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Histology at diagnostic gastroscopy predicts outcome after intestinal resection in pediatric Crohn's disease

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Abstract

Background and Aim: Pediatric Crohn's disease (CD) has been shown to have a high recurrence rate following surgical resection. Risk factors for postoperative CD recurrence in children are not well known. The aim of this study was to identify factors influencing postoperative recurrence in pediatric CD.

Methods: Pediatric CD patients who underwent surgical resection with primary anastomosis with a minimum follow up of 2 years were identified from databases at the Royal London Hospital and Massachusetts General Hospital. Patients were subdivided into a recurrence group defined by clinical, endoscopic, histological, radiological and/or surgical outcomes, and a nonrecurrence group. Patient demographics, initial gastroscopy and colonoscopy findings, Paris classification, and preoperative and postoperative pharmacotherapy were analyzed.

Results: Ninety-six children who underwent an ileal or ileocolonic resection with primary anastomosis were identified. Fifty-seven children had postoperative recurrence. Recurrence was associated with abnormal initial gastroscopy findings ($P = 0.0077$), ileocolonic disease location ($P = 0.03$), and perianal disease involvement ($P = 0.04$).

Patients with abnormal initial gastroscopy had higher rates of relapse (hazard ratio 3.42, 95% confidence interval [CI] [1.86–6.30], $P = 0.001$). Multivariate analysis demonstrated that abnormal diagnostic gastroscopy histology was a significant independent predictor of postoperative recurrence in this cohort (odds ratio 1.33, 95% CI [1.04–1.70], $P = 0.024$). The most common histological abnormality was non-*Helicobacter* gastritis, found in 29/46 (63%).

Conclusion: This dual-center study has shown that the presence of upper gastrointestinal tract inflammation, especially non-*Helicobacter* gastritis, at the time of diagnosis, is associated with an increased risk of postoperative recurrence in pediatric CD.

Introduction

Up to 65% of Crohn's disease (CD) patients require intestinal resection within 10 years of diagnosis.[1,2] Childhood-onset CD is often more aggressive, and children with CD are at higher risk for extensive intestinal resection compared with those with adult-onset CD.[3–5] Despite several large studies, including randomized trials in adults, optimal medical therapy after intestinal resection to prevent recurrence remains unclear.

In adults with CD, upper gastrointestinal (GI) involvement, younger age at diagnosis, penetrating disease, smoking, and previous resections have been shown to increase risk for early postoperative recurrence (POR).[6] Gender may also predict CD recurrence in adults.[2,7–9] In pediatric CD, there are no unequivocal predictors of POR in the current literature.[10]

Up to 71% of pediatric CD patients have upper GI involvement,[11–15] This is significantly more common in childhood-onset CD than in adult-onset CD.[13] Upper GI location at diagnosis may increase risk for POR as it indicates disease extension and has been associated with poorer outcomes.[16] Routine gastroscopy is recommended in the diagnostic work-up of pediatric patients with new onset inflammatory bowel disease (IBD), but not in adults.[14,17] However, a recent study in newly diagnosed adults with IBD who all underwent gastroscopy showed that 54% of Crohn's patients had gastritis and the majority had no upper GI symptoms.[18] The significance of these findings, both clinically and in pathogenesis, is unknown.

The role of postoperative medical prophylaxis in preventing POR in CD has been investigated in adults, but there is limited data in the pediatric population.[2,19–21] Postoperative medical prophylaxis guided by recurrence risk, together with ileocolonoscopy 6 months after resection and step-up treatment for POR, may have a role in the prevention of POR in adults.[6,19] Studies have suggested that anti-tumor necrosis factor-α therapy may be effective

in preventing and treating POR.[6,10,22] However, optimal postoperative treatment remains unknown in both adults and children and requires further investigation.[23,24] Importantly, identification of risk factors for early POR in children with CD may help better guide postoperative evaluation and therapy on a more individualized basis.

Aim

The aim of this study was to investigate the factors that may predict POR after intestinal resection in pediatric CD.

