

Association of extraintestinal manifestations and disease severity in paediatric inflammatory bowel disease: a multicentre cohort study

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ABSTRACT

Objective Extraintestinal manifestations (EIMs) are common in paediatric inflammatory bowel disease (IBD), often impairing quality of life. Our aim was to assess whether EIMs at diagnosis are associated with disease severity in paediatric IBD.

Methods We conducted a post hoc analysis from the Hungarian Pediatric IBD Registry (2010–2020), including children with Crohn's disease (CD) or ulcerative colitis (UC). Outcomes (relapse, steroid dependency, biological therapy (BT), surgery) were compared between patients with EIMs at diagnosis and those without, using Kaplan-Meier and Cox regression analyses.

Results Among 1590 patients, EIMs were more frequent in CD than in UC (25% vs 14%, $p<0.0001$). In CD, EIMs were linked to earlier steroid dependency ($p=0.0047$) and BT initiation ($p=0.00049$). Patients without EIMs had a higher risk of intestinal resection (HR 3.2; 95% CI 1.572 to 6.472; $p=0.001$). In UC, EIMs were not associated with relapse ($p=0.600$), steroid dependency ($p=0.890$) or need for BT ($p=0.081$). Colectomy occurred earlier in the patients with EIMs ($p=0.032$).

Conclusion In patients with CD, EIM at diagnosis more often required BT, but underwent fewer surgeries. In patients with UC, EIMs at diagnosis appeared to be associated with an increased risk of BT and colectomy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Extraintestinal manifestations are common in paediatric inflammatory bowel disease (IBD) and often complicate disease management.
- ⇒ There is insufficient evidence to determine whether the presence of extraintestinal manifestations is associated with the severity of intestinal disease.

WHAT THIS STUDY ADDS

- ⇒ While patients with Crohn's disease presenting with extraintestinal manifestations at diagnosis were more likely to require earlier biologic therapy, they underwent fewer surgical interventions independent of early biologic use; in ulcerative colitis, the presence of such manifestations at diagnosis was a clear predictor of a more severe disease course.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Extraintestinal manifestations may signal a poorer intestinal disease course in IBD, underscoring the need for closer monitoring.

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease-unclassified (IBD-U). It is a chronic inflammatory disorder of the gastrointestinal tract that affects numerous aspects of patient's life.¹

Although IBD mainly affects the intestines, it can lead to immune-mediated pathologies outside of the digestive system. These extraintestinal manifestations (EIMs) can

affect multiple organs, including the skin, eyes, joints and liver. The pooled prevalence of EIMs at the time of IBD diagnosis ranges approximately from 10% to 25% in the paediatric population depending on the definition used to define EIMs.^{2–4}

The course of IBD can vary significantly. Some patients achieve long-term clinical remission with minimal disease activity, while others experience a more severe disease course characterised by frequent flare-ups.^{5,6} Moreover, EIMs often complicate disease management, as they can emerge independently of gastrointestinal activity and sometimes precede the onset of intestinal symptoms.



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Thus, in addition to IBD, EIMs can further impair the patient's quality of life and may require additional treatment beyond managing intestinal symptoms.^{3 7–9}

Still, it remains uncertain whether patients diagnosed with EIMs experience a more severe intestinal disease course. While some studies have suggested that EIMs might be associated with more aggressive disease progression, relapses, the need for biological therapy (BT) and corticosteroids, or higher intestinal surgery rates, definitive evidence is limited. However, the presence and treatment of an EIM may also reduce gastrointestinal disease activity, leading to a milder course of the disease.^{2 9 10} A similar association has been observed in patients with sclerosing cholangitis (SC) and UC, where UC often presents with a less aggressive course.^{11–14}

Early intensified treatment may help prevent complications in paediatric IBD.¹⁵ The identification of poor prognostic factors could improve patient management by allowing individualised treatment approaches, reducing the risk of disease progression.¹⁶ In accordance with this approach, the current European Society for Paediatric Gastroenterology Hepatology and Nutrition guideline recommends a step-down strategy when poor prognostic factors are present at diagnosis (e.g., deep ulcerations, extensive disease).^{17 18}

Therefore, we aimed to analyse whether the presence of EIM at diagnosis is a poor prognostic factor in paediatric IBD based on a large population-based cohort from Hungary.

