5/31, 16%) in our institution is comparably lower to the prevalence reported in literature (33%), due to approaches in operative technique. Specifically, surgeons at our institution perform short (around 8cm) J-pouches with the understanding that it may be

associated with less pouchitis risk. Strengths of this study include the use of a standardized protocol for assessing histopathology, effective blinding of gastrointestinal pathologists to the outcome of post-operative complications during the de novo slide examination, slide review of histological changes conducted by two pediatric gastrointestinal pathologists independently, implementation of rigorous statistical techniques, and the application of robust and validated scoring tools in a unique inpatient pediatric setting, characterized by a diverse population.

Limitations

Limitations of this study include our modest sample size. Given the small sample size in our study, statistical analyses may have been underpowered to detect significant associations or near-significant associations, as in the case for neutrophils in the epithelium, crypt destruction of the rectum margin, and time interval between surgeries. Furthermore, a subgroup analysis to examine histopathology parameters by prevalent complications could not be performed, because of insufficient sample size. Due to the retrospective nature of this study design, we were not able to gather data from the eight participants with missing data on clinical information at UC diagnosis, such as PUCAI score, Bristol Stool Scale score, and Mayo score at endoscopy. Another limitation, inherent with the exploratory nature of this study, is that the Spearman's correlation performed may have revealed a non-causal correlation resulting from a chance association or conditioned on another unmeasured variable.

Future studies are encouraged to further investigate the potential role and predictive capacity of histopathological factors in post-operative complications of the J-pouch procedure, including inflammation of the J-pouch and crypt shortening in the intestine length. Another area of future study would be to determine whether histopathology or time interval between surgeries are associated with the presence of certain post-operative complications, like pouchitis. Lastly, regression models adjusting for confounders, such as previous medications recently introduced in the treatment management of pediatric UC, is recommended to better tease the relationship between histopathology and post-operative complications. Such future studies should implement prospective multi-centre study designs with large sample sizes to detect important differences.

Conclusions

In both the Geboes et al. and PROTECT study scores, our study cautiously found that Paneth cell metaplasia in the rectum length may lead to decreased odds of post-operative complications following the J-pouch procedure in pediatric patients with UC. Neither scores established any histological predictors of complications. The time interval between colectomy and ileo-anal anastomosis did not impact postoperative complications. This knowledge is clinically important and relevant for pathologists and gastroenterologists who may consider using the PROTECT score to identify histopathological parameters that could predict the presence of post-operative complications. Consequently, they can communicate relevant findings to surgeons during post-operative treatment planning.

Declarations

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Author contributions

NI – Investigation; Roles/Writing – original draft; Writing – review & editing

IO – Project administration; Resources; Supervision; Writing – review & editing

DR – Formal analysis; Investigation; Visualization; Methodology; Writing – review & editing

RW – Formal analysis; Investigation; Visualization; Methodology; Writing – review & editing

JDN – Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Writing -review & editing

DED – Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Writing -review & editing

AN – Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing

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