Methods

Study design. This was a dual-center retrospective cohort study. Patients were identified at two tertiary pediatric IBD centers: one in East London, UK, and one in Boston, USA. Consecutive patients diagnosed with CD before 18 years of age who underwent ileal or ileocolonic resection with primary anastomosis from 2000–2013 at Royal London Hospital (54 patients) and 2000–2014 at Massachusetts General Hospital (42 patients) were included.

All patients were diagnosed with CD before age 18 by their treating physicians using a combination of clinical, laboratory, radiological, endoscopic, and histological features. The patients in this study were divided into two groups: a recurrence group defined by clinical, endoscopic, surgical, and radiological and/or histological recurrence and a nonrecurrence group of patients without CD recurrence during the follow-up period.

Clinical recurrence was defined as the requirement for treatment escalation of active CD. Endoscopic recurrence was defined as evidence of macroscopic lesions and/or inflammation at repeat endoscopy at the anastomosis and/or colon. Histological recurrence was defined as evidence of active inflammation in mucosal biopsy specimens obtained during repeat endoscopy. Radiological recurrence was defined as evidence of active CD including inflammation, abscesses, and strictures on magnetic resonance imaging, computed tomography, and barium studies. Surgical recurrence was defined as a repeat intestinal resection for recurrent CD.

Demographics of the study population were recorded, including age at diagnosis, sex, date of birth, weight at diagnosis, and age at the time of surgery. Preoperative data included endoscopic and histologic findings (gastroscopy and colonoscopy), disease phenotype and location based on the Paris classification,[25] and preoperative medication regimens.

Abnormal gastroscopy histology findings were defined as any evidence of esophagitis, gastritis, and/or duodenitis diagnosed by GI histopathologists after the exclusion of well-defined conditions such as *Helicobacter pylori*-associated gastritis or duodenitis and/or eosinophilic esophagitis that are not related to CD. Postoperative data included postoperative medication regimens and changes in medications after surgery. Time to POR was analyzed in the relapse group.

Statistical analysis was performed using the following techniques. Univariate analyses between patient groups were calculated with *t*-tests (Microsoft Office Excel) and relative risk analysis (MedCalc Version 19.1.3). A Kaplan–Meier survival analysis (Graphpad Prism version 7.00) was used to compare the rate of recurrence between patients with abnormal histology and patients with normal histology on gastroscopy. A multivariate analysis of variance was performed with Statplus:mac version 6.2.0.1, AnalystSoft inc, to analyze the significance of the factors investigated in this study in relation to postoperative CD recurrence.

The study was approved by the Partners Healthcare Institutional Review Board (2016P002504). According to the UK Health Research Authority Decision Tool,[26] the evaluation of outcomes from routine care identified from the Barts Health database did not require formal ethical approval. There are no financial conflicts of interests to disclose.

Results

Ninety-six patients diagnosed with CD before age 18 who had undergone a CD-related ileal or ileocolonic resection with primary anastomosis were identified between the two centers. Three patients had ileal resections and 93 patients had ileocolonic resections. Indications for surgery included small bowel obstruction, strictures, severe ileitis, and intra-abdominal abscesses. None of the 96 patients were excluded from the analysis.

Table 1 illustrates the baseline demographics of the study population including the Paris classification of the patients. In this study, growth data were not uniformly available and were not included in the analyses. The mean age at CD diagnosis was 13.2 years, and the mean age at surgery was 16.5 years. The median disease duration prior to resection was 2.56 years. The majority of patients (80%) were aged 10 to < 17 at diagnosis (A1b Paris classification).