METHODS

We present our results following the Strengthening the Reporting of Observational Studies in Epidemiology statement (see checklist in online supplemental table 1).¹⁹

Study design

A post hoc, real-world, longitudinal observational cohort analysis was conducted to compare the intestinal disease course of paediatric patients with IBD who had EIM at diagnosis with those who did not present with EIMs at diagnosis or during follow-up. Data were prospectively collected from the structured, multicentre, follow-up Hungarian Paediatric IBD Registry (HUPIR).

Data collection

All data were registered in the HUPIR database. The included patients had a baseline chart at the time of diagnosis, and yearly questionnaires were completed by the treating gastroenterologist. The case report forms are validated by an expert (KEM). The survey collected the data anonymously. The diagnosis of IBD was based on the Porto criteria.²⁰ Patients were followed up from diagnosis until their transition to the adult healthcare system or were lost to follow-up for various reasons (e.g., moving abroad, not participating in follow-up appointments).⁴

Patient selection

Patients under 18 years of age diagnosed with IBD and enrolled from HUPIR between 1 January 2010 and

31 December 2020 were included. Exclusion criteria were age at diagnosis older than 18 years, a follow-up period of <1 year, the presence of a co-existing autoimmune disease and patients without informed consent. Patients with IBD-U, and those who developed an EIM only during follow-up, were excluded from the statistical analysis due to the low number of such cases. Only those EIMs that fulfilled the criteria of the European Crohn's and Colitis Organisation (ECCO) for classical EIMs and were accurately recorded in the case report forms were included.²¹

Outcomes/Variables

For each case, baseline characteristics were collected, including age at diagnosis, sex, presence of EIMs, diagnosis of EIM, C reactive protein levels at diagnosis, disease localisation and phenotype based on the Paris Classification,²² activity indices measured by the Pediatric Crohn's Disease Activity Index and the Pediatric Ulcerative Colitis Activity Index.^{22 23} We also extracted the time to first clinical relapse, the need for BT, necessity of intestinal surgery, steroid dependency/refractoriness during the follow-up period. Steroid-refractory colitis is defined as the persistence of active disease despite treatment with prednisolone at a dose of up to 0.75 mg/kg/day for at least 4 weeks. Steroid-dependent colitis is defined as either the inability to reduce corticosteroid therapy below the equivalent of prednisolone 10 mg/day within 3 months of initiation without recurrence of active disease, or relapse of disease within 3 months after complete discontinuation of corticosteroid therapy.^{17 18 24}

Data quality and representativeness

Online supplemental table 2 lists the proportions of available data for each parameter. Online supplemental figure 1 shows the selection process for the cohort.

Statistical analyses

Descriptive statistics summarised the data: continuous variables were reported as means with SD or medians with IQRs, and categorical variables as counts and percentages.

Group comparisons used Welch's two-sample t-test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables, depending on expected cell counts. Time-to-event outcomes were analysed using Kaplan-Meier survival curves to estimate survival probabilities, with differences assessed using the log-rank test. Median survival times with 95% CIs were reported where applicable.

A multivariable Cox proportional hazards model evaluated associations between selected predictors and the time-to-event outcome. HRs with 95% CIs were estimated. Proportional hazard assumptions were verified, and missing data were handled by case-wise deletion. Model performance was assessed using the concordance index.

