

**SEMMELWEIS EGYETEM
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Ph.D. értekezések

3550.

TÍMÁR ÁGNES ESZTER

**Gyermekekori betegségek klinikuma, élettana és prevenciója
című program**

Programvezető: Dr. Szabó Attila, egyetemi tanár
Témavezető: Dr. Müller Katalin Eszter, főiskolai docens

CLINICAL IMPACT OF EXTRAINTESTINAL MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASE

Ph.D. Thesis

Ágnes Eszter Tímár M.D.

Translational Medicine Program

Károly Rácz Conservative Medicine Division

SEMMELWEIS UNIVERSITY



Supervisor:

Katalin Eszter Müller M.D., Ph.D.

Official reviewers:

Andrea Takács M.D., Ph.D.

Barbara Dorottya Lovász M.D., Ph.D.

Head of the Complex
Examination Committee:

Miklós Szabó M.D., D.Sc.

Members of the Complex

Examination Committee:

Eero Kajantie M.D., D.Sc.

Klára Horváth M.D., Ph.D.

István Balogh M.D., D.Sc.

Péter Fehérvári Ph.D.

Budapest

2026

***"It is good to have an end to journey toward;
but it is the journey that matters, in the end."***

Ernest Hemingway

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1. LIST OF ABBREVIATIONS

BT	Biological therapy
CD	Crohn's disease
CI	Confidence interval
CRP	C-reactive protein
ECCO	European Crohn's and Colitis Organisation
EIM	Extraintestinal manifestation
EN	Erythema nodosum
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard ratio
HUPIR	Hungarian Pediatric IBD registry
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease unclassified
IQR	Interquartile range
JAK	Janus kinase inhibitor
PCDAI	Pediatric Crohn's Disease Activity Index
PG	Pyoderma gangrenosum
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PSC	Primary sclerosing cholangitis
PUCAI	Pediatric Ulcerative Colitis Activity Index

QUIPS	Quality in Prognostic Studies
SD	Standard deviation
TNFi	Tumor necrosis factor inhibitor
TOFA	Tofacitinib
UC	Ulcerative colitis
UST	Ustekinumab
VDZ	Vedolizumab

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve the long-term management and outcomes of patients with inflammatory bowel disease (IBD) through evidence-based, patient-centered approaches, with particular emphasis on extraintestinal manifestations. My mission is to better define the clinical relevance of extraintestinal manifestations in IBD, to emphasize how their presence influences disease phenotype, therapeutic decision-making, and prognosis, and to assess their impact on disease course and treatment strategies.



My specific objectives were to determine the prevalence and spectrum of extraintestinal manifestations (EIM) at diagnosis and during follow-up, to evaluate their association with disease characteristics and outcomes, and to investigate how EIMs affect the need for advanced therapies and surgical interventions in patients with IBD.

2.2. Scientometrics

Number of all publications:	6
Cumulative IF:	41.1
Av IF/publication:	6.85
Ranking (SCImago):	D1:4, Q2:2,
Number of publications related to the subject of the thesis:	2
Cumulative IF:	11.6
Av IF/publication:	5.8
Ranking (Sci Mago):	D1:1, Q2:1
Number of citations on Google Scholar:	36
Number of citations on MTMT (independent):	28
H-index:	3

The detailed bibliography of the student can be found on page 82.

2.3. Future plans

My future plans include completing my residency training in pediatrics, with a long-term goal of specializing in pediatric gastroenterology. I aim to further develop my clinical and research expertise in IBD, with particular emphasis on EIMs.

I plan to continue my scientific work in close collaboration with my supervisor, expanding ongoing research projects and initiating new studies in the field of IBD. In addition, I am committed to actively participating in the education and mentorship of medical students, including involvement in supervising student research projects and supporting their engagement in scientific activities. Alongside my clinical training, I intend to strengthen my methodological skills in clinical research and contribute to high-quality, collaborative studies.

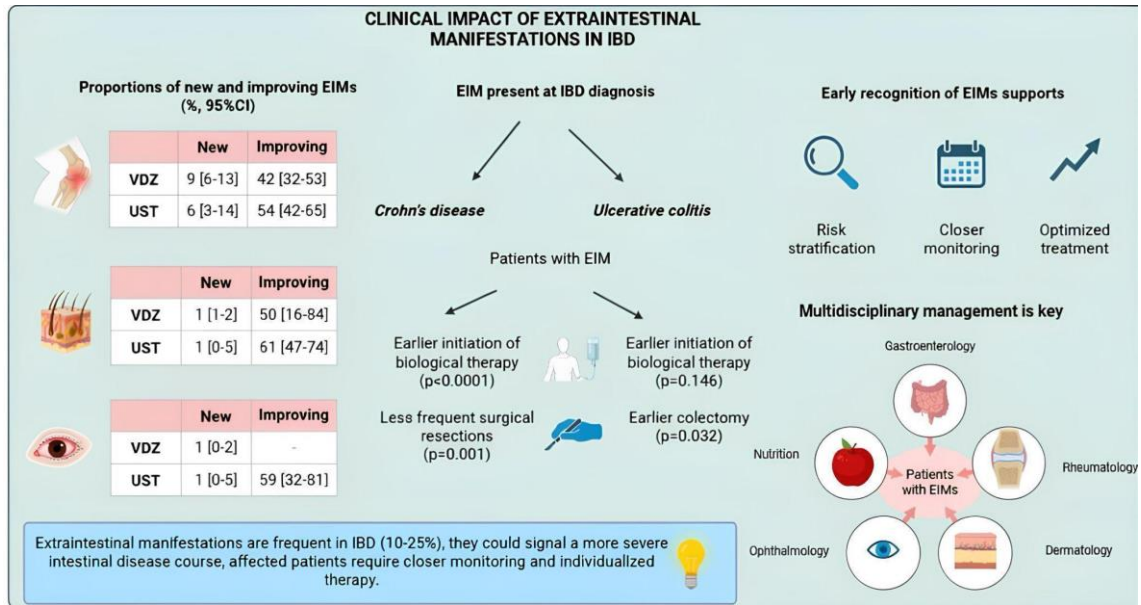
3. SUMMARY OF THE THESIS

IBD, including Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U), is a chronic inflammatory condition with a heterogeneous clinical course. In addition to intestinal inflammation, IBD is frequently associated with EIMs, which significantly contribute to morbidity and reduced quality of life. The management of IBD is particularly complex in the presence of EIMs, as their relationship with intestinal disease activity is variable, and their response to advanced therapies remains incompletely understood.

