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Outcomes following pouch formation in paediatric UC - experience does count: a study from the Paediatric IBD Porto group of ESPGHAN

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ABSTRACT

Objectives: Given sparse pediatric data, we aimed to assess outcomes and predictors in children with UC/IBD-unclassified who underwent colectomy and ileal-pouch-anal-anastomosis (IPAA) during childhood.

Methods: This was a multicenter retrospective cohort study from 17 pediatric IBD centers from the Pediatric IBD Porto group of ESPGHAN. An electronic REDcap system was used to collate explicit baseline characteristics, clinical, management and surgical data, including short and long-term outcomes.

Results: Of the 129 included children, 86 (67%) developed pouchitis during follow-up (median 40 months (IQR 26-72)), including 33 (26%) with chronic pouchitis. Patients operated on by surgeons performing <10 surgeries/year had a higher rate of chronic pouchitis (11/27 (41%) vs 8/54 (15%), p=0.013) on both univariate and multivariate analyses. Surgeon's experience was also associated with time to any pouchitis and chronic pouchitis. At last follow-up, overall pouch performance was rated good/excellent in 86 patients (74%). Time from colectomy to pouch formation was not associated with pouch outcomes. Children undergoing colectomy at <10 years of age had more surgical complications at 1-year post pouch formation (7/16 (44%) vs 10/92 (11%), p=0.003) but there was no difference in functional outcome of the pouch or pouchitis rate.

Conclusions: Pouchitis rate is high in children with UC/IBDU. Surgeon experience is a modifiable risk factor for pouch outcome. Our data do not preclude constructing pouches in young children, as despite higher rate of non-severe surgical complications, functional outcome did not differ with respect to age of pouch formation.

BACKGROUND

Pediatric-onset ulcerative colitis (UC) confers a higher risk for developing acute severe colitis, and subsequently colectomy, as compared with adult onset disease[1]. In real life cohorts, 15-25% of children with UC required colectomy within 6-7 years[1-4] and a meta-analysis of population-based studies showed a 10-year risk of 22%[5]. The most frequently employed surgical procedure in UC involves a restorative staged proctocolectomy with the formation of an ileal pouch anal anastomosis (IPAA), most commonly a J-pouch[6]. Although most patients report improved quality of life after surgery[7], many develop complications such as acute, recurrent or chronic pouchitis, cuffitis, irritable pouch syndrome, and Crohn's–like disease of the pouch[8].

Pouchitis is the most common complication following pouch surgery [9,10] but the reported pouchitis rate in children with IBD is very heterogeneous, ranging from 31 to 73% [11-14]. A systematic review found chronic pouchitis in 16-36% of children in two pediatric studies[15]. Only 3 studies to date explored predictors of pouchitis in children with IBD. The largest, published in 2003, included 151 children who underwent the now historic S and W pouches [16], and the other two were small cohorts from single centers [12,13]. More predictive data are available in adults and include disease extent, severity of inflammation, presence of upper gastrointestinal (UGI) involvement, extra-intestinal manifestations, and backwash ileitis[17-21]. As almost all of these variables are more common in pediatric-onset UC, we hypothesized that pouchitis would be very common in children, with unique predictive variables.

While colectomy is not a procedure that can be delayed in the face of refractory disease, the optimal timing, technique, and setting for performing IPAA can be adjusted based on appropriate predictive variables (e.g. age and interval from the colectomy, as well as surgical technique and experience of the surgeon). There are sparse data regarding outcome in younger children with some authors suggesting delaying IPAA until adolescence[22] due to concerns regarding functional outcome and complications.

We therefore aimed to describe outcomes of children undergoing IPAA on a sizable cohort of children, as well as the rate of complications. We also aimed to explore

predictors of such outcomes. Finally, we aimed to explore whether performing the pouch at an early age (<10 years) or in low volume centers was associated with less favorable functional, pouch-related, and surgical outcomes.

METHODS

This retrospective multi-center study included children under the age of 18 years with a diagnosis of UC or IBDU who underwent restorative proctocolectomy with IPAA during childhood from June 1994 to July 2016 at the sites of the authors, all affiliated with the Paediatric IBD Porto group of ESPGHAN. In all centers, ethical approval for this study was either obtained or waived.

Explicit data were recorded on standardized REDcap web-based case-report forms, managed by the data coordinating center (DCC) at Shaare Zedek Medical Center in Jerusalem. Recorded data included: baseline characteristics; indication for colectomy (refractory acute severe colitis (ASC), steroid dependency, acute surgical complications, dysplasia, or others); explicit medications throughout the follow-up period; whether the procedure was open or laparoscopic; whether performed by an adult or pediatric surgeon; the surgeon's experience; type of pouch formation; whether hand-sewn or stapled; and type of surgery. The latter was defined as 1 step when proctocolectomy and pouch were performed together without an ileostomy; 2a as in 1 step but with ileostomy; 2b when proctocolectomy and ileostomy performed first and subsequently pouch formation without an ileostomy; and 3 steps when proctocolectomy and ileostomy are performed first, followed by pouch formation and eventually ileostomy closure. Surgical complications were recorded 1 month and 1 year post colectomy and, separately, post pouch formation, including small bowel obstruction, wound infection, sepsis, pelvic/abdominal abscess, gastrointestinal bleeding, urinary tract infection, significant electrolyte disturbances, acute renal failure, cardiac and pulmonary complications, anastomotic leak and wound dehiscence.

The following pouch outcomes were recorded: pouchitis episodes, Crohn's like disease of the pouch, cuffitis, irritable pouch syndrome, pouch stricture, fistula, prolapse, dysplasia, cancer, and infections of the pouch (CMV or *Clostridium*

difficile). The treatment and outcome of each pouchitis episode (up to 5 episodes per child) were explicitly recorded.