Fifty-seven patients (59%) had POR at the time of last follow up (median follow up, 7 years). Among the recurrence patients, the

Table 1 Baseline demographics of the study population

Characteristic	Variable	Study population $N = 96$
Age at diagnosis—years (± SD)		
	Mean	13.2 (± 2.68)
Sex—no. (%)		
	Female	42 (44)
	Male	54 (56)
Age at surgery—years (± SD)		
	Mean	16.5 (± 3.29)
Disease duration prior to resection—years (IQR)		
	Median	2.56 (1–4.94)
Paris classification—no. (%)		
Age	A1a	11 (11)
	A1b	77 (80)
	A2	8 (8.3)
Location	L1	49 (51)
	L2	0 (0)
	L3	44 (46)
	L4	3 (3.1)
Disease behavior	B1	33 (34)
	B2	42 (44)
	B2B3	14 (15)
	B3	7 (7.3)
Perianal disease	p	18 (19)

IQR, interquartile range.

median time to recurrence was 1.88 (interquartile range 0.8–4) years. As shown in Figure 1 (and Table S1), the majority of the patients (36 of 57 patients) had evidence of endoscopic recurrence, followed in frequency by histologic, clinical, radiographic, and surgical recurrence. Many patients met more than one criterion for POR (Fig. 1). For example, 24 patients had both histologic and endoscopic recurrence; one patient had endoscopic, histological, and radiological recurrence. Four patients had surgical recurrence requiring further intestinal resection after evidence of endoscopic, histological, and/or radiographic recurrence. Three patients had evidence of clinical recurrence only and were not reassessed by endoscopy, histology, and/or radiography within the follow-up time period.

Among the recurrence patients, 65% (37/57) of patients underwent postoperative endoscopy in the follow-up period. Thirty-six of 37 patients had evidence of endoscopic recurrence. Seventy percent of these patients had focal inflammation on endoscopy, and 11% had aphthous lesions as shown in Table 2.

There was no significant difference in gender ($P = 0.11$) or age at diagnosis ($P = 0.065$) between recurrence and nonrecurrence patients (Table 3). CD location and severity at diagnosis were classified according to the Paris classification. Patients with ileocolonic disease location ($P = 0.03$) and perianal disease ($P = 0.04$) were significantly more likely to have POR. Penetrating and/or stricturing behavior in CD was not associated with POR ($P = 0.49$).

In this study population, 46 of 57 recurrence patients and 27 of 39 nonrecurrence patients had a diagnostic gastroscopy prior to intestinal resection. Among those that did have a gastroscopy, patients with abnormal histology from gastroscopy were more likely to have recurrence than patients with normal histology ($P = 0.0077$). Eighty-seven percent of recurrence patients had abnormal diagnostic gastroscopy findings while 52% of nonrecurrence patients had abnormal gastroscopy findings (Table 3). Abnormal gastroscopy histology included esophagitis, duodenitis, and/or gastritis and the presence of granulomas, erosions, and ulcerations as shown in Table 4. The most common abnormal gastroscopy finding was chronic gastritis (63%) after the exclusion of *H. pylori,* eosinophilic esophagitis, and coeliac disease. Nine patients (23%) had focally enhanced gastritis, and six patients (13%) had mucosal granulomas present in their upper GI tract. Overall, 43 of the patients with abnormal histology (93%) had some form of gastritis either in isolation or in combination with other inflamed sites.

Table 2 Classification of endoscopic postoperative recurrence of Crohn's disease among recurrence patients who had repeat endoscopy

Classification of endoscopic recurrence	Number of patients (%), $N = 37$
Normal endoscopy	1 (3)
Presence of apthous lesions	11 (30)
Focal inflammation	26 (70)
Diffuse inflammation	6 (16)

As shown in Figure 2, the cumulative incidence of POR was significantly higher at 5 (77.1% *vs* 28.3%, $P = 0.024$) and 10 years (82.2% *vs* 42.7%, $P = 0.0019$) for children with abnormal histology at diagnostic gastroscopy compared with those with normal histology. There was a significant increase in the rate of recurrence in patients with abnormal histology compared with those with normal findings (hazard ratio 3.42, 95% confidence interval [1.86–6.30], $P = 0.001$) (Fig. 2).