A significance level of $p < 0.05$ was considered statistically significant. Kaplan-Meier curves were compared

Table 1 Baseline characteristics of patients with CD

Characteristic	Patients with CD with EIM	Patients with CD without EIM	P value
Patients, n (%)	223 (25)	685 (75)	–
Male sex, n (%)	130 (58)	395 (58)	0.87
Age, year, median (IQR)	14.00 (11.00, 16.00)	14.00 (11.00, 16.00)	0.83
Follow-up time-years, mean (SD)	3.26 (2.10)	3.21 (2.15)	0.79
CD, localisation, n (%) (L1/L2/L3)	L1: 38 (18) L2: 60 (29) L3: 108 (52)	L1: 164 (26) L2: 110 (18) L3: 354 (56)	<0.001
CD perianal involvement, n (%)	35 (16)	109 (16)	0.94
CD, behaviour, n (%) (B1/B2/B3)	B1: 215 (96) B2: 5 (2.2) B2/B3: 1 (0.4) B3: 2 (0.9)	B1: 605 (88) B2: 52 (7.6) B2/B3: 8 (1.2) B3: 20 (2.9)	0.003
PCDAI, mean (SD)	32.20 (16.71)	28.20 (14.20)	0.002
Family history, n (%)	38 (18)	125 (19)	0.68
CRP, mean (SD)	41.80 (40.23)	34.38 (39.53)	0.018
Cumulative incidence of outcomes during follow-up			
Biological therapy, n (%)	89 (43)	205 (30)	<0.001
GI relapse, n (%)	116 (56)	357 (52)	0.30
Steroid dependency/refractoriness, n (%)	34 (17)	65 (9.5)	0.005
Intestinal resection, n (%)	10 (4.9)	98 (14)	<0.001

Values in bold indicate statistically significant results ($p < 0.05$).

B1, non-stricturing, non-penetrating disease; B2, stricturing disease; B3, penetrating disease; CD, Crohn's disease; CRP, C reactive protein; EIM, extraintestinal manifestation; GI, gastrointestinal; L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; PCDAI, Paediatric Crohn's Disease Activity Index.

using the log-rank test for illustration, while the Cox model was the main inferential tool.

All analyses were conducted in R (V.4.4.2; R Core Team, 2024). Survival analyses, including Kaplan-Meier and Cox models, used the survival and survminer packages.

RESULTS

Participants

Between 1 January 2010 and 31 December 2020, 1980 patients with IBD were recorded in the HUPIR database. We included a total of 1590 patients (CD: 951, UC: 545, IBD-U: 94). Of the 951 patients with CD, 223 (23%) had EIMs at diagnosis and 685 (72%) children did not develop any EIMs during the follow-up. In the UC group, 71 (13%) patients had EIMs at diagnosis and 447 (82%) did not experience any EIM during follow-up. The mean follow-up time for patients with CD was 3.3 years with EIMs and 3.2 years without EIMs. For patients with UC, the mean follow-up was 3.7 years for those with EIMs and 3.3 years for those without. Most patients who received BT (CD: 294, UC: 75, IBD-U: 12) were treated with antitumour necrosis factor therapy (anti-TNF). Only a minority of patients received vedolizumab (10.5%) or ustekinumab (2.9%) as second-line therapy. Baseline characteristics are presented in [tables 1 and 2](#).

EIMs at diagnosis

We included 309 patients from the database who collectively experienced 340 EIMs. Joint manifestations were the most common, reported in 159 patients (CD: 115, UC: 37, IBD-U: 7). Aphthous stomatitis was observed in 82 patients (CD: 66, UC: 13, IBD-U: 3). SC occurred in 45 patients (CD: 18, UC: 23, IBD-U: 4), while erythema nodosum was observed in 44 patients (CD: 36, UC: 6, IBD-U: 2). Seven patients (CD: 6, UC: 1) were diagnosed with pyoderma gangrenosum. Additionally, three patients with CD exhibited episcleritis ([table 3](#)).

Overall, EIMs were more common in patients with CD compared with patients with UC (25.0% vs 14.0 %, $p < 0.00001$). There was no association between EIMs and age or sex. Patients with UC who had pancolitis were more likely to develop EIMs compared with those with distal colitis ($p = 0.019$). Similarly, patients with CD with ileocolonic involvement tended to have EIMs more often than those with isolated colonic or ileocaecal disease ($p < 0.001$). Children with CD who had EIMs were less likely to present with a stricturing disease phenotype ($p < 0.001$).