Acute pouchitis was defined as at most 1 episode of pouchitis during 2-years, lasting <4 weeks; acute-recurrent pouchitis as 1-4 episodes per year, each lasting <4 weeks and chronic pouchitis as >4 episodes of pouchitis per year or at least one episode lasting >4 weeks or need for >4 weeks of medical treatment (antibiotics, steroids, biologics, 5ASA, or immunomodulators but excluding probiotics)[23]. Crohn's-like disease of the pouch was defined as fistulae or stenosis (occurring >1 year from surgery; otherwise considered as surgical complication) or a long segment of inflamed pre pouch small bowel. Cuffitis was defined as recurrence of inflammation at the level of residual rectal mucosa[24].
Data were collected regarding how pouchitis episodes were usually diagnosed as well as how they were diagnosed in each of the first five episodes, when available, (clinical symptoms only, clinical symptoms and blood/fecal markers, clinical symptoms and macroscopic appearance at pouchoscopy, and clinical symptoms and microscopic appearance at pouchoscopy).

Functional outcomes of the pouch were assessed at 1 month and 1 year post "ileal continuity" (defined herein as IPAA and ileostomy closure when performed), as well as at last follow-up using physician global assessment (PGA). In order to standardize the global assessment, general anchors for each category were provided as previously described (ranking based on the worst parameter) [25]: <u>excellent function:</u> no pouchitis, full control of sphincter, no nocturnal stooling, <7 stools/24 hours and without anti-diarrheal medications; <u>good function:</u> >=7 stools/24 hours but with full continence without anti-diarrheal medications, and at most one rapidly resolving pouchitis; <u>fair function</u>: occasional incontinence, use of anti-diarrheal medications, need to wear a pad at night, and recurrent pouchitis; <u>poor function:</u> frequent incontinence, social restrictions, and chronic pouchitis requiring immunosuppression; <u>very poor function:</u> pouch failure, the need of corrective surgery. Individual outcome parameters were also recorded at 1 month and 1 year post ileal continuity including stooling frequency, nocturnal stools, and need to wear a pad.

Statistical Analysis

Data are presented as mean ± standard deviation, or medians (interquartile range (IQR)), as appropriate. Fisher's exact test or chi-square test were used to compare categorical variables and Student *t* test or Wilcoxon rank sum test for continuous variables.

Outcomes were assessed for association with age <10 years at colectomy, age <10 years at pouch formation, interval <6 months to stoma closure, surgeon experience, adult/pediatric surgeon, and surgical technique (laparoscopic or open), as these were determined *a-priori* as modifiable factors. Time-to-all pouchitis and to chronic pouchitis were analyzed using Kaplan-Meier survival estimate; log rank test was used to compare possible predictors with clinical outcome. Cox proportional hazard models were constructed for both all and chronic pouchitis after verifying the proportionality assumption, to control for potential confounding variables. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY). A *P* value of <0.05 was used to indicate a statistically significant difference.

RESULTS

Records of 138 children from 17 centers were reviewed, 9 were excluded due to insufficient data and 129 were included (120 (93%) UC and 9 (7%) IBDU) (Table 1). The median post colectomy follow-up period was 40 months (IQR 27-74); 125 (97%) children had at least 6 months follow-up. The median post-IPAA follow-up period was 37 months (IQR 22-65). Eight children of the entire cohort (6%) underwent a 1-step procedure, 76/129 (59%) 2-step procedure (51/76 (67%) step 2a and 25/76 (33%) step 2b), and 45/129 (35%) a 3-step procedure (Table 1). Eight of the 57 children (14%) who underwent colectomy before 2010 had a laparoscopic procedure vs. 40/66 (75%) thereafter. Additionally, 4/53 (7%) underwent laparoscopic pouch formation before 2010, vs. 22/67 (33%) thereafter.

Pouchitis and other pouch outcomes

During the follow-up period, 86 children (67%) developed pouchitis: 25/129 (19%) acute, 28 (22%) recurrent, 23 (18%) chronic, and 10 (8%) Crohn's-like disease of the pouch. However, in a subgroup analysis of the 63/129 children with ≥36 months follow-up, as many as 54 (86%) had developed at least one pouchitis episode. Median time from ileostomy closure to first episode of pouchitis was 8.4 months (IQR 3.2-

21). Among the 70/86 children who developed pouchitis for whom time to pouchitis was available, 43% had the first pouchitis by 6 months, 60% by 1 year, 79% by 2 years and 90% by 4 years. Of the 78 children with pouchitis and available diagnostic data, 34 (44%) were diagnosed without pouchoscopy at the first episode.

Eight of 9 (89%) IBDU patients developed pouchitis as compared to 78/120 (65%) UC patients (p=0.27). Cuffitis was diagnosed in 16 children (12%), and irritable pouch syndrome in 3 (2.4%). There were no cases of cancer or infections, despite follow up of 544 person years. Cuffitis rate did not differ between stapled (13/101 (13%)) vs hand-sewn (3/19 (16%)) pouch (p=0.717).

Surgical-related pouch outcomes included pouch stricture in 14 (11%), pouch fistula in 12 (9%), prolapse in three (2.3%), pelvic floor dysfunction in one (0.8%) and anal sphincter dysfunction in one (0.8%). At 1 year, 1 patient (0.9%), and at last follow up, 5 patients (4.3%) developed pouch failure (4 due to chronic pouchitis and one internal fistula), three of whom required surgical revision. Of the entire cohort, 11 (8.6%) children had a change of diagnosis to Crohn's disease (CD); one had no pouchitis, 2 had acute pouchitis, and 8 had chronic pouchitis (7 of whom had Crohn's like disease of the pouch). Median time to change of diagnosis was 24 months (IQR 6-43; Range 4-103 months). Ultimately, 7/10 (70%) of patients with Crohn's like disease of the pouch had change of diagnosis to CD. There was no association between age <10 years at diagnosis and diagnosis of IBDU (median diagnosis age 12 years (IQR 8-14), nor was there an association between age at diagnosis and change of diagnosis to Crohn's disease after pouch formation. There was no association between baseline diagnosis (UC vs IBDU) and Crohn's like disease of the pouch (1/9 patients with IBDU had Crohn's like disease and 9/120 with UC), nor between baseline diagnosis and change of diagnosis to Crohn's disease (2/9 patients with IBDU had change of diagnosis vs 9/120 with UC).