This thesis aimed to investigate both the therapeutic and prognostic relevance of EIMs in IBD in two separate studies. In Study I, which is a meta-analysis and systematic review, the cumulative incidence and course of EIMs were analyzed in patients receiving advanced therapies. The results indicate that the cumulative incidence of newly developing EIMs is relatively low, and importantly, the presence of pre-existing EIMs alone should not lead to deprioritizing vedolizumab (VDZ) as a treatment option. However, caution may be warranted in patients with articular manifestations. In Study II, that is a registry-based post-hoc analysis, the prognostic significance of EIMs at diagnosis was evaluated in pediatric IBD. The findings show that in CD, patients with EIMs tend to require earlier initiation of biological therapy (BT) while undergoing fewer surgical resections, whereas in UC, the presence of EIMs at diagnosis is associated with a more severe disease course.

Overall, these results highlight the clinical importance of EIMs in both therapeutic decision-making and disease prognosis, supporting a more individualized and comprehensive approach to IBD management.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

IBD, comprising CD and UC, represents a chronic, relapsing–remitting disorder of the gastrointestinal tract (1). Although IBD primarily affects the intestines, it is increasingly recognized as an immune-mediated inflammatory disease with potential involvement beyond the gastrointestinal system. EIMs most commonly affect the joints, eyes, skin, and hepatobiliary tract. At the time of IBD diagnosis, the pooled prevalence of EIMs is reported to range between 10% and 25%; however, during the course of the disease, approximately half of patients develop at least one EIM (2–5).

5.1.2. What is the problem to solve?

Despite significant therapeutic advances, the management of IBD remains challenging, particularly in the presence of EIMs. These manifestations complicate the disease course, as some are associated with intestinal activity while others follow an independent clinical course or may even precede gastrointestinal symptoms. Consequently, controlling intestinal inflammation alone is often insufficient to manage the overall disease burden (4,6–8). In addition, the expanding range of advanced therapies—including biologics and small-molecule agents has introduced uncertainty regarding optimal treatment selection, especially in patients with EIMs, as their effectiveness varies across different manifestations and may even contribute to the development of new EIMs (9,10). Furthermore, the prognostic significance of EIMs remains unclear, particularly whether their presence at diagnosis is associated with a more severe disease course, increased need for aggressive therapy, or poorer outcomes, especially in pediatric populations (11–13).

5.1.3. What is the importance of the topic?

This topic is of considerable clinical importance because EIMs significantly contribute to morbidity and reduced quality of life in patients with IBD, in some cases exceeding the burden of intestinal symptoms. Their presence necessitates a more complex, multidisciplinary approach to management. A better understanding of the relationship between EIMs and intestinal disease activity is essential for optimizing treatment strategies. Moreover, clarifying whether EIMs serve as prognostic markers could enable

earlier risk stratification and facilitate personalized therapeutic approaches. This is particularly crucial in pediatric IBD, where early identification of high-risk patients and timely intervention may prevent long-term complications and disease progression (14,15).

5.1.4. What would be the impact of our research results?

The results of this research are expected to have important clinical implications. By evaluating the development of new EIMs and the progression of pre-existing manifestations under various advanced therapies, the study may provide valuable evidence to support more informed and individualized treatment decisions in IBD. Additionally, assessing the prognostic role of EIMs at diagnosis in pediatric IBD may contribute to improved risk stratification and guide early, targeted therapeutic strategies. Ultimately, these findings may lead to more effective disease control, encompassing both intestinal and extraintestinal aspects of IBD, thereby improving patient outcomes and overall quality of life.

6. OBJECTIVES

6.1. Study I. – Beyond the Gut: A Systematic Review and Meta-analysis of Advanced Therapies for Inflammatory Bowel Disease-associated Extraintestinal Manifestations

The objective of this study was to evaluate the impact of different advanced therapies on EIMs in patients with IBD. Specifically, this study aimed to determine the frequency of newly-developed EIMs and to assess the clinical course of pre-existing EIMs, including both improvement and deterioration, during treatment with various biological agents and small-molecule therapies. By analyzing these outcomes, the study sought to provide evidence to support therapeutic decision-making in IBD patients with concomitant EIMs and to clarify whether certain advanced therapies should be prioritized in specific EIM subtypes.

6.2. Study II. – Association of Extraintestinal Manifestations and Disease Severity in Pediatric Inflammatory Bowel Disease: A Multicentre Cohort Study

The aim of this study was to investigate whether the presence of EIMs at the time of diagnosis constitutes a poor prognostic factor in pediatric IBD. Based on a large, population-based Hungarian cohort, we sought to examine the association between EIMs at diagnosis and subsequent indicators of disease severity, including therapeutic escalation, need for BT or corticosteroids, and surgical interventions. Through this analysis, the study aimed to clarify the prognostic relevance of EIMs present at diagnosis and to contribute to improved risk stratification and evidence-based, individualized management strategies in pediatric IBD.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

For our first study, the systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and followed the recommendations of the Cochrane Handbook (16,17). The study protocol was prospectively registered in the PROSPERO database of the National Institute for Health Research (registration number: CRD42022366812), and the review was conducted in full accordance with the registered protocol (18).

7.1.2. Eligibility Criteria

The study population comprised patients with IBD receiving advanced therapy, irrespective of age. Advanced therapies included non-TNF inhibitor (TNFi) biologics (VDZ, ustekinumab [UST], mirikizumab, etrolizumab) and oral small molecules (tofacitinib [TOFA], upadacitinib, filgotinib, ozanimod). The primary outcome was the proportion of new EIMs during advanced treatment. Secondary outcomes included improvement, resolution, deterioration, or recurrence of pre-existing EIMs. EIMs were defined according to the 6th scientific workshop of the European Crohn's and Colitis Organisation (ECCO) and comprised joint involvement, cutaneous manifestations (erythema nodosum [EN], pyoderma gangrenosum [PG]), hepatobiliary disease (primary sclerosing cholangitis [PSC]), and mucosal and ocular manifestations (19,20). Given the heterogeneity of joint involvement in IBD, data were collected for overall joint manifestations and separately for spondyloarthritis, peripheral and axial involvement, and arthralgia (joint pain without clinical inflammatory arthritis). Eligible studies included randomized controlled trials, non-randomized controlled trials, post hoc analyses, prospective and retrospective cohort studies, and case series reporting EIMs during advanced therapy. Conference abstracts were also considered. Case reports were excluded. Studies with patients treated with anti-TNFs were also excluded.