At the time of resection, 86 of 96 patients (90%) were on immunomodulatory therapy and/or biological therapy, seven patients were not on any medications, two patients were on corticosteroids only, and one patient was on metronidazole only. Seventy-seven percent of recurrence patients and 64% of nonrecurrence patients were on systemic corticosteroids preoperatively (Table S2). There was no significant difference in changes in postoperative pharmacotherapy between the recurrence and the nonrecurrence groups ($P = 0.73$).

Multivariate analysis of variance of the factors investigated in this study showed that abnormal diagnostic gastroscopy was a

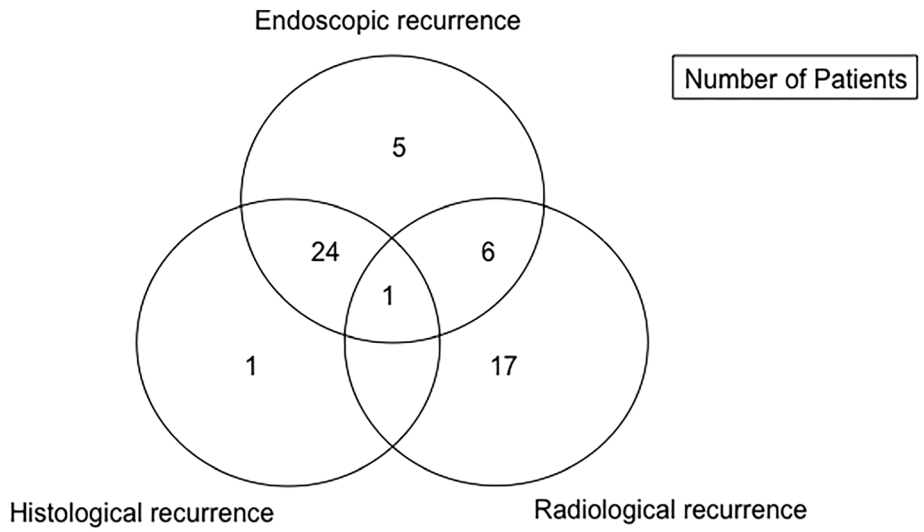

Figure 1 Venn diagram of the classification of postoperative recurrence.

Table 3 Analysis of factors comparing recurrence and nonrecurrence patients

Features	Variable	Recurrence patients, $N = 57$	Nonrecurrence patients, $N = 39$	Univariate P value	Relative risk (95% CI)
Gender—no. (%)					
Female		29 (51)	13 (33)	0.11	1.53 (0.91–2.55)
Male		28 (49)	26 (67)	0.08	0.74 (0.52–1.04)
Mean age at diagnosis—years (± SD)					*Mean difference*
		12.89 (± 3.0)	13.70 (± 2.0)	0.065	1.03 (−0.63–2.13)
Paris classification					
Age at diagnosis in years—*no. (%)*					
0 to < 10	A1a	8 (14)	3 (7.7)	0.35	1.82 (0.51–6.5)
10 to < 17	A1b	43 (75)	34 (87)	0.14	0.87 (0.72–1.05)
17 to 40	A2	6 (11)	2 (5.1)	0.36	2.05 (0.44–9.65)
Location—*no. (%)*					
Ileocolonic	L3	31 (54)	12 (31)	0.03	1.77 (1.04–3.00)
Not ileocolonic	L1, L2, L4a, L4b	26 (46)	27 (69)	0.02	0.66 (0.46–0.94)
Behavior—*no. (%)*					
Stricturing and/or penetrating	B2, B3	39 (68)	24 (62)	0.49	1.11 (0.82–1.50)
Nonstricturing nonpenetrating	B1	18 [32]	15 (38)	0.48	0.82 (0.47–1.42)
Perianal disease	p	15 (26)	3 (7.7)	0.04	3.42 (1.06–11.03)
Diagnostic gastroscopy histology findings—no. (%)					
		Recurrence patients, $N = 46$	Nonrecurrence patients, $N = 27$	Univariate P value	Relative risk (95 %CI)
Abnormal histology		40 (87)	14 (52)	0.0077	1.67 (1.15–2.45)
Normal histology		6 (13)	13 (48)	0.0024	0.27 (0.12–0.63)
Postoperative pharmacotherapy—no. (%)					
Change in medications		51 (89)	34 (87)	0.74	1.02 (0.88–1.19)
No change in medications		6 (10)	5 (13)	0.35	0.82 (0.27–2.50)

CI, confidence interval.

significant predictor for postoperative CD recurrence (odds ratio 1.33, 95%confidence interval [1.04–1.70], $P = 0.024$) (Table 5).

