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Alimentary Tract

Pouchitis in pediatric ulcerative colitis: A multicenter study on behalf of Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition

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ABSTRACT

Background: Data on the epidemiology and risk factors for pouchitis following restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA) in pediatric patients with ulcerative colitis (UC) are scarce.
Aims: To determine incidence, risk factors and clinical outcome of pouchitis following IPAA in children.
Methods: This multicenter, retrospective cohort study, included all pediatric UC patients who underwent colectomy and IPAA from January 2010 to December 2016.
Results: Eighty-five patients were enrolled. During a median post-surgical period of 24.8 (range: 1.0–72.0) months following IPAA, 38 (44.7%) patients developed pouchitis, including 6 (15.8%) who developed chronic pouchitis. Kaplan–Meier survival estimates of the cumulative probability for pouchitis were 14.6% at 1 year and 27.3% and 51.5% at 2 and 5 years, respectively. Multiple Cox regression model showed that older age at colectomy (hazard ratio, HR: 0.89, $p = 0.008$) was a protective factor, whereas chronic active colitis as indication for surgery (HR: 4.45, $p < 0.001$), and a 3-stage IPAA (HR: 2.86, $p = 0.028$) increased the risk for pouchitis.
Conclusions: Long-term risk for pouchitis is significantly high in pediatric-onset UC after IPAA. Younger age at colectomy, chronic active colitis as indication for surgery and 3-stage IPAA may increase the risk for pouchitis.

1. Introduction

Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is the recommended elective surgery for children with ulcerative colitis (UC) [1]. IPAA involves a total proctocolectomy with construction of an ileal reservoir anastomosed to the anus. The surgery restores intestinal continuity, preserves sphincter function, and maintains continence. Nonspecific inflammation of the ileal pouch reservoir, called pouchitis, is the most common complication following IPAA [1,2]. The symptoms and severity of pouchitis vary from patient to patient, but typically include increased stool frequency and urgency, loose watery stools, abdominal pain, and hematochezia. Duration of pouchitis can be categorized as acute (<4 weeks), chronic (>4 weeks) or recurrent pouchitis (≥3 episodes of acute pouchitis a year) [1]. The reported prevalence of pouchitis

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in children with UC undergoing IPAA is inconsistent [3–8], and data on predictive factors for the development of pouchitis in children are scarce [4]. The aims of the study were to determine incidence of pouchitis among patients with pediatric-onset UC after IPAA, and to identify predictive factors, at diagnosis and at the time of colectomy, associated with the development of subsequent pouchitis in the major national centres for paediatric gastroenterology.

2. Materials and methods

We conducted a multicentre national study in a retrospective cohort from January 1, 2010 to December 31, 2016. All SIGENP (Italian Society of Pediatric Gastroenterology Hepatology and Nutrition) centres were invited to participate in the study through the society's mailing list and journal. All patients younger than 18 years who had undergone restorative proctocolectomy and IPAA for UC were included in the study. Pouchitis was diagnosed using the Pouchitis Disease Activity Index (PDAI) [9], a combined clinical, endoscopic, and histological score. A PDAI score ≥ 7 suggests a diagnosis of pouchitis. Data on demographics, age at diagnosis of UC, extent and severity of colitis, extraintestinal manifestations, indications for surgery, age at the time of surgery, number of surgical stages, use of steroids, 5-ASA, immunomodulators (azathioprine/6-mercaptopurine), cyclosporine, and biologics during the 6 months before surgery, pouchitis occurrence, medical therapy at the time of the onset of pouchitis, and clinical and endoscopic outcome at 6 and 12 months of follow-up were collected. The Paris classification for UC [10], and the Mayo score disease activity index were used to assess the extent and severity of colitis, respectively. Indication for surgery was represented by chronic active colitis or acute severe colitis, represented by a Pediatric Ulcerative Colitis Activity Index (PUCAI) score ≥ 65. The deadline for data collection was set as January 31, 2017. The study protocol (number 114/17) was approved by the Institutional Review Board of all participating sites. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