Predictors of pouchitis

The occurrence of acute and chronic pouchitis were frequently seen in children operated on by surgeons with lower volume of pouch operations, but only the chronic pouchitis reached statistical difference (Figure 1). The best cutoff of number of annual pouch surgeries to balance sensitivity (69%) and specificity (68%) of developing

chronic pouchitis was ≥10 surgeries per year (Figure 2 and 3). Presence of backwash ileitis ever, was associated with time to any pouchitis (log rank test, p=0.013), though for chronic pouchitis only a numerical trend was found (p=0.088). Age at diagnosis (<10 years of age vs ≥10), disease extent, UGI involvement, extraintestinal manifestations, Jewish Ashkenazi ethnicity, pANCA positivity, Pediatric Ulcerative Colitis Activity Index (PUCAI) score at diagnosis and prior to colectomy, pediatric or adult surgeon, number of steps in IPAA, and time to stoma closure (<6 months vs longer) were not associated with time to any pouchitis or to chronic pouchitis (data not shown).

Surgeon experience (<10 surgeries per/year) remained highly associated with time to any pouchitis (HR=2.6, 95%CI 1.3-5.0) even when adjusting for potential confounders in a multivariable cox proportional hazard model (age at diagnosis (HR=1.1, 95%CI 0.98-1.2), disease duration (HR=1.0, 95%CI 0.9-1.0), male gender (HR=1.6, 95%CI 0.8-2.9), and presence of backwash ileitis (HR=1.6, 95%CI 0.8-3.3)). Similar results have been found in a model of time to chronic pouchitis (surgeons' experience <10 surgeries per year HR=3.6, 95%CI 1.3-10.2; age at diagnosis (HR=1.1, 95%CI 0.96-1.2), disease duration (HR=0.99, 95%CI 0.97-1.0), male gender (HR=3.2, 95%CI 1.1-9.4) and backwash ileitis (HR=2.0, 95%CI 0.71-5.4)).

Pouchitis in young children

Of the 125 children for whom dates were available, 19 (15%) underwent colectomy prior to 10 years of age, in whom 16 (13%) IPAA was also constructed prior to age 10. There was no association between age <10 years at IPAA vs older age and any pouchitis (11/16 (69%) vs 71/109 (65%), respectively; p=1.0) or chronic pouchitis (5/16 (31%) vs. 28/109 (26%); p=0.8). In the 19 children who underwent colectomy prior to 10 years of age, 10/15 (67%) whose stoma was closed <10 years of age had pouchitis vs 4/4 (100%) of those whose stoma was closed later, p=0.179.

Treatment of pouchitis

The first episode of pouchitis was treated mainly with antibiotics, 16/86 (19%) ciprofloxacin, 30/86 (35%) metronidazole, 21/86 (24%) ciprofloxacin and metronidazole, 1 (1.2%) azithromycin; 25/86 (29%) probiotics of different strains;

7/86 (8.1%) enemas; and 5/86 (5.8%) others (azathioprine, adalimumab, prednisone, and budesonide). Response to treatment was available for 125 episodes though the heterogeneous combinations of treatment preclude comprehensive comparison of efficacy (Table 2). Nonetheless, there was no impression that complete clinical response differed between ciprofloxacin (13/18 (72%)), metronidazole (19/23 (83%)), or a combination of both (19/25 (76%); p=0.72).

Functional outcome of the pouch

PGA of overall pouch performance was rated good or excellent in 71/108 (66%) patients at 1 month, 79/111 (71%) at 1 year post-IPAA, and 86/116 (74%) at last follow-up (Figure 4).

Median number of daily stools at 1 year post ileal continuity was 5 (IQR 4-6; range 2-12); 42/106 with sufficient data (40%) had nocturnal bowel movements, of whom 21/40 (53%) had >1 nocturnal bowel movement (Table 3). Of the 30/108 (28%) children who required a pad at night 1 month post stoma closure, 24/30 (80%) required the pad most nights, and of the 15/103 (15%) who required a pad at 1 year post stoma closure, 11/15 (73%) required the pad most nights (Table 3). Number of daily/nocturnal stool, as well as PGA at 1 month and 1 year post IPAA were not associated with surgical technique (laparoscopic or open), age at colectomy, age younger than 10 years at pouch formation, interval <6 months to stoma closure, and surgeon experience (data not shown).

Surgical complications in children younger than 10 years

Children who underwent colectomy before the age of 10 years experienced more complications than older children (at least one complication was seen in 8/18 (44%) vs 16/94 (17%), respectively, p=0.023), as did children who underwent IPAA before the age of 10 years (7/16 (44%) vs 10/92 (11%), p=0.003). Of the reported complications within 1 year of colectomy, bleeding was more common in the younger children (5/18 (28%) vs 4/92 (4.3%), p=0.006) with no differences in the occurrence of small bowel obstruction, wound dehiscence, sepsis, or others. One year post IPAA, small bowel obstruction, urinary tract infection, and significant electrolyte imbalances were more common in those undergoing the procedure younger than 10 years of age but with very low frequency (1/16 vs 0/92, p=0.016 for each of the above).

For the 19 children who underwent colectomy before age 10 years, there was no difference in surgical complications whether the pouch was constructed before or after age 10 years, but the sample size was too small to elucidate definite conclusions (data not shown).

DISCUSSION

In this cohort study from the Porto group of ESPGHAN, we characterized pouch outcomes in children and highlighted important predictors for pouchitis Pouchitis was the most common complication in this cohort, affecting 67% of patients. Although the majority of patients who developed pouchitis did so within the first year, as found in additional studies [19,26], many first episodes occurred after 2 and even 3 years post ileal continuity. Indeed, children with at least 3 years follow-up had a pouchitis rate as high as 86%, supporting our initial hypothesis that pouchitis is very common in pediatric onset UC. In comparison, pouchitis rate has been reported to be 23-46% in adult studies[23],though one adult study did report a pouchitis rate of 70%[27].

Our findings are in the higher range of previously reported pouchitis rates in children with IBD, 31-73% [11-13] depending on definition and time of follow-up. We also found that 71% of patients had good or excellent pouch function at 1 year with a median of 5 (IQR 4-6) bowel movements daily, consistent with existing pediatric data [11,14,28,29].