7.1.3. Information Sources and Search Strategy

The systematic search was performed on November 15, 2022, across four online databases: EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. The following predefined search key was applied across all databases: ("inflammatory bowel disease" OR IBD OR Crohn* OR "ulcerative colitis" OR colitis OR UC) AND (UST OR "anti-IL12/IL23" OR "anti-IL-12/23" OR "anti-IL-12/IL-23" OR Stelara OR vedolizumab OR "anti- α 4 β 7 integrin" OR " α 4 β 7 integrin inhibitor" OR " α 4 β 7 integrin antagonist" OR Entyvio OR etrolizumab OR "rhuMAb β 7" OR "anti- β 7 integrin" OR " β 7 integrin inhibitor" OR " β 7 integrin antagonist" OR ozanimod OR "sphingosine 1-phosphate receptor modulator" OR "S1PR modulator" OR mirikizumab OR "anti-IL23" OR "anti-IL-23" OR "IL-23 antibody" OR "IL23 inhibitor" OR "IL23 antagonist" OR tofacitinib OR filgotinib OR upadacitinib OR "JAK inhibitor" OR "Janus kinase inhibitor" OR XELJANZ OR Jyseleca OR Rinvoq OR "small molecule therapy" OR "small molecular therapy" OR biologicals) AND (extraintestinal OR "extra-intestinal" OR EIM OR uveitis OR iritis OR scleritis OR episcleritis OR arthr* OR arthritis OR spondyloarthritis OR spondyloarthropathy OR arthropathy OR arthralgia OR sacroileitis OR "pyoderma gangrenosum" OR "erythema nodosum" OR "primary sclerosing cholangitis" OR "sclerosing cholangitis" OR "autoimmune sclerosing cholangitis" OR PSC).

In addition, Citationchaser was employed to identify further potentially relevant studies by screening the reference lists of the included articles as well as publications citing those studies (21). No restrictions were imposed with respect to the publication period. Furthermore, no language or other limitations were applied during the literature search.

7.1.4. Study Selection and Data Extraction

The identified studies were imported into reference management software (EndNote 20, Clarivate Analytics). Following automatic and manual removal of duplicates, three independent authors (ÁT, KB, and EK) performed the title and abstract screening. Full-text articles were subsequently assessed by two investigators (ÁT and KB). Any disagreements were resolved through discussion with a third author (MH). Cohen's kappa coefficient was calculated after each phase of the selection process to measure inter-

reviewer reliability. The included conference abstracts and full-text publications were carefully assessed for potential overlap in study populations. When multiple reports appeared to originate from the same study or patient cohort, we compared the study characteristics, including study setting, recruitment period, sample size, baseline characteristics, and follow-up duration, to identify potential duplication. Where overlapping populations were identified, only the most complete or relevant report was included in the meta-analysis. For data collection, two independent researchers (ÁT and KB) extracted relevant information from the eligible studies using a structured data extraction form created in Excel (Office 365, Microsoft). Any uncertainties or discrepancies arising during data extraction were resolved by discussion. The following variables were collected from each study: first author, year of publication, digital object identifier, study design, study period, country, number of participating centers, total number of patients, mean or median age of the population, sex distribution, type of IBD, duration of IBD, concomitant treatments, proportion of bio-experienced patients, type and number of EIMs at baseline, type and number of newly-developed EIMs, number of patients with worsening, improving or resolving, and recurring EIMs, as well as follow-up duration. EIM designations reported in the individual studies were grouped into domains according to underlying pathomechanisms and affected organ systems; where feasible, individual EIM entities were also analyzed separately. Within each domain, four possible outcomes were defined: new occurrence, recurrence, worsening, and resolution or improvement. The overall occurrence of new EIMs was additionally analyzed across all EIM types.

7.1.5. Risk of Bias and Quality of Evidence Assessment

Two reviewers (ÁT and KB) independently assessed the risk of bias for each included study using the Quality in Prognostic Studies (QUIPS) tool (22). Any discrepancies were resolved through consultation and discussion with a third author (MH). The overall risk of bias was classified as low, moderate, or high. All six domains of the QUIPS tool were evaluated, and the final judgment was based on the following aspects: (1) study participation, (2) study attrition, (3) measurement of the prognostic factor, (4) outcome

measurement, (5) handling of confounding, and (6) statistical analysis and reporting (Appendix Table 1.).

The overall quality of evidence was appraised according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (23). Two independent investigators (ÁT and KB) performed the certainty assessment, with disagreements resolved by consensus involving a third reviewer (MH). For each outcome, the evidence was evaluated with respect to risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall certainty of evidence was categorized as very low, low, moderate, or high (See Appendix Tables 2.,3.,4.,5.).

7.1.6. Data Synthesis and Analysis

Proportions were pooled with corresponding 95% confidence intervals (CIs) using a random-effects model, irrespective of follow-up duration.

To estimate the overall frequency of EIMs independent of specific treatments, event counts and total sample sizes from different treatment arms within the same study were combined. These aggregated proportions were then pooled together with proportions derived from studies evaluating a single treatment.

In mixed-effects models, only subgroup-specific pooled estimates by drug were reported, including 95% CIs and prediction intervals; no overall pooled estimate across all treatments was calculated. If fewer than three studies were available within a given domain and subgroup, results were presented descriptively in forest plots without statistical pooling. Between-study heterogeneity was quantified using Higgins and Thompson's I^2 statistic and the τ^2 estimate of between-study variance. Meta-analytic results were displayed graphically using forest plots (24).

When pooled estimates were available for at least two subgroups (i.e., at least three studies in at least two treatment groups), subgroup differences were examined using Cochran's Q test at a 5% significance level (25). Where feasible, a separate Q test comparing VDZ and UST was also conducted. In instances where individual studies

contributed data to more than one subgroup, analyses were performed both using the original data structure and applying a leave-one-out approach to each configuration. If multiple such overlapping studies were identified, a multivariate meta-analysis was conducted according to Viechtbauer's method, incorporating treatment as a moderator and study as a higher-level clustering factor (26).

Potential small-study effects and publication bias were evaluated through visual inspection of funnel plots and by applying Peters' test for proportions. A p-value <0.10 was considered indicative of possible small-study bias, acknowledging the limited statistical power of these tests when fewer than ten studies are available (27).

Given the limited total sample size for several outcomes, a sensitivity analysis was conducted excluding pooled estimates based on fewer than ten patients. Additional sensitivity analyses excluded studies published solely as conference abstracts and those judged to have a high risk of bias, provided that at least three studies remained eligible for pooling after exclusion.

Results are presented as point estimates with their corresponding 95% CIs (lower limit–upper limit). All statistical analyses were performed using R (R Core Team 2023, version 4.2.3), employing the meta (v6.2.1) and dmetar (v0.0.9000) packages for primary and influence analyses, and the metafor (v4.0.0) package for multivariate meta-analysis (28–30).