2.1. Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQR), and categorical variables as frequency and percentage. Mann–Whitney U-test and $\chi 2$ tests (or Fisher's exact test, where needed) were used for comparison of continuous and categorical variables, respectively. Descriptive time to event analysis was conducted to assess the cumulative incidence of pouchitis using the Kaplan–Meier method. Pouchitis-free survival period was defined as the time between the date of restorative proctocolectomy and IPAA and the date of the first episode of pouchitis or the date of the last patients' follow-up (December 31, 2016) (censored patients). The following variables were assessed in order to identify predictive factors of the outcome: sex, age at diagnosis, disease duration, extent of colitis, severity of colitis, extraintestinal manifestations, indication for surgery, age of the patient at the time of surgery, number of surgical stages, use of steroids, 5-ASA, immunomodulators (azathioprine/6-mercaptopurine), cyclosporine and biologics.

A multiple Cox proportional hazard regression model was performed to examine the association between pouchitis and potential predictive factors: the final model was selected using a backward elimination approach based on the Akaike Information Criterion; results were considered statistically significant when $p \leq 0.05$. Proportional hazard assumptions were tested using Schoenfeld residuals tests and were not violated. All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria [11]).

3. Results

3.1. Demographics and disease characteristics

Eight gastroenterology units participated in the study. A total of 85 cases were collected (43 males and 42 females; male:female ratio 1.02), with a median age at UC diagnosis of 10 years (IQR, 5.0–12.0). Characteristics of patients are shown in Table 1. Sixty-eight (80%) patients had pancolitis (E4) at diagnosis, while disease was extensive, left-sided and proctitis in 9 (10.6%), 5 (5.9%) and 3 (3.5%) patients, respectively. The Mayo disease activity index prior to surgery was 3 in 65 (46.5%) patients, 2 in 18 (21.2%) patients and 1 in 1 (2.3%) patient. Extraintestinal manifestations were present in only 8 (9.4%) patients, and included arthritis, sclerosing cholangitis, osteoporosis and profound venous thrombosis.

3.1.1. Surgical data

Sixty-one (71.8%) patients underwent urgent colectomy with a PUCAI score ≥ 65 (acute severe colitis), while surgical indications were chronic active colitis in 23 (27.1%) patients and colonic inflammatory pseudopolyps in 1 (1.2%) patient. Median age at colectomy was 12.7 years (IQR = 9.0–15.0). Surgery was performed a median time of 16.0 months (IQR 12.0–45.0) after diagnosis of UC. Sixty-five (76.5%) patients underwent a 3-stage IPAA, 19 (22.4%) patients underwent a 2-stage IPAA and only 1 (1.2%) patient a 1-stage IPAA. Preoperative medication exposure included steroids in 71 (83.5%) patients, mesalazine in 37 (43.5%), azathioprine/6-MP in 36 (42.4%), anti-TNF-α in 40 (47.1%), cyclosporine in 41 (48.2%), thalidomide in 8 (9.4%), tacrolimus in 3 (3.5%), and methotrexate in 2 (2.3%).

3.1.2. Pouchitis

Thirty-eight (44.7%) patients developed pouchitis. The median age at first episode of pouchitis was 13.0 (IQR: 10.3–16.0) years. Median PDAI score at diagnosis was 8.0 (IQR 7.0–10.0). The median duration between IPAA and the first episode of pouchitis was 24.8 (IQR: 1.0–72.0) months. Medical therapies were required in 36 (94.7%) patients at pouchitis diagnosis; antibiotics, either metronidazole or ciprofloxacin, were used in 29 (76.3%) patients, enemas in 28 (73.6%), probiotics in 4 (10.5%), steroids in 3 (7.9%), and other minor therapies in 1 (2.6%). Only 7 (18.4%) patients failed first-line antibiotic therapy and were started on biologics, either infliximab (N = 2), or adalimumab (N = 4), or both (N = 1). Clinical follow up was performed 6 and 12 months after IPAA. In all 38 patients, 22 (57.9%) underwent pouchoscopy at 6-months, and 31 (81.5%) at 12-months follow up. Among patients who underwent endoscopy, histology was performed in 6 (27.2%) and 9 (29%) patients at 6-months and 12-months follow up, respectively. Median PDAI score was 4.0 (IQR: 1.3–8.0) at 6-months and 3.0 (IQR: 2.0–5.0) at 12-months follow up (Fig. 1). Thirty-two (84.2%) patients developed acute pouchitis (twenty-four patients had only one episode, whereas eight patients had more than one episode but less than three distinct episodes per year), whereas 6 developed chronic refractory pouchitis or recurrent pouchitis (3 and 3, respectively).