EIMs during follow-up

Seventy-seven patients who developed EIMs during follow-up were excluded from the analysis due to the

Table 2 Baseline characteristics of patients with UC

Characteristic	Patients with UC with EIM	Patients with UC without EIM	P value
Patients, n (%)	71 (14)	447 (86)	–
Male sex, n (%)	37 (52)	230 (51)	0.92
Age, year median (IQR)	12.00 (10.00, 15.00)	13.00 (10.00, 15.00)	0.31
Follow-up time-years, mean (SD)	3.72 (2.48)	3.26 (2.14)	0.17
UC, extent, n (%) (E1/E2/E3/E4)	E1: 5 (7.6) E2: 10 (15) E3: 5 (7.6) E4: 46 (70)	E1: 72 (17) E2: 92 (22) E3: 46 (11) E4: 204 (49)	0.02
PUCAI, mean (SD)	37.64 (20.10)	37.18 (17.91)	0.86
Family history, n (%)	9 (13)	83 (20)	0.19
CRP, mean (SD)	20.89 (36.93)	10.94 (22.60)	0.03
Cumulative incidence of outcomes during follow-up			
Biological therapy, n (%)	15 (23)	60 (13)	0.03
GI relapse, n (%)	40 (63)	282 (63)	0.91
Steroid dependency/refractoriness, n (%)	11 (17)	67 (15)	0.65
Colectomy, n (%)	5 (7.8)	11 (2.5)	0.04

Values in bold indicate statistically significant results ($p < 0.05$).

CRP, C reactive protein; E1, proctitis; E2, left-sided colitis; E3, extensive colitis; E4, pancolitis; EIM, extraintestinal manifestation; GI, gastrointestinal; PUCAI, Pediatric Ulcerative Colitis Activity Index; UC, ulcerative colitis.

small sample size in this subgroup (CD: 43 (55.8%), UC: 27 (35.1%) and IBD-U: 7 (9.1%)). Among these, nine patients (CD: 1, UC: 7, IBD-U: 1) were diagnosed with SC, seven (CD: 3, UC: 2, IBD-U: 1) with erythema nodosum and one patient with UC and pyoderma gangrenosum. Joint manifestations were observed in 51 patients (CD: 30, UC: 15, IBD-U: 6), and nine patients with CD developed aphthous stomatitis. Notably, 93.5% of these patients experienced their EIMs within the first 2 years of their IBD diagnosis.

Disease course in patients with CD

Gastrointestinal relapse

During follow-up, 473 patients with CD (116 with (56.3%) and 357 without (52.2%) EIM) had relapses. The Kaplan-Meier curves showed a similar likelihood of relapses over

time between patients with and without EIMs ($p = 0.290$). In patients with CD, there was no significant difference in the risk of relapse between those with and without EIM (HR 0.892, 95% CI 0.690 to 1.153; $p = 0.383$). In the multivariate Cox regression analysis, ileocolonic involvement was significantly associated with the hazard of relapse (HR 1.374; 95% CI 1.033 to 1.828; $p = 0.029$).

Steroid dependency/refractoriness

Thirty-four patients with CD with EIMs (16.5%) and 65 without EIMs (9.5%) were identified as steroid-dependent or steroid-refractory at the time of IBD diagnosis. Kaplan-Meier curves revealed that patients with EIMs developed steroid dependency or refractoriness significantly earlier than those without EIMs ($p = 0.0047$). In the multivariate Cox regression analysis, patients with

Table 3 Distribution of extraintestinal manifestations at the time of diagnosis

Number of patients	CD (n=223)	UC (n=71)	IBD-U (n=15)	P value (CD vs UC)
Extraintestinal manifestation, n	244	80	16	<0.0001
Joint manifestations, n (%)	115 (47.7)	37 (46.3)	7 (43.8)	0.96
Aphthous stomatitis, n (%)	66 (27.4)	13 (16.2)	3 (18.7)	0.15
Sclerosing cholangitis, n (%)	18 (7.5)	23 (28.8)	4 (25.0)	<0.001
Erythema nodosum, n (%)	36 (14.9)	6 (7.5)	2 (12.5)	0.15
Pyoderma gangrenosum, n (%)	6 (2.5)	1 (1.2)	0 (0.0)	0.55
Episcleritis, n (%)	3	0	0	0.44

Bold values indicate results that reached statistical significance according to the predefined threshold ($p < 0.05$).