Discussion

This large, dual-center cohort was used to analyze factors predicting recurrence after surgical resection in pediatric CD. We have demonstrated that an abnormal histology at diagnostic gastroscopy (presence of upper GI tract CD involvement) is associated with postoperative CD recurrence in children. This was the only examined factor found to be predictive of POR in our multivariate analysis.

It is known that patients with more extensive disease have a worse prognosis in CD, including postoperative outcomes.[5] Indeed, it has previously been shown that children with colonic involvement (Paris L3 classification) fare more poorly after small bowel resection.[27] Thus, it is plausible that patients with upper GI tract involvement might have higher recurrence rates because the presence of inflammation in these locations may be a marker of more severe disease.

Table 4 Classification of abnormal initial gastroscopy findings among recurrence patients

Classification of gastroscopy findings	Number of patients (%), $N = 46$
Chronic gastritis (excluding *Helicobacter pylori*)	29 (63)
Focally enhanced gastritis	9 (23)
Duodenitis	13 (33)
Esophagitis	10 (25)
Eesophagitis, duodenitis, and gastritis	5 (13)
Presence of granulomas	6 (13)
Presence of lymphoid aggregates	5 (11)
Presence of ulcerations	2 (4)
Presence of erosions	1 (2)

In our study, gender was not associated with POR risk, similar to studies in adults with CD.[2,14–16] There was a trend towards women having a higher recurrence rate, consistent with previous studies in pediatric CD.[28,29] We found that there was no significant difference in mean age of diagnosis between the recurrence and nonrecurrence CD patients. Studies in adults have shown that young age is a predictive factor for POR,[9] although our cohort includes only pediatric patients up to 18 years old.

This study demonstrated a significant difference in CD location between recurrence and nonrecurrence patients, with more ileocolonic and perianal involvement among relapse patients. Perianal involvement has been associated with poor outcomes after resection in adults.[30] Studies in adults have also identified penetrating disease phenotype as a risk factor for POR.[31,32] In contrast, we did not find that penetrating behavior or stricturing behavior influenced POR, although the number of these patients was limited in our study.

In our population, the median time to POR was 1.88 years in the recurrence patients, similar to prior studies where the median time to POR has been shown to be 1 year.[33] The slightly longer duration in our study may be due to improved postoperative management including the increased use of immunomodulators and/or biologic agents during the period of our study compared with older studies, although direct comparisons were not possible.