3.2. Predictive factors associated with pouchitis

Patients who developed pouchitis following IPAA had younger age at UC diagnosis (9.0 vs. 11.0, p = 0.052) and at colectomy

Table 1
Patient characteristics at baseline.

		Overall	No pouchitis	Pouchitis	p-Value
N		85	47	38	
Gender (%)	Female	43 (50.6)	24 (51.1)	19 (50.0)	1
Age at UC diagnosis (years, median, IQR)		10 [5,12]	11.0 [5.5, 12.5]	9.0 [5.0, 11.8]	0.052
Disease extension (%)	E1	3 (3.5)	1 (2.1)	2 (5.3)	0.759
	E2	5 (5.9)	3 (6.4)	2 (5.3)	
	E3	9 (10.6)	4 (8.5)	5 (13.2)	
	E4	68 (80.0)	39 (83.0)	29 (76.3)	
Extra-intestinal manifestation (%)	Yes	8 (9.4)	5 (10.6)	3 (7.9)	0.954
	Arthritis	*3 (3.5)*	*1 (2.1)*	*2 (5.2)*	
	Sclerosing cholangitis	*3 (3.5)*	*3 (6.4)*	*0 (0.0)*	
	Sclerosing cholangitis and osteoporosis	*1 (1.2)*	*0 (0.0)*	*1 (2.6)*	
	Profound venous thrombosis	*1 (1.2)*	*1 (2.1)*	*0 (0.0)*	
	No	77 (90.6)	42 (89.4)	35 (92.1)	
Mayo score (median, IQR)		3.0 [3.0,3.0]	3.0 [3.0, 3.0]	3.0 [3.0, 3.0]	0.967
MAYO SCORE (%)	Mayo 1	1 (2.3)	1 (2.1%)	1 (2.6%)	0.988
	Mayo 2	18 (21.2)	10 (21.3%)	8 (21.1%)	
	Mayo 3	65 (46.5)	36 (76.6%)	29 (76.3%)	
Age at colectomy (years, median, IQR)		12.7 [9.0, 15.0]	13.0 [11.2, 15.0]	12.0 [7.0, 14.0]	0.012
Disease duration (months, median, IQR)		16.0 [12.0, 30.1]	22.0 [8.0, 53.0]	12.5 [12.0, 36.0]	0.555
Indication to surgery (%)	Colonic inflammatory pseudo polyps	1 (1.2)	0 (0.0)	1 (2.6)	0.350
	Acute severe colitis	61 (71.8)	36 (76.6)	25 (65.8)	
	Chronic active colitis	23 (27.1)	11 (23.4)	12 (31.6)	
Surgery type (%)	1-stage IPAA	1 (1.2)	1 (2.1)	0 (0.0)	0.468
	2-stage IPAA	19 (22.4)	12 (25.5)	7 (18.4)	
	3-stage IPAA	65 (76.5)	34 (72.3)	31 (81.6)	
Preoperative medication exposure (%)	Steroids	71 (83.5)	39 (83.0)	32 (84.2)	1
	Mesalazine	37 (43.5)	13 (27.7)	24 (63.2)	0.200
	Azathioprine/6-MP	36 (42.4)	17 (36.2)	19 (50.0)	0.288
	Anti TNF-α	40 (47.1)	23 (48.9)	17 (44.7)	0.867
	Cyclosporine	41 (48.2)	22 (46.8)	19 (50.0)	0.941
	Other therapy	18 (21.2)	5 (10.6)	13 (34.2)	0.170
	Thalidomide	*8 (9.4)*	*1 (2.1)*	*7 (18.4)*	
	Tacrolimus	*3 (3.5)*	*2 (4.3)*	*1 (2.6)*	
	IV steroid	*3 (3.5)*	*1 (2.1)*	*2 (5.3)*	
	Methotrexate	*2 (2.4)*	*1 (2.1)*	*1 (2.6)*	
	Carbamazepine	*1 (1.2)*	*0 (0.0)*	*1 (2.6)*	
	Levetiracetam	*1 (1.2)*	*0 (0.0)*	*1 (2.6)*	