CD, Crohn's disease; IBD-U, inflammatory bowel disease unclassified; UC, ulcerative colitis.

EIMs had a 1.71-fold higher hazard of developing steroid dependency or refractoriness over time compared with those without EIMs (HR 1.710; 95% CI 1.040 to 2.790; $p=0.033$).

Biological therapy

A total of 89 patients with CD with EIMs (43.2%) and 205 without EIMs (29.9%) received BT. Kaplan-Meier curves revealed that patients with EIMs required BT significantly earlier than those without EIMs ($p=0.00049$). Similarly, Cox regression showed a significantly lower hazard for requiring biologics in patients without EIM compared with patients with EIM (HR 0.597, 95% CI 0.445 to 0.803; $p<0.001$) in CD. Some patients may be initiated on BT due to EIMs rather than therapy refractoriness, especially those with joint involvement. Unfortunately, data on the specific indications for BT were not available in the registry. Therefore, as a next step, we separately evaluated the initiation of BT in patients with joint-related and other EIMs. Of the 214 patients with CD who received BT, 24 presented with joint involvement (11.2%), while 44 exhibited other types of EIMs (20.6%). Kaplan-Meier analysis revealed that the presence of EIMs, particularly non-joint EIMs at the time of diagnosis, was associated with an earlier initiation of BT ($p<0.0001$). Cox regression analysis revealed no significant difference in the risk of requiring biological treatment between patients without EIMs and those with joint involvement (HR 0.759; 95% CI 0.487 to 1.183; $p=0.224$), nor between patients with joint manifestations and those with other types of EIMs (HR 1.483; 95% CI 0.891 to 2.468; $p=0.130$). Among the analysed variables, perianal involvement and the presence of granulomas were significantly associated with the hazard of BT (HR 3.108; 95% CI 1.458 to 6.625; $p=0.003$ and HR 1.410; 95% CI 1.054 to 1.886; $p=0.020$, respectively).

Surgical procedures

Ten patients with EIMs (4.9%) and 98 without EIMs (14.3%) underwent bowel resection during the follow-up period. Based on the Kaplan-Meier analysis, patients without EIMs required resection surgery significantly earlier ($p=0.00037$).

In the multivariable Cox regression analysis, patients without EIM were found to have a 3.2-fold higher hazard for intestinal resection compared with those with EIM (95% CI 1.572 to 6.472; $p=0.001$) in CD. Among the variables analysed, stricturing and penetrating phenotypes, as well as a history of BT, were identified as strong predictors of intestinal resection risk (HR 2.586; 95% CI 1.519 to 4.403; $p<0.001$ and HR 3.071; 95% CI 1.341 to 7.033; $p=0.008$, respectively).

Since BT has been identified as a strong predictor of surgery and EIMs may serve as an indication for BT, we conducted a further analysis of this population ($n=891$). An additional Kaplan-Meier curve illustrates surgery-free survival probability in patients with CD, stratified by the presence of EIMs at diagnosis and need for BT. Patients without EIMs who received BT exhibited the

lowest surgery-free survival probability among the groups analysed ($p=0.00016$). Those with EIMs receiving BT and those without EIMs not receiving BT demonstrated an intermediate risk for resection surgery. Meanwhile, patients with EIMs who did not receive BT maintained the highest surgery-free survival probability throughout the follow-up period (online supplemental figure 2).

Kaplan-Meier survival curves are presented in online supplemental figures 3–6, whereas the variables included in the Cox regression analysis, along with their corresponding HRs, are detailed in [table 4](#).

Disease course in patients with UC

Gastrointestinal relapse

A total of 322 patients with UC experienced relapses, including 40 with EIMs (62.5%) and 282 without EIMs (63.2%). Kaplan-Meier curves indicated a similar probability of relapse over time for patients with and without EIMs ($p=0.600$). The HR for relapse showed no difference between patients without EIMs compared with those with EIMs (HR 0.990, 95% CI 0.684 to 1.432; $p=0.956$) for UC.