7.2. Study II.

7.2.1. Study Design

A post hoc, longitudinal cohort study was conducted to evaluate differences in the intestinal disease course of pediatric IBD patients with EIMs at diagnosis compared with those who did not exhibit EIMs either at diagnosis or throughout follow-up. Data were prospectively collected within the structured, multicenter framework of the Hungarian Pediatric IBD Registry (HUPIR).

7.2.2. Study Setting

All relevant clinical information was systematically recorded in the HUPIR registry. For each enrolled patient, a baseline record was completed at the time of diagnosis, and standardized annual questionnaires were subsequently filled out by the attending gastroenterologist. Data collection was conducted anonymously.

The diagnosis of IBD was established in accordance with the Porto criteria (31). Patients were monitored from the time of diagnosis until transfer to adult care services or until follow-up was discontinued for other reasons, such as relocation abroad or failure to attend scheduled follow-up visits.

7.2.3. Ethics and Patient Consent

The registry was approved by the Hungarian Scientific and Research Ethics Committee of the Medical Research Council (IV/2162/2020EKU). The study was conducted in accordance with the principles of the Declaration of Helsinki, as revised in 2013. Written informed consent was obtained from the legal guardians of all participating patients.

7.2.4. Participants

Children and adolescents younger than 18 years with a confirmed diagnosis of IBD who were registered in HUPIR between January 1, 2010, and December 31, 2020, were eligible for inclusion. Patients were excluded if they were older than 18 years at diagnosis, had a follow-up duration of less than one year, had a concomitant autoimmune disorder, or lacked documented informed consent.

Due to the small number of cases, patients diagnosed with IBD-U, as well as those who developed an EIM only during the follow-up period, were omitted from the statistical analyses. Only EIMs meeting the ECCO criteria for classical EIMs and properly documented in the case report forms were considered for evaluation (19,20).

7.2.5. Variables and Data Sources

For every patient, baseline demographic and clinical data were recorded, including age at diagnosis, sex, presence and type of EIMs, serum C-reactive protein (CRP) levels at diagnosis, as well as disease location and behavior according to the Paris Classification. Disease activity at presentation was assessed using the Pediatric Crohn's Disease Activity Index (PCDAI) and the Pediatric Ulcerative Colitis Activity Index (PUCAI). All of the above-mentioned demographic and clinical parameters were entered as covariates into the Cox proportional hazards regression model (32,33).

In addition, we collected data on time to first clinical relapse, requirement for BT, need for intestinal surgery, and the occurrence of steroid dependency or steroid refractoriness during follow-up. Steroid-refractory colitis was defined as ongoing active disease despite treatment with prednisolone at a dose of up to 0.75 mg/kg/day for a minimum of four weeks. Steroid-dependent colitis was defined as either failure to taper corticosteroids below the equivalent of 10 mg/day prednisolone within three months of initiation without recurrence of disease activity, or relapse within three months after complete withdrawal of corticosteroid therapy (19,20,34).

7.2.6. Statistical Methods

Descriptive analyses were performed to characterize the study population. Continuous variables are presented as either means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate, while categorical variables are expressed as absolute numbers and percentages.

Between-group differences were assessed using Welch's two-sample t-test for continuous variables. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test, depending on the expected cell frequencies (35,36).

Time-to-event data were evaluated using Kaplan–Meier survival analysis to estimate survival probabilities, and differences between groups were examined with the log-rank

test. Where relevant, median survival times and their corresponding 95% confidence intervals (CIs) were reported (37,38).

To investigate the relationship between selected covariates and time-to-event outcomes, a multivariable Cox proportional hazards regression model was applied. Hazard ratios (HRs) with 95% CIs were calculated. The proportional hazards assumption was tested, and missing data were addressed through case-wise deletion. Model discrimination was quantified using the concordance index (39).

A two-sided p-value < 0.05 was considered statistically significant. Kaplan–Meier curves with log-rank testing were primarily used for descriptive comparison, whereas the Cox regression model served as the principal inferential method.

All statistical analyses were conducted using R software (version 4.4.2; R Core Team, 2024). Survival analyses, including Kaplan–Meier estimation and Cox regression, were performed using the *survival* and *survminer* packages (28).

8. RESULTS

8.1. Study I.

8.1.1. Study Search and Selection and Description of the Included Studies

A total of 13,544 records were identified through the systematic search. Following duplicate removal, 10,987 records underwent screening. After title and abstract assessment (Cohen's kappa = 0.82), 61 studies were deemed eligible at the full-text review stage (Cohen's kappa = 0.85). Of these, 55 studies were ultimately included in the quantitative synthesis. The selection process is shown in Figure 1.

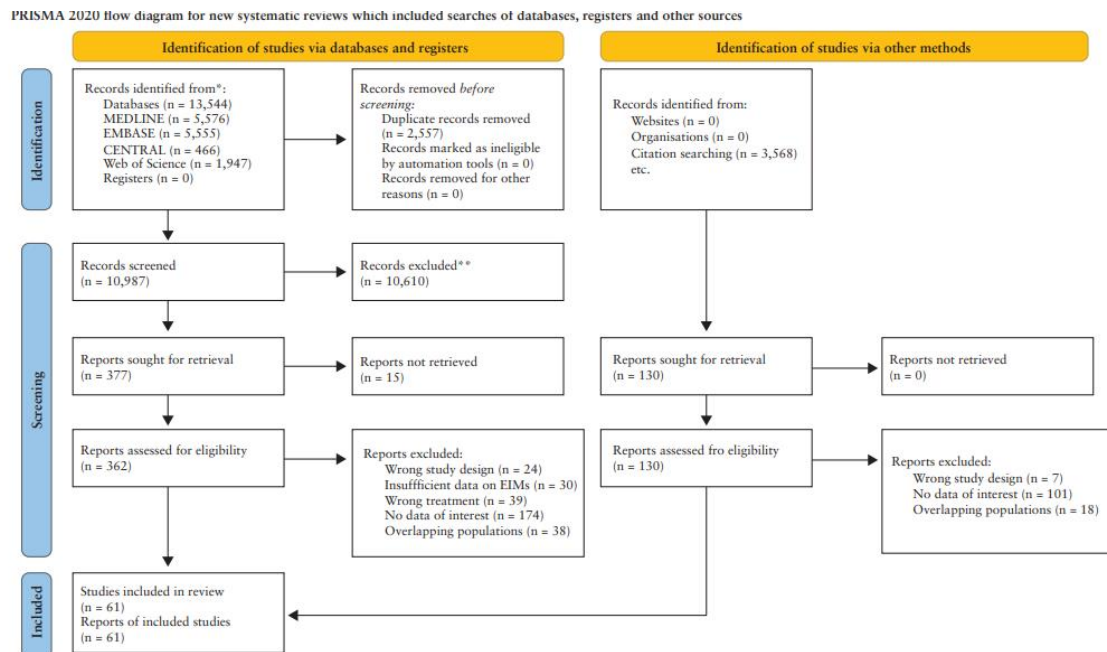


Figure 1. PRISMA 2020 flowchart representing the study selection process (40).