UC = ulcerative colitis, IQR = interquartile range, IPAA = ileal pouch-anal anastomosis, 6-MP = mercaptopurine, TNF = tumour necrosis factor, IV = intravenous.
Italic values mean the different types of EIMs and "Other therapy".

(12.0 vs. 13.0, p = 0.012) compared to those who did not. As shown in Table 1, sex, colitis extent and severity, extraintestinal manifestations, indications for surgery, number of surgical stages, and preoperative therapeutic regimens, were not associated with the development of pouchitis.

Patients were followed-up for a median time of 34.0 months (19.5 months of follow-up for patients who developed pouchitis and 43.0 for those who did not). The Kaplan–Meier survival estimates for patients who developed pouchitis are shown in Fig. 2. The cumulative probability of developing pouchitis (1 minus the probability of pouchitis-free survival) were 14.6% at 1 year and 27.3% and 51.5% at 2 and 5 years, respectively and the median survival time was 59.0 months.

3.3. *Predictors of pouchitis by multiple Cox regression analysis*

The results of a Cox regression analysis regarding the development of pouchitis after restorative proctocolectomy and IPAA in pediatric UC are presented in Table 2. Although univariate analysis did not show an association between indication for surgery and risk of pouchitis, in the multiple Cox regression model analysis, chronic active colitis as indication for surgery increased the risk of pouchitis (HR: 4.45, 95% CI 2.00–9.92, p < 0.001). Similarly, multiple Cox model demonstrated that 3-stage IPAA increased the risk of pouchitis (HR: 2.86, 95% CI 1.12–7.32, p = 0.028) compared with 2-stage operation. Increasing age at colectomy was associated to a reduced risk of developing pouchitis (HR = 0.89, 95% CI 0.82–0.97, p = 0.008). Multiple Cox regression model did not show further significant factors.

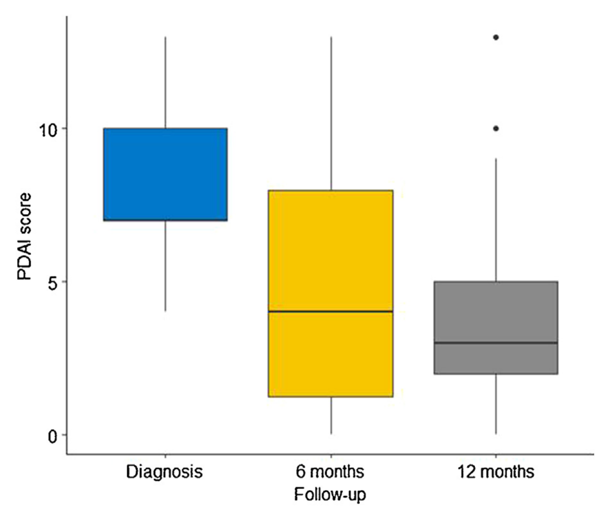

Fig. 1. PDAI score during follow-up.

In the analysis of the subgroup of patients who developed pouchitis (n = 38), a significant association between younger age at UC diagnosis (age > 6 years) and the development of chronic pouchitis during follow-up (p = 0.023) emerged. There was no significant association between the development of chronic