Chronic pouchitis, a particularly disabling complication, was found in 26% of patients in our cohort. This finding compares favorably with two recent pediatric studies[12,13], but is higher than another[16]. Adult studies described a similar chronic pouchitis rate[20,30,31,40] suggesting that while acute pouchitis appears to be more common overall in children, chronic pouchitis may be less age dependent, possibly relating to a different pathogenesis[23]. This is probably one of the factors why almost one third of our cohort were rated as having fair/poor pouch function or pouch failure. The high rate highlights the importance of exploring modifiable predictors for improving pouch outcome.

We found several predictors of pouch outcome including perhaps the most salient finding of this study, that the surgeon experience in IPAA surgeries, a modifiable predictor, was strongly associated with development of any pouchitis as well as

chronic pouchitis. Children operated on by surgeons who perform <10 annual pouches had 2.6 fold higher risk for all pouchitis and 3.6 fold risk for chronic pouchitis. It is possible that the surgeon experience served merely as a proxy for the overall competency of the entire medical center which may influence timing of medical care, nutritional status, pre and post-operative care, and other factors unrelated to the hands of the surgeon. Regardless of the reason, surgeon's experience seems a good overall predictor of pouch outcome. Lending credence to this finding, a study including 5771 primary elective pouch procedures in children and adults[32] found that pouch failure was higher among patients treated in low compared with highest volume centers (7.8%; $\leq$1 procedure per year vs 5.3%; $\geq$12 procedures per year; p=0.032 on univariate analysis and p=0.031 on multivariable analyses). The association between pouch failure and surgeon experience was not repeated in our study, perhaps due to the low rate of pouch failure (4.3%). Pouch failure has been described in 0-13%[11,16,33-35] of children, compared with 4-7% in adults[32,36-38]. A large cohort with greater than 10 years follow up, has shown similar pouch retention rates between children and adults[39] as did the study by Diederen et al[31].

Another significant predictor for chronic pouchitis in our cohort was male gender, consistent with a large adult study[40] though two recent pediatric studies[12,13] and one adult study[27] did not find such association. As previously found[19,38], backwash ileitis was associated with time to any pouchitis, with a trend to significance for chronic pouchitis, a finding which has strong biologic reasoning. On univariate analysis, Ashkenazi Jewish ethnicity was associated with chronic pouchitis, consistent with a study of 399 adults with UC[41], although no such association was found in two other pediatric[12] and adult[27] studies.

In this cohort, longer disease duration prior to colectomy was not significantly associated with all pouchitis. This is in agreement with a pediatric [12] as well as an older adult study[38] which did not find any association for either acute or chronic pouchitis. Other data are conflicting, with one pediatric study showing poorer outcome with longer duration prior to colectomy[16], and another adult study showing the opposite[27].

One small pediatric study[13] found an association between both acute and chronic pouchitis and PUCAI ≥65 at diagnosis, suggesting that initial disease activity, [13] or aggressive inflammatory phenotype of disease course until colectomy, [27] are associated with development of pouchitis. Our data as well as others[12] did not support this observation.

While some suggest delaying creation of pouch until adolescence[22], our cohort provides reassuring data that the overall risk of pouchitis and functional outcome are comparable between children younger than 10 years at IPAA formation and older ones. Although surgical complication rate within 1 year after colectomy and IPAA were higher in the younger age group, the low frequency of complications makes the clinical implication of this statistical association doubtful. Wu et al showed a nonsignificant trend to a higher rate of procedure-related complications in children after IPAA compared to adults (20% vs 13%, p=0.52), including pouch strictures; nonetheless, the overall pouch failure was similar between the groups[39]. Studies show that performing IPAA during childhood is associated with similar or lower bowel movement than adults[14,31,42] suggesting that adaptation of the pouch may be better in children further justifying performing IPAA in younger children when necessary.

Our conclusion that a pouch may also be constructed in younger children is supported by a case series of 13 children younger than 10 years[43]. Pouchitis rate was 75% and all families rated the outcome of the procedure as "excellent"[43]. Two pediatric cohorts, one including 65 patients (41 with UC)[44] and the other 64 UC patients[45] reported similar postoperative complications, pouchitis, and functional outcomes in both younger and older children. One of the reasons often quoted to support the delay of pouch formation is the higher risk of changing the diagnosis to Crohn's disease in younger patients [22,46]. In our cohort, however, we did not identify such an association, in line with another recent study [44].

This was a large multicenter cohort but it is not without limitations, mainly stemming from its retrospective design. Outcomes such as response to prophylactic probiotics and long term fertility, were not available or incomplete. Some of the reported variables, such as irritable pouch syndrome or cuffitis lacked uniformity in the diagnosis and relied on the physicians' discretion. Our finding that many pouchitis episodes are being diagnosed without endoscopic evaluation underscores the

importance of disseminating the new ESPGHAN/ECCO guidelines that recommends pouchoscopy at the first suspected episode of pouchitis[47].

This study has several clinically important observations. We highlighted several predictors of pouch outcome, with surgeon experience being of particular importance as it provides a modifiable variable to potentially improve outcomes. There was no apparent advantage whether the procedure was performed by an adult or pediatric surgeon and thus only the volume of at least 10 annual procedures should prevail. Nonetheless, it is reasonable to suggest that the youngest children should be operated in specialized centres with close collaboration between pediatric and adult surgeons. We did not find evidence to support delaying pouch surgery after the age of 10 years although families of younger should be advised of a potential for a minimal increase in surgical complications.We also did not find evidence to support delaying ileostomy closure after IPAA as time to closure was not associated with increased risk for pouchitis or functional outcome. These findings may help provide guidance in selecting the appropriate surgeon and timing for IPAA in children.