The 61 eligible studies were published between 2015 and 2022, comprising 22 single-centre and 31 multicentre investigations; in eight studies, the number of centres was not specified. The dataset included 26 conference abstracts (41–65), 26 retrospective cohort studies (66–91), six prospective cohorts (92–97), and three post hoc analyses of randomized controlled trials (98–100).

Geographically, 13 studies originated from the United States, two from Canada, 26 from Europe, and four from the Middle East; ten were international, while six did not report country of origin. Sample sizes ranged from 5 to 941 participants. The studies evaluated mucosal, articular, cutaneous, ocular, and hepatic manifestations, primarily in patients treated with VDZ or UST, and less frequently with TOFA (five studies) or upadacitinib (three studies). Follow-up duration varied substantially, ranging from 6 weeks to a median of 4 years. Data are shown in Table 1.

Table 1. Characteristics of included studies in the meta-analysis and systematic review

Author, year of publication	Country	Study design	Number of patients	Age (years)	Therapy	Type of EIM	Follow-up time
Aboubakr et al., 2021(41)	N/A	retrospective cohort (abstract)	170 CD	N/A	UST	joint, skin, ocular involvement	831 days ^e
Anjur et al., 2022(42)	California, USA	prospective cohort (abstract)	21 IBD	15.02±4.65 ^a	UST	arthritis	N/A
Bacaksiz et al., 2019(43)	Turkey	case series (abstract)	10 CD	37 (22-58) ^b	UST	axial joint involvement	N/A
Bar-Gil Shitrit et al., 2019(44)	Israel	prospective cohort (abstract)	106 CD	38 (21-74) ^b	UST	joint involvement	24 weeks ^d
Baumgart et al., 2016(67)	Germany	retrospective cohort	97 CD	36 (34-42) ^b	VDZ	joint involvement, arthritis, EN	14 weeks ^d
Biemans et al., 2019(93)	Netherlands	prospective cohort	191 CD	36.8 (27-52.5) ^c	VDZ	joint, ocular, mucosal involvement, PG, EN	104 weeks (104-104) ^c
Biemans et al., 2020(92)	Netherlands	prospective cohort	221 CD	38.2 (29.3-52.2) ^c	UST	joint, ocular, mucosal involvement, EN	52 weeks (49.3-58.4) ^c
Bor et al., 2017(45)	Hungary	retrospective cohort (abstract)	41 IBD	40 (18-67) ^b	VDZ	any type of EIM	14 weeks ^d
Buisson et al., 2022(68)	France	retrospective cohort	126 UC	39.8±20.8 ^a	tofacitinib	joint involvement	16 weeks

Buisson et al., 2022(68)	France	retrospective cohort	178 UC	42.7±18.6 ^a	VDZ	joint involvement	16 weeks
Cai et al., 2018(69)	Massachusetts, USA	retrospective cohort	367 IBD	41.2±14.8 ^a	VDZ	joint involvement	85.3 months±69.8 ^a
Caron et al., 2019(70)	France, Belgium	retrospective cohort	75 IBD	20.9 (16.6-34.2) ^c	VDZ	PSC	54 weeks
Chaparro et al., 2022(46)	Spain	retrospective cohort (abstract)	335 UC	44±15 ^a	tofacitinib	any type of EIM, peripheral joint involvement	18 months (10-27) ^c
Christensen et al., 2018(94)	Illinois, USA	prospective cohort	136 IBD	39 (28-50) ^c	VDZ	joint involvement	52 weeks
Cohen et al., 2022(71)	Illinois, USA	retrospective cohort	97 UC	40.8±13.3 ^a	tofacitinib	peripheral joint involvement, PSC, PG	32 weeks (3-252) ^c
Colombel et al., 2022(72)	USA, China, Austria, Ireland	retrospective cohort	660 UC	N/A	upadacitinib	any type of EIM, joint involvement	8 weeks
Conrad et al., 2016(95)	Pennsylvania, USA	prospective cohort	21 IBD	13-21 ^f	VDZ	EN	22 weeks
De Galan et al., 2022(73)	Belgium, Spain	retrospective cohort	584 IBD	43 (33-57) ^c	VDZ	joint involvement	2 years
De Galan et al., 2022(73)	Belgium, Spain	retrospective cohort	327 IBD	43 (32-55) ^c	UST	joint involvement	2 years
Di Ruscio et al., 2021(74)	Italy	retrospective cohort	90 IBD	54.3 ^d	VDZ	peripheral joint involvement	12 months

Diaz et al., 2020(75)	Florida, USA	retrospective cross-sectional study	71 IBD	43 (28.5-59.5) ^c	VDZ	joint involvement (axial), EN,PG, ocular involvement	3.75 months (1.38-5.75) ^c
Drvarov et al., 2015(47)	N/A	retrospective cohort (abstract)	43 CD, 35 UC	CD: 38, UC: 39 _d	VDZ	peripheral joint involvement	14 weeks
Dubinsky et al., 2018(66)	USA (research database)	retrospective cohort	756 CD, 544 UC	CD: 44±14.3 , UC: 43.7±15 ^a	VDZ	joint, mucosal, ocular involvement, PSC, PG, EN	251 days± 194 ^a
Dupré et al., 2020(76)	France	retrospective cohort	112 IBD	39.9±16 ^a	VDZ	joint involvement	11.3 months± 8.6 ^a
Fages et al., 2020(48)	Spain	retrospective cohort (abstract)	37 CD	45 ^e	UST	EN	N/A
Favale et al., 2019(77)	Italy	retrospective cohort	97 UC	46 (32-57) ^c	VDZ	joint involvement, arthritis	45.6 weeks (22.8-54) ^c
Feagan et al., 2019 -GEMINI 2(98)	USA	RCT post hoc analysis	814 CD	N/A	VDZ	joint, mucosal,ocular involvement, PG, EN	6 weeks
Feagan et al., 2019 -GEMINI 3(98)	USA	RCT post hoc analysis	209 CD	N/A	VDZ	joint, mucosal,ocular involvement, PG, EN	6 weeks
Ferretti et al., 2022(78)	Italy	retrospective cohort	259 IBD	52±17 ^a	VDZ	joint, skin involvement	4 years (1-16) ^b