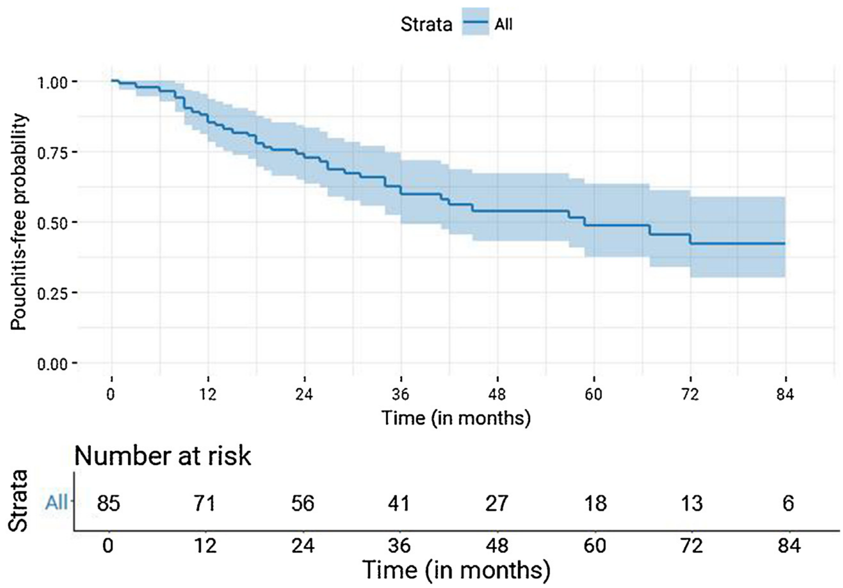

Fig. 2. Overall pouchitis-free survival (±95% confidence interval) estimated according to Kaplan–Meier method and table with number of subjects at risk.

pouchitis during follow-up and other variables assessed either at diagnosis or before colectomy. Notably, a statistically significant association was found between disease extent at onset (proctitis, E1) and the need for biologics for pouchitis ($p = 0.019$).

4. Discussion

Although medical therapies for UC have progressed during the last several decades, surgery still remains a viable and potentially curative strategy. Elective colectomy should be considered in children with active, or steroid-dependent, UC despite optimized medical therapy, and in those with colonic dysplasia [1]. As described in previous studies, pouchitis is the most frequent complication after an IPAA [1,3].

4.1. Epidemiology

The reported incidence of pouchitis in previous studies is largely variable because of the differences in the nature and duration of follow-up and particularly because of several diagnostic criteria that have been used to define pouchitis. Dharmaraj et al. [4] reported that pouchitis occurred in 25% of pediatric patients with UC based on clinical symptoms alone, thus leading to diagnostic bias. A recent multicenter, retrospective cohort study from the Paediatric IBD Porto Group of ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition) included 129 children who underwent IPAA (93% UC and 7% IBD unclassified) and showed that 86 children (67%) developed pouchitis during follow-up, including 33 (26%) who developed chronic pouchitis [12]. In an older cohort of 399 UC children with a mean age of 18 ± 3 years at colectomy, 121 (36%) had at least 1 episode of acute pouchitis, and 29 (9%) pouch failure [13]. In our study, pouchitis occurred in 44.7% of patients diagnosed with UC after an IPAA, of whom 15.8% developed chronic pouchitis. The low proportion of chronic pouchitis may have stemmed mainly from the relatively short follow-up period.