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LEGEND TO FIGURES

Figure 1. Surgeon's experience and risk for all pouchitis and chronic pouchitis

Figure 2. ROC curve for all pouchitis and chronic pouchitis stratified by surgeon's experience

Figure 3. Time to all pouchitis (3a) and to chronic pouchitis (3b) stratified by surgeon's experience

Figure 4. Physician global assessment of pouch function following IPAA

TABLES

Table 1. Baseline characteristics of children undergoing ileal pouch-anal anastomosis (n (%), median (IQR) or mean± SD are presented as appropriate); denominators apply for available data

	All patients (n=129)	**Chronic Pouchitis(-) (n=96)**	**Chronic Pouchitis(+) (n=33)**	**p-value**
Male	64 (50%)	45/96 (47%)	19/33 (58%)	0.32
Age at diagnosis, years	11 ± 4.2	11 ± 4.0	9.55 ± 4.5	0.13
Ashkenazi Jewish ethnicity	15/118 (13%)	8/15 (53%)	7/15 (47%)	**0.04**
Disease extent				
Left sided	7/123 (5.7%)	5/94 (5.0%)	2/29 (7%)	0.95
Extensive/Pancolitis	116/123 (94%)	89/94 (95%)	27/29 (93%)	
PUCAI at diagnosis	56 ± 20	57 ± 15	56 ± 21	0.66
PUCAI pre-surgery	58 ± 23	57 ± 23	60 ± 19	0.74
Backwash ileitis	16/110 (15%)	10/86 (12%)	6/24 (25%)	0.11
UGI involvement	29/92 (32%)	21/71 (30%)	8/21 (38%)	0.59
Extraintestinal manifestations	24/128 (19%)	19/96 (20%)	5/32 (16%)	0.80
Indication for surgery				
Steroid dependency	69/121 (57%)	50/93 (54%)	19/28 (68%)	0.42
Acute severe colitis	46/121 (38%)	38/93 (41%)	8/28 (29%)	
Other[a]	6/121 (5.0%)	5/93 (5.4%)	1/28 (3.6%)	
Age at colectomy, years	13.4 ± 4.0	13.6 ± 3.9	13.0 ± 4.2	0.41
Age colectomy < 10 years	19/126 (15%)	12/81 (15%)	7/33 (21%)	0.27
Disease duration to colectomy (months),	17 (8-35)	16 (8-35)	22 (11-38)	0.28
Medications prior to colectomy				
Steroids		68/88 (77%)	22/24 (92%)	0.15
Oral 5-ASA		42/85 (49 %)	16/24 (67%)	0.17
Immunomodulators		50/84 (60%)	9/24 (38%)	0.07
Anti TNF		40/84 (48%)	9/23 (39%)	0.49
Cyclosporine/tacrolimus		5/85 (5.9%)	5/24 (21%)	**0.04**
IPAA stages				
1 stage	8 (6.2%)	7/96 (7.3 %)	1/33 (3.0%)	0.49
2 stage	2a: 51 (40%) 2b: 25 (19%)	54/96 (56%)	22/33 (67%)	
3 stage	45 (35%)	35/96 (37%)	10/33 (30%)	
Laparoscopic pouch formation	26/127 (21%)	21/94 (22%)	5/33 (15%)	0.46
Months from colectomy to ileal continuity	6.0 (3.0-12.0)	6.0 (3-12.3)	4.0 (2.7-12)	0.24
Surgeon experience ≥10 surgeries/year	54/81 (67%)	46/62 (74%)	8/19 (42%)	**0.01**

a Dysplasia or acute complications

PUCAI, Pediatric Ulcerative Colitis Activity Index; UGI, upper gastrointestinal; IPAA, Ileal pouch anal anastomosis

Table 2. Management of all pouchitis and treatment response

Treatment	Episodes treated (n)	Treatment Response		
		Responder	**Partial Responder**	**Non-responder**
Ciprofloxacin	18/125	13/18 (72%)	4/18 (22%)	1/18 (6%)
Ciprofloxacin + Other[a]	19/125	7/19 (37%)	12/19 (63%)	0
Metronidazole	23/125	19/23 (83%)	4/23 (17%)	0
Metronidazole + Other[b]	8/125	3/8 (37.5%)	3/8 (37.5%)	2/8 (25%)
Ciprofloxacin + Metronidazole	25/125	19/25 (76%)	5/25 (20%)	1/25 (4%)
Ciprofloxacin + Metronidazole +Other[c]	14/125	7/14 (50%)	4/14 (29%)	3/14 (21%)
Probiotics	5/125	2/5 (40%)	2/5 (40%)	1/5 (20%)
Other[d]	13/125	8/13 (61%)	4/13 (31%)	1/13 (8%)

a Probiotics, enema, oral 5ASA, prednisone, not specified
b Probiotics, enema, 5ASA, other antibiotic
c Probiotics, enema, Oral 5ASA
d Probiotic+5ASA, steroids, 5ASA, other antibiotic, antibiotic+steroid, enema

Table 3. Functional Outcomes 1 month and 1 year post IPAA
(n (%) or medians (IQR) are presented as appropriate)

	1 month post IPAA	**1 year post IPAA**
Median number of daily stools (n=105)	6 (4-8) range 1-20	5 (4-6) range 2-12
Nocturnal stools	65/108 (60%)	42/106 (40%)
Need for wearing pad at night	30/108 (28%)	15/103 (15%)
Use of antidiarrheal medication	31/111 (30%)	31/109 (28%)

All outcomes relate to pouchitis-free periods.