Galindo et al., 2021(49)	Spain	retrospective cohort (abstract)	551 IBD	49.7 (38-60) ^c	VDZ	peripheral, axial joint involvement, ocular involvement, EN, PG	12 months
Gold et al., 2018(50)	N/A	retrospective cohort (abstract)	332 IBD	N/A	VDZ	joint involvement	N/A
Iborra et al., 2020(79)	Spain	retrospective cohort	407 CD	45.28 (34.86-55.93) ^c	UST	any type of EIM	52 weeks
Knyazev et al., 2022(96)	Russia	prospective cohort	88 CD	36.4±4.8 ^a	UST	joint, skin involvement	8 weeks
Kokkotis et al., 2021(51)	Greece	retrospective cohort (abstract)	115 IBD	N/A	VDZ	joint involvement	9 months ^c
Kopylov et al., 2021(52)	Belgium, Denmark, Israel, Netherlands, Switzerland	retrospective cohort (abstract)	99 IBD	44 (19-80) ^b	VDZ	joint (peripheral, axial), mucosal, ocular involvement, PSC, EN	12 months
Latras Cortés et al., 2022(53)	Spain	retrospective cohort (abstract)	16 UC	49.74±17.04 ^a	UST	arthritis	17.81 months ±12.57 ^a
Lewis et al., 2020(54)	N/A	prospective cohort (abstract)	5 UC	N/A	tofacitinib	PSC	N/A
Livne-Margolin et al., 2022(80)	Israel	retrospective cohort	58 IBD	43±19 ^a	VDZ	joint, ocular, axial joint involvement, PG, EN	52 weeks

Livne-Margolin et al., 2022(80)	Israel	retrospective cohort	53 IBD	39±15 ^a	UST	joint, ocular, axial joint involvement, PG, EN	52 weeks
Lynch et al., 2019(81)	Europe, North America	retrospective cohort	102 IBD	31.4±14.2 ^a	VDZ	PSC	412 days (37-2609) ^b
Macaluso et al., 2019(55)	Sicily	prospective cohort (abstract)	169 IBD	N/A	VDZ	joint involvement	10 weeks
Macaluso et al., 2020(56)	Italy, Sicily	prospective cohort (abstract)	131 CD	N/A	UST	joint involvement (axial, peripheral)	24 weeks
Narula et al., 2021(99)	North and South America, Asia, Australia, Europe	RCT post hoc analysis	941 CD	38.2±12.8 ^a	UST	joint, ocular involvement, PG, EN	6 weeks
Orlando et al., 2017(97)	Italy	prospective cohort	53 IBD	51.5±15.7 ^a	VDZ	joint involvement	2.6 months±1.6 ^a
Paccou et al., 2019(82)	France	retrospective cohort	171 IBD	37.8±12.9 ^a	VDZ	axial and peripheral joint involvement	14.3 months±12 ^a
Patel et al., 2016(57)	Wisconsin, USA	retrospective cohort (abstract)	40 IBD	N/A	VDZ	joint, mucosal involvement, PG, EN	24 weeks
Peyrin-Biroulet et al., 2019(58)	USA, Europe	RCT post hoc analysis (abstract)	220 CD	N/A	upadacitinib	any type of EIM, joint involvement	16 weeks

Ramos et al., 2021(83)	Connecticut, USA	retrospective cohort	201 IBD	38.4 (29-52.4) ^c	VDZ	skin, mucosal, ocular involvement, peripheral and axial joint involvement	17 months (7- 33) ^c
Reinglas et al., 2019(84)	Canada	retrospective cohort	130 IBD	46 ^d	VDZ	joint, ocular, skin involvement, PSC	12 months
Ritter et al., 2020(59)	N/A	retrospective cohort (abstract)	77 IBD	46±16.2 ^a	VDZ	joint involvement	12 months
Rubin et al., 2021(100)	US, Brazil, Austria, Switzerland	RCT post hoc analysis	902 UC	N/A	tofacitinib	peripheral, axial joint involvement, mucosal, ocular involvement, PG, EN	8 weeks
Scribano et al., 2022(85)	Italy	retrospective cohort	140 CD	45 (36.3-54) ^c	UST	joint involvement (peripheral and axial), EN	52 weeks
Sedano et al., 2022(86)	Canada	retrospective cohort	229 CD	45.8±14.7 ^a	UST	joint involvement	3 months
Shelton et al., 2015(87)	Massachusetts, USA	retrospective cohort	172 IBD	40±13.8 ^a	VDZ	joint involvement, arthritis, PG	14 weeks

Singh et al., 2017(60)	Ohio, USA	retrospective cohort (abstract)	17 CD	38±3.21 ^a	UST	joint, skin involvement	3.5 months
Stallmach et al., 2016(88)	Germany	retrospective cohort	67 CD, 60 UC	CD: 37 (18-75), UC: 40.5 (19-69) ^b	VDZ	joint involvement	54 weeks ^e
Suárez Ferrer et al., 2020(56)	Spain	retrospective cohort (abstract)	31 CD	N/A	UST	joint involvement	N/A
Tadbiri et al., 2017(89)	France	retrospective cohort	294 IBD	39.8±14.0 ^a	VDZ	joint, mucosal, ocular involvement, PG, EN	54 weeks
Tauqir et al., 2022(53)	Great Britain	prospective cohort (abstract)	24 IBD	N/A	VDZ	joint involvement	24 weeks
Traboulsi et al., 2022(90)	USA	retrospective cohort	12 CD	40.5 (29.1-48) ^c	upadacitinib	joint involvement	5.2 months (2.8-6.8) ^c
Truyens et al., 2021(62)	Belgium, Spain	retrospective cohort (abstract)	528 IBD	45.2±15.5 ^a	VDZ	joint, skin, ocular involvement	1 year
Truyens et al., 2021(62)	Belgium, Spain	retrospective cohort (abstract)	328 IBD	44.1±14.8 ^a	UST	joint, skin, ocular involvement	1 year
Tse et al., 2017(63)	N/A	retrospective cohort (abstract)	39 IBD	29 (22-39) ^c	VDZ	PSC	16 months (9-24) ^c
Tzadok et al., 2021(64)	Israel	retrospective cohort (abstract)	46 IBD	N/A	VDZ	any type of EIM	52 weeks
Williamson et al., 2017(65)	Great Britain	prospective cohort (abstract)	11 IBD	27 ^d	VDZ	PSC	206 days (43-90) ^b

Zingone et al., 2020(91)	Italy	retrospective cohort	117 IBD	47 (36-56) ^c	VDZ	peripheral, axial joint involvement, EN	52 weeks
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Abbreviations: IBD- inflammatory bowel disease, CD- Crohn's disease, UC-ulcerative colitis, EIM- extraintestinal manifestation, PSC- primary sclerosing cholangitis, PG- pyoderma gangrenosum, EN- erythema nodosum, N/A- not available, a: mean $\pm$ SD, b: median (range), c: median (IQR), d: mean, e: median, f: range

8.1.2. Primary Outcomes

8.1.2.1. Proportion of New EIMs during Advanced Therapy

A total of 42 studies including 10,826 IBD patients receiving advanced therapy reported on new EIMs. Overall, new EIMs occurred in approximately 8% of patients, and this estimate remained unchanged after sensitivity analysis. Subgroup analysis showed higher rates with VDZ (11%) compared to UST (6%) and TOFA (3%), with a statistically significant difference across all treatments. However, the difference between VDZ and UST was not significant. Overall, substantial heterogeneity was observed across studies. Results are shown in Figure 2.