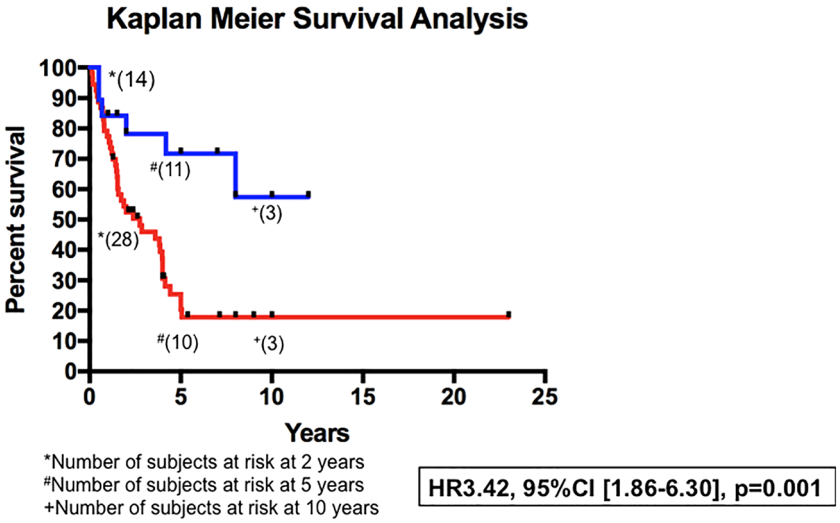

Figure 2 Comparison of the rate of recurrence between patients with normal histology at diagnostic gastroscopy and patients with abnormal histology. CI, confidence interval; HR, hazard ratio. , Normal histology (19 patients); , Abnormal histology (54 patients). [Color figure can be viewed at wileyonlinelibrary.com]

This study has its limitations as a retrospective mixed cohort study. Not all patients underwent gastroscopy at diagnosis as this was not routinely performed before 2012. In addition, the variation in reporting of macroscopic findings from gastroscopies made it impossible to include this as a variable, despite other research finding important macroscopic and histological correlates in Crohn's patients.[34] Despite the exclusion of other known causes of pathology, we cannot prove or disprove whether the histological pathologies found on initial gastroscopy are directly or otherwise linked to the patient's CD. There are also variations in timing and methods of postoperative evaluation across the cohort.

Unfortunately, not all potential risk factors could be assessed and unknown potential confounders could still exist. Specifically, growth failure, smoking status, and the role of postoperative antibiotics were not considered in this study as these data were not available. In addition, clinical scores such as the Rutgeerts score and Pediatric Crohns Disease Activity Index were not used in defining endoscopic and clinical recurrence as they were not routinely used in both centers during the study period. Indeed, three patients were categorized in the recurrence group solely on the basis of clinical findings. We cannot exclude that these patients simply had functional symptoms, but their exclusion would not change the major findings in this work. Finally, we were unable to assess the histological margins of resection specimens, although this has not been shown to predict recurrence.[35]

In adults, and even more so in children, the management of CD patients after intestinal resection remains controversial. Our findings suggest that gastroscopy findings may help risk stratify patients, although it remains unclear what the optimum preventive treatment strategy would be. Whether this finding would be similar in adults, who do not routinely undergo gastroscopy at the time of CD diagnosis, is unclear. It must also be noted that the gastroscopies were performed at diagnosis. It is unclear if a perioperative gastroscopy would yield similar findings. Therefore, we are unable to recommend routine preoperative gastroscopies for all patients undergoing intestinal resection for risk stratification on the basis of the findings in this study.

While adults do not routinely undergo diagnostic gastroscopy, it has been shown that a majority of adults with CD have histological gastritis at diagnosis.[18] No data exist on the prognostic value of these data in adults, but the high proportion of non-*Helicobacter* upper GI abnormalities in adults and children with CD may suggest a line of investigation for studying the gastric microbiome and host response in the pathogenesis of IBD.

This large dual-center cohort has examined a large number of factors in the outcomes after intestinal resection in pediatric CD. For the first time, we have shown that the presence of upper GI tract inflammation, largely gastritis, at the time of diagnosis is independently associated with POR in pediatric CD. This may have implications for characterization, risk stratification, and even the pathogenesis of children and potentially adults with CD considering surgical resection.

Table 5 Multivariate analysis of the factors influencing postoperative CD recurrence

Factors influencing postoperative CD recurrence	Odds ratio (95% confidence Interval)	Multivariate *P* value
Female gender	1.18 (0.95–1.47)	0.135
Age at CD Diagnosis	0.99 (0.95–1.03)	0.677
Ileocolonic CD location	1.11 (0.89–1.39)	0.347
Perianal disease	1.26 (0.95–1.67)	0.114
Diagnostic histologic gastroscopy findings	1.33 (1.04–1.70)	0.024
Change of postoperative pharmacotherapy	1.24 (0.86–1.79)	0.251

CD, Crohn's disease.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Classification of post-operative recurrence of Crohn's Disease.
Table S2. Pre-operative and post-operative pharmacotherapy in recurrence and non-recurrence patients.