Figure 1

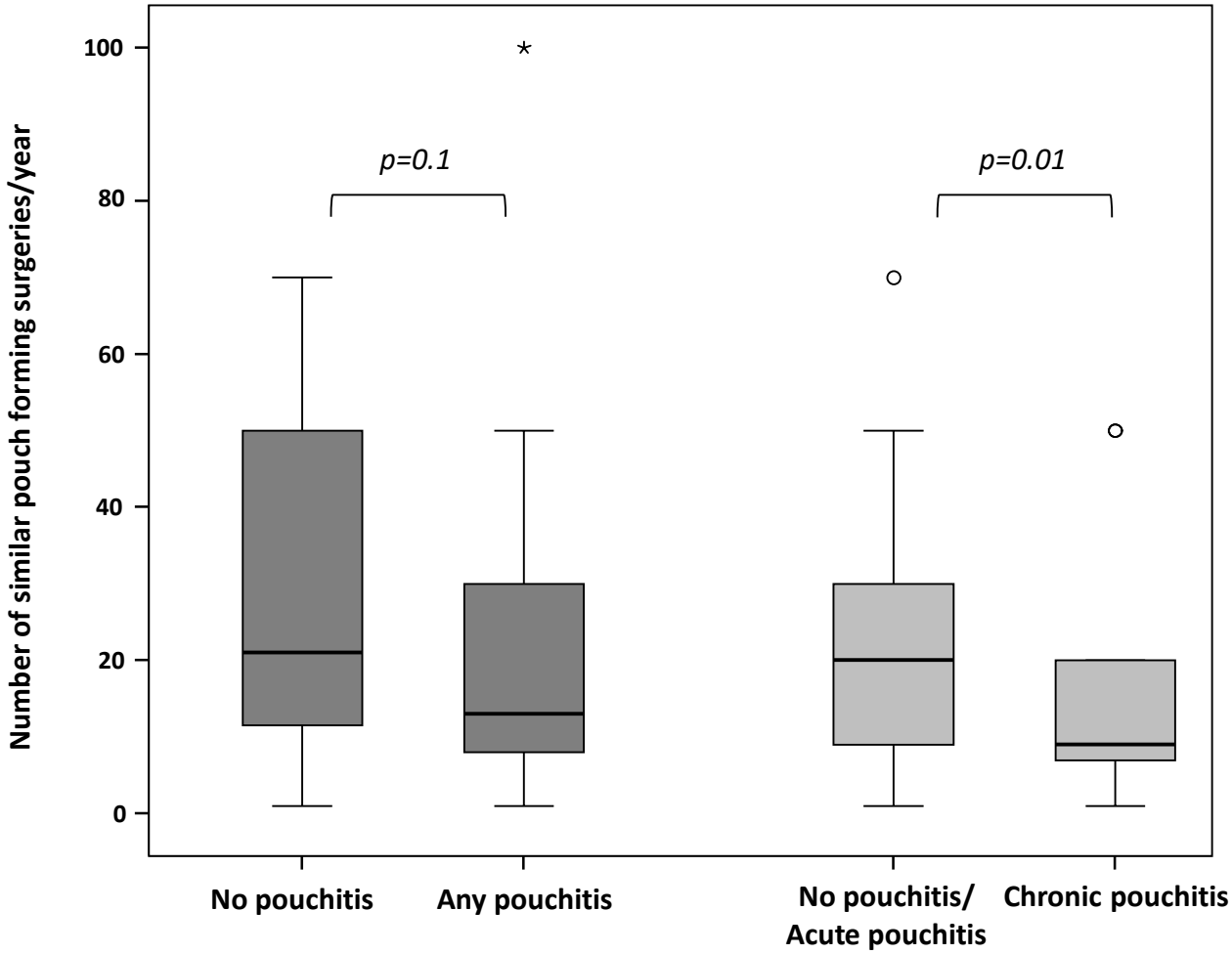

Number of similar pouch forming surgeries/year
100
80
60
40
20
0
p=0.1
p=0.01
No pouchitis
Any pouchitis
No pouchitis/
Acute pouchitis
Chronic pouchitis

Figure 2

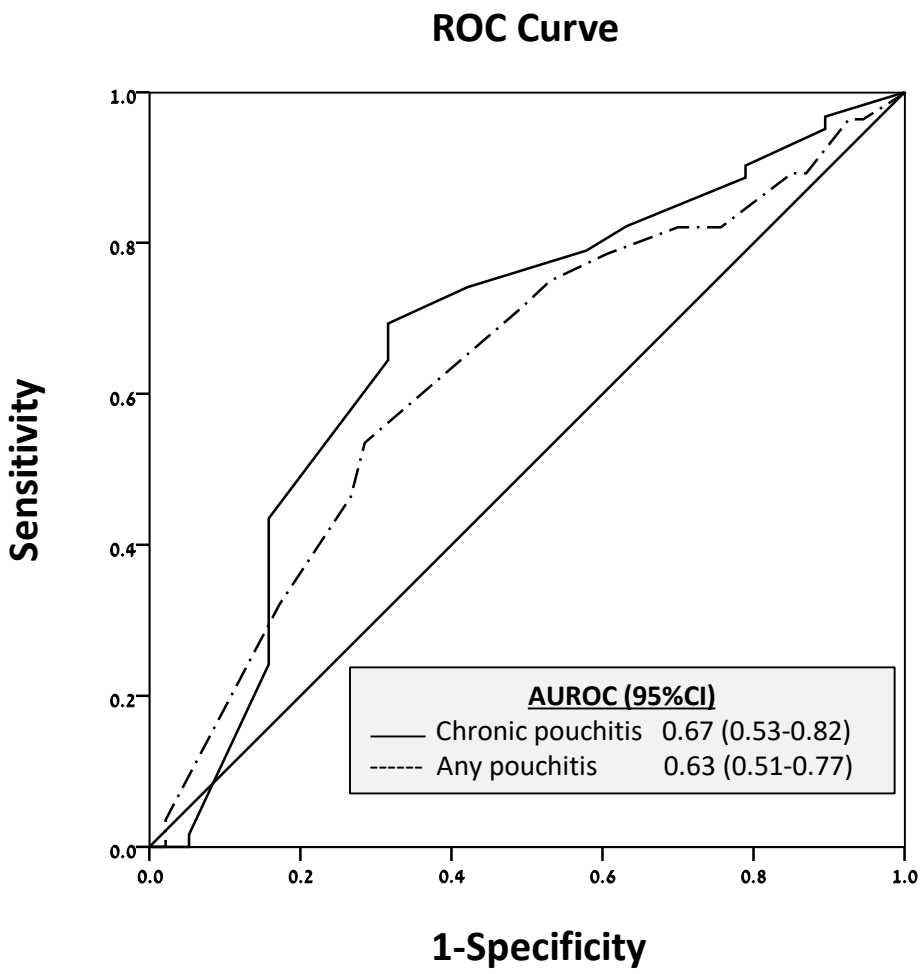

ROC Curve
Sensitivity
1-Specificity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
AUROC (95%CI)
Chronic pouchitis 0.67 (0.53-0.82)
Any pouchitis 0.63 (0.51-0.77)

Figure 3a.