4.2. Predictive factors

Several variables may predict the risk of pouchitis. Clinical risk factors for pouchitis have been studied extensively in adults. Younger age at onset, younger age at colectomy, extensive colitis, backwash ileitis, extraintestinal manifestations, preoperative steroid use, smoking status, regular use of nonsteroidal anti-inflammatory drugs, preoperative perinuclear antineutrophil cytoplasmic antibody positivity, anti-CBir1 flagellin, and genetic factors (IL-1 receptor antagonist, NOD2/CARD15, and tumour necrosis factor genes) have been reported as independent risk factors for pouchitis [14–29]. Data on predictive factors for the development of pouchitis in children are scarce [4]. In our study, sex, colitis severity, extraintestinal manifestations, preoperative use of steroids, immunomodulators and biologics, were not related to the occurrence of pouchitis. The most striking feature of the present study was the significant association between younger age at colectomy, chronic active colitis as indication for surgery, and 3-stage IPAA, and the subsequent development of pouchitis. Our finding of an association between younger age at colectomy and increased risk for the subsequent development of pouchitis is in agreement with two previous adult studies [14,30], and with a pediatric one [31], which reported that patients who developed pouchitis were significantly younger at colectomy compared to patients who did not develop pouchitis. In the study by Ozdemir et al. [13], age at colectomy had no impact on whether patients developed pouchitis. In the present study, we identified chronic active colitis as indication for surgery to be significantly associated with the development of pouchitis. Previous reports found that more severe disease activity ($PUCAI \geq 65$) in the preoperative period poses an increased risk for the development of pouchitis both in adult [32] and pediatric patients [4]. On the contrary, other studies found no association between the severity of disease activity and an increased risk of subsequent pouchitis [21,33]. Notably, Achkar et al. [16] reported that fulminant colitis as indication for surgery had a protective effect against the development of chronic pouchitis in adults. Surgery for pediatric UC may require up to 3-staged procedures—first stage, subtotal colectomy with end-ileostomy; second stage, restorative procto-colectomy with ileal pouch-anal anastomosis or ileo-rectal anastomosis (with or without covering ileostomy); third stage, closure of the covering ileostomy [1]. Three-stage procedure is recommended for patients with acute severe colitis, or unclear diagnosis of IBD, or in high-risk patients with recent steroid therapy and/or poor nutritional status [1]. However, today among the majority of authors, there is no consensus with regard to choosing either 2- or 3-stage IPAA in UC patients [34,35], and

Table 2
Cox PH regression model estimates for the risk of developing pouchitis.

	HR	[95% CI]	p-Value
Surgery type (3-stage IPAA vs 2-stage IPAA)	2.86	[1.12, 7.32]	**0.028**
Indication to surgery (chronic active colitis vs acute severe colitis)	4.45	[2.00, 9.92]	**<0.001**
Age at surgery (1-year increment)	0.89	[0.82, 0.97]	**0.008**

CI = confidence intervals.
Bold p-values indicates statistical significance.

the final choice of the surgical approach should be individualized [1]. To our knowledge, this is the first time that 3-stage IPAA has been implicated in the development of pouchitis. No significant association between the number of surgical stages and the development of pouchitis had been found previously [13,31,35]. In the present study, the preoperative therapeutic regimens had no impact on whether patients developed pouchitis. Previously reports focused on the relationship between the occurrence of pouchitis and preoperative steroid use (either higher cumulative steroid dose before colectomy or a higher monthly steroid dose before colectomy) [23,17,36]. On the contrary, Dharmaraj et al. [4] did not observe any difference in the steroid dose in pediatric patients with pouchitis.

A few studies showed a difference between patients with left-sided colitis and those with pancolitis in terms of the frequency of pouchitis [25], but we could not ascertain it, because of the exiguity of the chronic pouchitis group. A significant association was found between disease extent at onset (proctitis, E1) and the need for biologics for pouchitis, but further studies are warranted to confirm it.

We are aware of some limitations. First, this present study is a retrospective study, so recruited cases and clinical management are the confounding variables. Second, some missing data are most likely to occur in this present study, and also confounders might affect difference of the factors. Third, it might be difficult to compare our results with previous reports that analyzed the predictive factors for pouchitis development after IPAA, since the present study included the perioperative and postoperative factors in the risk analysis of pouchitis, whereas most of the reported studies have not included these clinical factors. The strength of this present study is the largest sample size compared with previous studies on pediatric UC [4,31,26], (even if the number of patients is spanned over a duration of 7 years and comes from 8 centres), and the use of the validated PDAI score to diagnose pouchitis, to avoid any diagnostic bias [4].

In conclusion, younger age at colectomy, chronic active colitis as indication for surgery, and a 3-stage IPAA seem to be risk factors for pouchitis. Although the reasons explaining why the development of pouchitis was specifically related to these preoperative factors are not completely clear, further studies on these observations may provide valuable insights into the pathogenesis of pouchitis. Assessment of pouchitis risk at the time of surgery may enable clinicians to detect refractory conditions and optimize therapeutic regimens to alter the natural history of disease and prevent postsurgical complications.

Author contributions

All authors contributed equally to the realization of the study.

Conflict of interest statement

None declared.

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