Steroid dependency/refractoriness

Eleven patients with UC with EIMs (17.2%) and 67 without EIMs (15.0%) were classified as steroid-dependent or steroid-refractory. Kaplan-Meier curves showed a comparable probability of developing steroid dependency/refractoriness over time between the two groups ($p=0.890$). The HR for steroid dependency or refractoriness in patients with UC without EIMs compared with those with EIMs was 1.215 (95% CI 0.597 to 2.473; $p=0.591$), indicating no significant difference between the groups.

Biological therapy

Fifteen patients with UC with EIMs (23.4%) and 60 without EIMs (13.4%) underwent BT. Kaplan-Meier curves demonstrated a comparable likelihood of requiring BT over time between patients with UC with and without EIMs ($p=0.081$). In Cox regression analysis, the hazard of requiring biologics in patients without EIM was 0.6-fold lower compared with patients with EIM; however, the difference was not significant (95% CI 0.327 to 1.180; $p=0.146$).

Surgical procedures

During the follow-up period, five patients (7.8%) with EIMs and 11 (2.5%) without EIMs underwent colectomy. Kaplan-Meier analysis showed that patients with EIMs required colectomy significantly earlier than those without EIMs ($p=0.032$). Based on the Cox regression, the HR for requiring colectomy in patients without EIMs compared with those with EIMs did not reach the level of significance (HR 0.323, 95% CI 0.099 to 1.051; $p=0.060$) in UC.

Kaplan-Meier survival curves are presented in online supplemental figures 7–10, whereas the variables included in the Cox regression analysis, along with their corresponding HRs, are detailed in [table 5](#).

Table 4 HRs of the multivariable Cox regression analyses in patients with Crohn's disease

	Gastrointestinal relapse	Biological therapy	Surgery	Steroid dependence/ refractoriness
Non-EIM	0.892 (0.690 to 1.153)	0.597 (0.445 to 0.803)*	3.190 (1.572 to 6.472)*	0.586 (0.358 to 0.958)*
Age	1.004 (0.969 to 1.041)	0.991 (0.948 to 1.035)	1.085 (0.996 to 1.181)	1.003 (0.929 to 1.082)
Female sex	0.990 (0.792 to 1.237)	0.947 (0.717 to 1.252)	1.102 (0.702 to 1.731)	1.139 (0.713 to 1.818)
Family history	1.022 (0.768 to 1.358)	0.952 (0.662 to 1.370)	NA	0.892 (0.465 to 1.710)
Localisation (L3)	1.374 (1.033 to 1.828)*	1.161 (0.818 to 1.649)	0.718 (0.439 to 1.173)	1.718 (0.878 to 3.359)
Paris phenotype	1.312 (0.907 to 1.897)	1.299 (0.836 to 2.018)	2.586 (1.519 to 4.403)*	1.190 (0.539 to 2.630)
Perianal involvement	0.793 (0.418 to 1.507)	3.108 (1.458 to 6.625)*	2.854 (0.966 to 8.430)	1.282 (0.579 to 2.842)
CRP	1.003 (1.000 to 1.006)*	1.004 (1.001 to 1.008)*	1.003 (0.998 to 1.009)	1.004 (0.999 to 1.010)
Granuloma	1.177 (0.926–1.495)	1.410 (1.054–1.886)*	NA	1.078 (0.653–1.781)

Results are expressed as HR (95% CI).

*P<0.05.

CRP, C reactive protein; EIM, extraintestinal manifestation; L3, ileocolonic disease; NA, not available.

DISCUSSION

Using data from a prospective registry, this post hoc cohort analysis investigated the prevalence of EIMs among paediatric patients with IBD and assessed their association with intestinal disease progression.

Our findings revealed that patients with UC with EIMs faced an increased risk of requiring surgical intervention

compared with those without EIMs. Similarly, paediatric patients with CD who presented with EIMs were more likely to require BT compared with those without EIMs; however, the incidence of intestinal surgery was significantly lower among them.