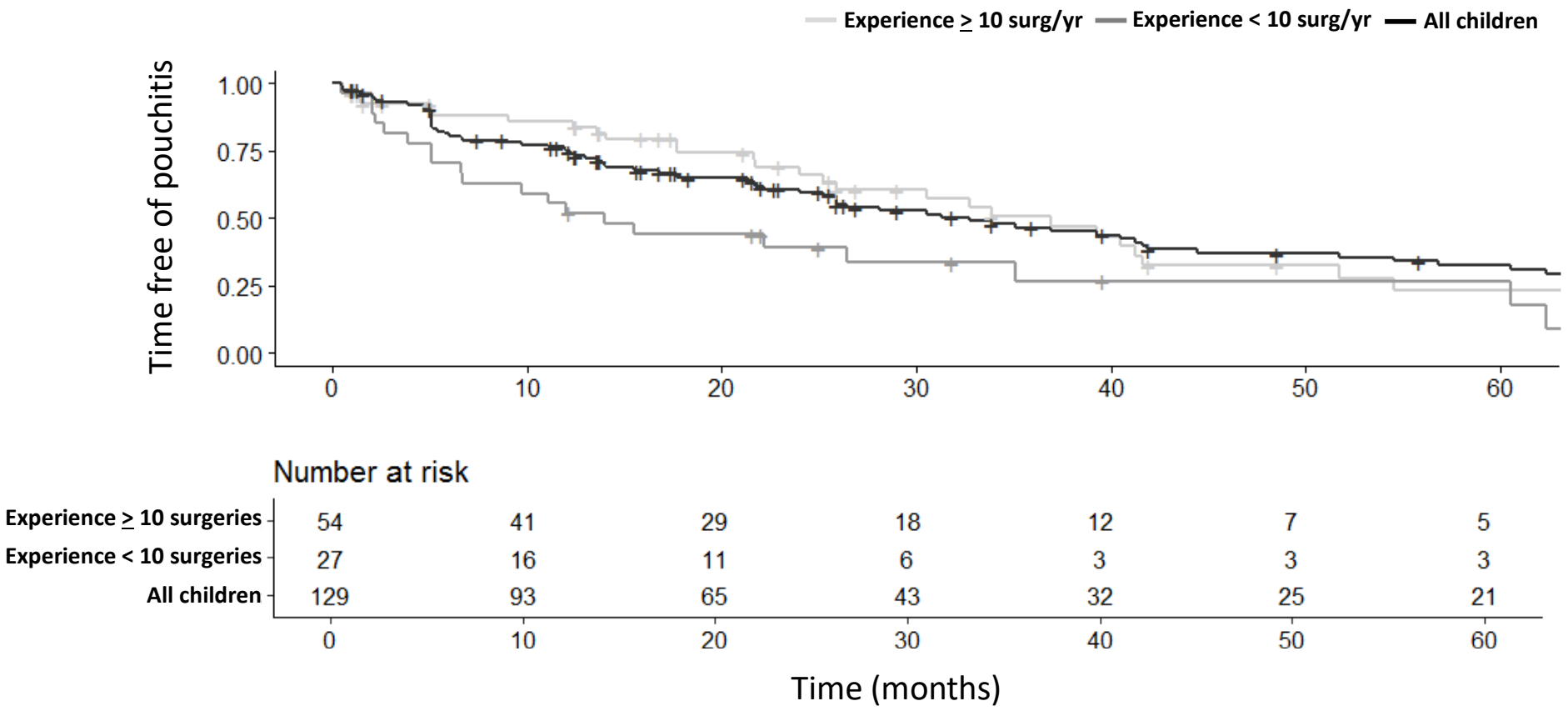

Experience ≥ 10 surg/yr
Experience < 10 surg/yr
All children
Time free of pouchitis
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
Number at risk
Experience ≥ 10 surgeries
54
41
29
18
12
7
5
Experience < 10 surgeries
27
16
11
6
3
3
3
All children
129
93
65
43
32
25
21
0
10
20
30
40
50
60
Time (months)

Figure 3b.