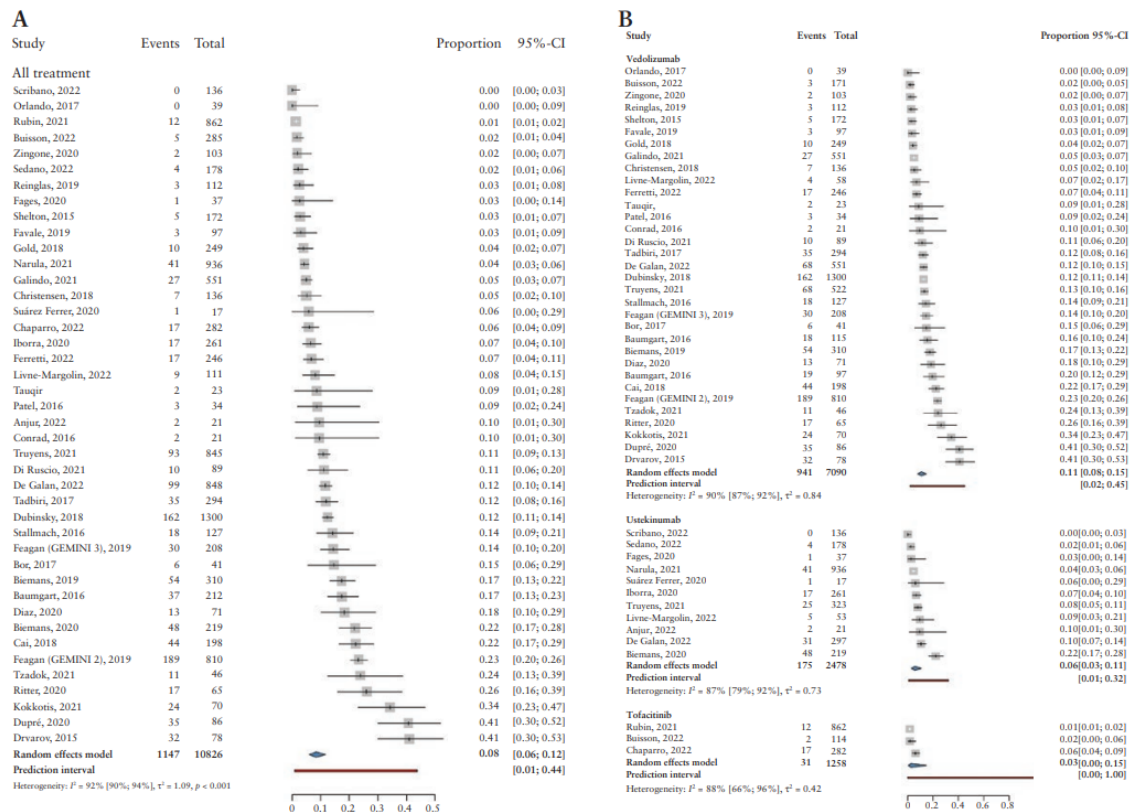


Figure 2. [A]Forest plot demonstrates the proportion of new extraintestinal manifestations [any type] during advanced therapy in patients with IBD. [B]Forest plot demonstrates the proportion of new extraintestinal manifestations [any type] with subgroup analysis based on advanced therapy (vedolizumab or ustekinumab) in patients with IBD.

During advanced therapy, the occurrence of new EIMs varied across organ systems. Joint manifestations were the most frequent, affecting approximately 7–8% of patients, with no significant difference between VDZ and UST. In contrast, new skin and ocular manifestations were rare, each occurring in about 1% of cases, with similar rates across therapies. Stomatitis was reported in around 3% of VDZ-treated patients. Liver manifestations were not observed in the included studies. Overall, no significant differences were found between therapies regarding the development of new EIMs, although heterogeneity across studies was considerable (Figure 3.).