In our study, 19.4% of patients presented with an EIM at the time of their IBD diagnosis, which aligns with

Table 5 HRs of the multivariable Cox regression analyses in patients with ulcerative colitis

	Gastrointestinal relapse	Biological therapy	Surgery	Steroid dependence/ refractoriness
Non-EIM	0.990 (0.684 to 1.432)	0.621 (0.327 to 1.180)	0.323 (0.099 to 1.051)	1.215 (0.597 to 2.473)
Age	1.007 (0.973 to 1.042)	0.987 (0.918 to 1.062)	1.078 (0.906 to 1.282)	0.983 (0.919 to 1.051)
Female sex	0.997 (0.783 to 1.269)	0.989 (0.597 to 1.639)	1.009 (0.353 to 2.887)	1.091 (0.675 to 1.763)
Family history	0.955 (0.704 to 1.296)	1.008 (0.518 to 1.959)	0.695 (0.153 to 3.151)	0.895 (0.464 to 1.727)
Localisation (E4)	0.573 (0.388 to 0.846)*	0.714 (0.274 to 1.860)	0.576 (0.101 to 3.274)	2.242 (0.654 to 7.695)
PUCAI	1.012 (1.005 to 1.019)*	1.023 (1.008 to 1.039)*	1.001 (0.970 to 1.034)	1.030 (1.015 to 1.044)*
CRP	1.001 (0.996 to 1.006)	1.010 (1.003 to 1.017)*	1.011 (1.002 to 1.021)*	1.008 (1.001 to 1.015)*

*P<0.05.

Results are expressed as HR (95% CI).

CRP, C reactive protein; E4, pancolitis; EIM, extraintestinal manifestation; PUCAI, Pediatric Ulcerative Colitis Activity Index.

previously published paediatric data.^{6 25 26} During the follow-up period, only 4.8% of patients were diagnosed with an EIM, which is notably lower compared with findings in other studies (11%–55%).^{3 9 26} EIMs were more frequently observed in patients with CD compared with those with UC. This finding is consistent with prior research reported by several studies.^{3 7 26–28}

Based on our results, concerning UC, patients with pancolitis were more likely to develop EIMs compared with those with isolated rectosigmoid disease, consistent with previous reports.^{26 27 29} In CD, ileocolonic involvement was associated with a higher likelihood of EIMs, contrasting with findings that reported no significant association.^{9 26 27} However, Duricova *et al*² and Vavricka *et al*⁷ both identified upper gastrointestinal involvement in CD as a potential risk factor for EIMs, suggesting a localisation-dependent risk profile.

In CD, no significant difference in relapse rates was observed between patients with and without EIMs; however, those with EIMs had a higher risk of corticosteroid dependence/refractoriness and initiated BT significantly earlier. Similar to our results, Greuter and Vavricka³ and Alizadeh *et al*³⁰ reported a higher need for BT among patients with EIMs. The reason behind this can be explained by the findings of Vavricka *et al*,⁷ who reported that BT was initiated due to EIMs in 43.2% of cases. Other studies by Jansson *et al*⁹ and Vegh *et al*²⁷ did not observe a significantly increased need for BT. However, the study by Jansson *et al*⁹ included only 169 patients with CD, while the analysis by Vegh *et al*²⁷ focused on adult patients in an era when the availability of BT was limited in Hungary.