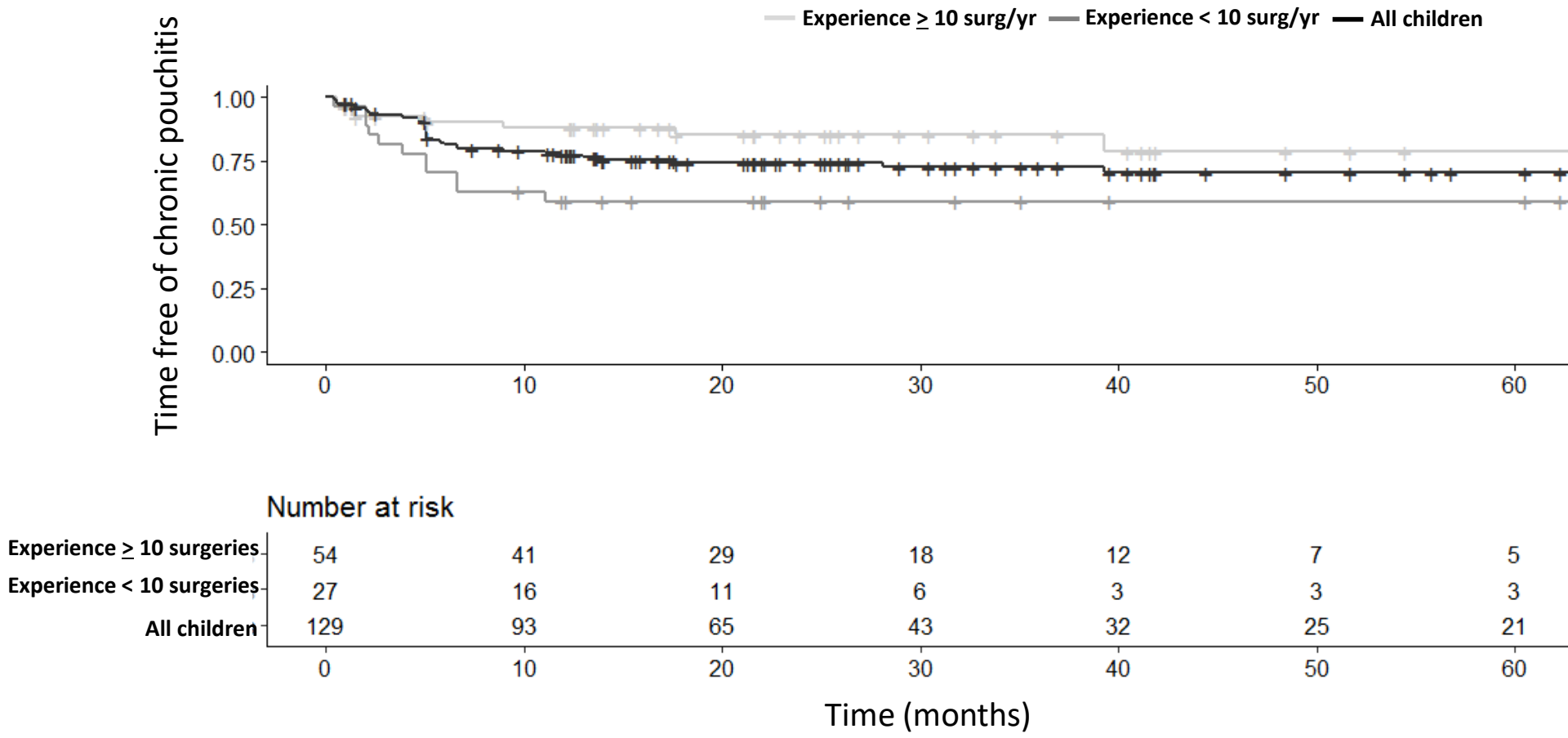
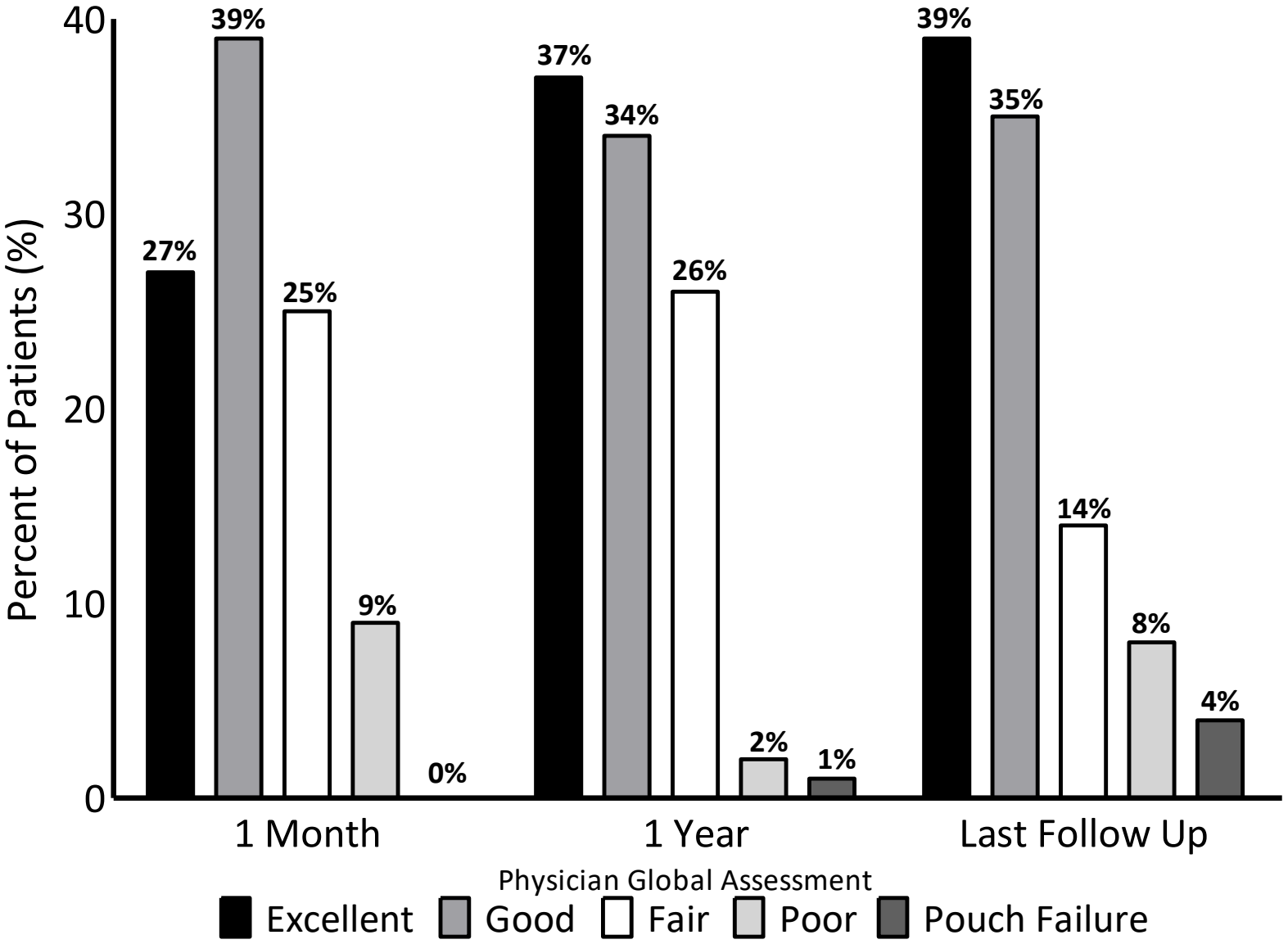

Experience ≥ 10 surg/yr
Experience < 10 surg/yr
All children
Time free of chronic pouchitis
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
Number at risk
Experience ≥ 10 surgeries
54
41
29
18
12
7
5
Experience < 10 surgeries
27
16
11
6
3
3
3
All children
129
93
65
43
32
25
21
0
10
20
30
40
50
60
Time (months)

Figure 4.


40
30
20
10
0
Percent of Patients (%)
27%
39%
25%
9%
0%
37%
34%
26%
2%
1%
39%
35%
14%
8%
4%
1 Month
1 Year
Last Follow Up
Physician Global Assessment
Excellent
Good
Fair
Poor
Pouch Failure