Interestingly, the rate of intestinal surgery was lower in patients with CD with EIMs in our cohort, which contrasts with the findings of Vavricka *et al*⁷ and the meta-analysis by Attauabi *et al*.¹⁰ The earlier initiation of biologics may partially explain this finding; however, additional analyses (online supplemental figure 1) indicate that patients with CD with EIMs who received BT still had an intermediate risk of requiring surgery, worse than those with EIMs who did not receive BT. Moreover, BT itself was identified as a significant predictor of surgical intervention (HR 3.10, 95% CI 1.34 to 7.03; p=0.008). This lower surgical rate may be related to disease localisation patterns, as isolated colonic disease—associated with a lower risk of resection—was more prevalent in patients with EIMs. A similar association between isolated colonic CD and the presence of EIMs was previously described in the CEDATA registry.³¹ The proportion of stricturing and/or penetrating CD was higher in patients without EIMs, which may partly explain the increased need for surgery in this group. However, the low number of such phenotypes among patients with EIMs limits definitive conclusions. Notably, EIMs were less frequent in patients with isolated L1 localisation, a disease pattern more commonly associated with stricturing and penetrating behaviour, suggesting distinct disease trajectories between the two groups. Further data collection is

required to more precisely address this specific research question.

In our cohort of patients with UC with EIMs, there was a higher need for colectomy, suggesting a more severe disease course. Although EIMs at diagnosis were not independently associated with initiation of BT in the time-to-event analysis, multiple findings consistently indicated more frequent biologic use among patients with UC with EIMs. These patients demonstrated earlier treatment initiation on Kaplan-Meier curves, a higher cumulative proportion receiving biologics and Cox regression point estimates suggesting an increased hazard compared with patients without EIMs. The direction of the effect was uniform across descriptive, graphical and regression analyses, despite not reaching statistical significance. However, the likelihood of relapse and corticosteroid refractoriness or dependence did not differ significantly between those with and without EIMs. Consistent with our findings, other studies have also reported indicators of a more challenging disease course in patients with UC presenting with EIMs. Duricova *et al*² and Vegh *et al*²⁷ reported a greater need for immunosuppressants and corticosteroids. The need for surgical intervention was significantly higher among patients with UC with EIMs, aligning with other paediatric cohorts and a meta-analysis.^{2 9 10} In contrast, some adult cohorts have reported no association between EIMs and the need for colectomy.^{7 27} These discrepancies among our and earlier studies may be attributable to differences in therapeutic strategies between adult and paediatric populations, as well as potential variations related to the inclusion of an older patient cohort. The increased need for colectomy may represent an indirect association: EIMs are linked to extensive colitis in several studies, which is known to be associated with a higher likelihood of surgery.^{26 27 29} However, according to the multivariate analysis, EIMs emerged as an independent risk factor for colectomy, a finding also reported by Parragi *et al*.³²

Our Kaplan-Meier analysis of BT initiation among patients with joint manifestations, other EIMs and no EIMs suggests that distinct EIM subtypes represent varying risks for poor prognosis. Unfortunately, due to the low number of events, we were unable to perform a detailed analysis of this question. Notably, in a Swiss cohort study, Hiller *et al*³³ demonstrated that a more severe disease course in patients with IBD (including higher intestinal surgery rates and anti-TNF demand) was significantly associated with the presence of joint manifestations.

Strengths and limitations

The primary strength of this study lies in the large overall sample size and careful selection of patients, ensuring robust and reliable findings. However, one limitation of this study is its nature as a post hoc analysis of data derived from this prospective registry. As a result, certain information could be lacking—such as the specific indications for therapy—which may limit the interpretation of some findings. Additionally, the study includes some groups

with low patient numbers, and no separate analysis was conducted for the different types of EIMs, which could have provided more detailed insights. Another strength of this study is that we addressed this issue by including only patients who met the ECCO-defined criteria for EIMs,²¹ ensuring consistency and standardisation.

Implication for practice and research

Our findings indicate that patients with EIMs require closer monitoring, as these manifestations may serve as negative prognostic factors for the intestinal disease course in IBD. To better understand and address this issue, further prospective studies with extended follow-up periods and stratified analyses of different EIMs are required.^{34 35}

Moreover, we recommend that future registries and studies adopt the standardised definition of EIMs as outlined by ECCO to enhance consistency and comparability across research efforts.

CONCLUSION

Patients with CD who presented with EIMs at diagnosis required BT earlier, while undergoing surgical interventions less frequently; this difference was not explained by the early initiation of BT. In contrast, in patients with UC, the presence of EIMs at diagnosis has emerged as a clear predictor of a more severe disease trajectory.

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