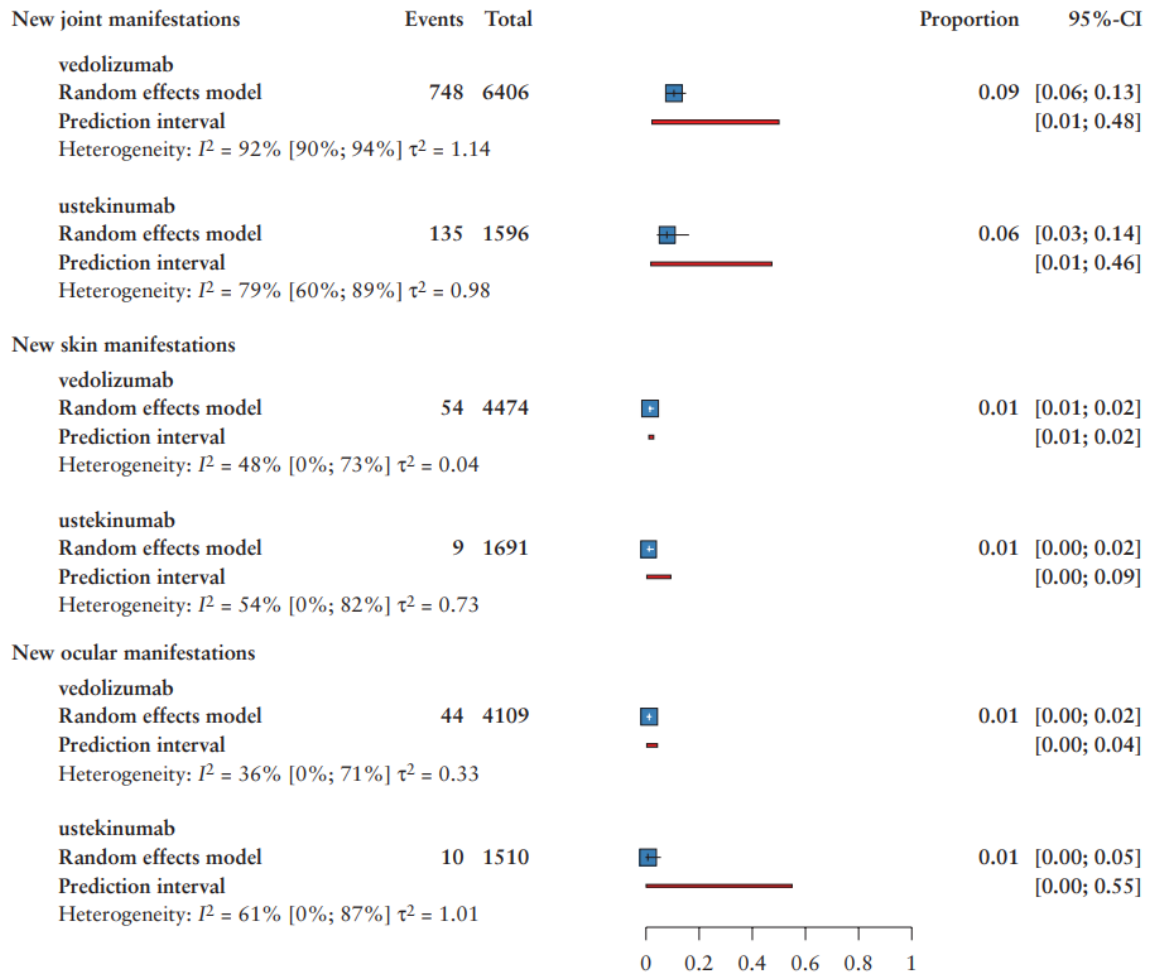


Figure 3. Summary plot demonstrates the proportions of new joint, skin, ocular manifestations with subgroup analysis based on advanced therapy (vedolizumab or ustekinumab).

In a sensitivity analysis excluding studies with a population size of fewer than 10 patients, the proportions of the most frequently reported new joint manifestations remained similar to those observed in the primary analysis, at 9% for vedolizumab and 6% for ustekinumab (Figure 4.).

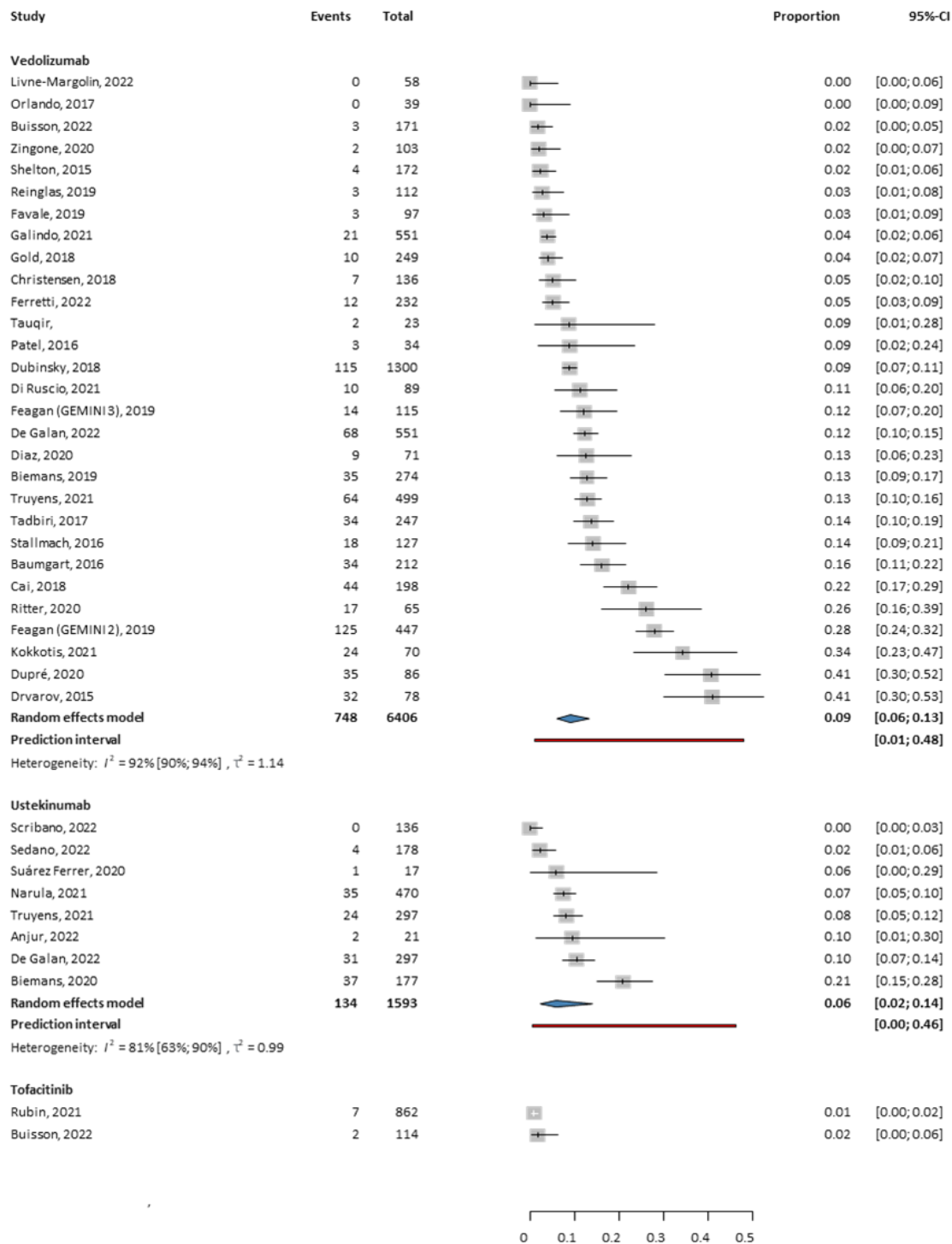


Figure 4. Sensitivity analysis for new joint manifestations during advanced therapy (excluded studies with less than 10 participants)

8.1.3. Secondary Outcomes

8.1.3.1. Change in the Activity of Pre-existing EIMs

Improvement in pre-existing joint manifestations was observed more frequently in patients treated with UST (54%, 95% CI: 42–65%) compared with VDZ (42%, 95% CI: 32–53%; $p=0.029$). Comparable improvement rates were reported for JAK inhibitors, including TOFA (47%) and upadacitinib (48%), although these estimates were associated with substantial heterogeneity (Figure 5.).

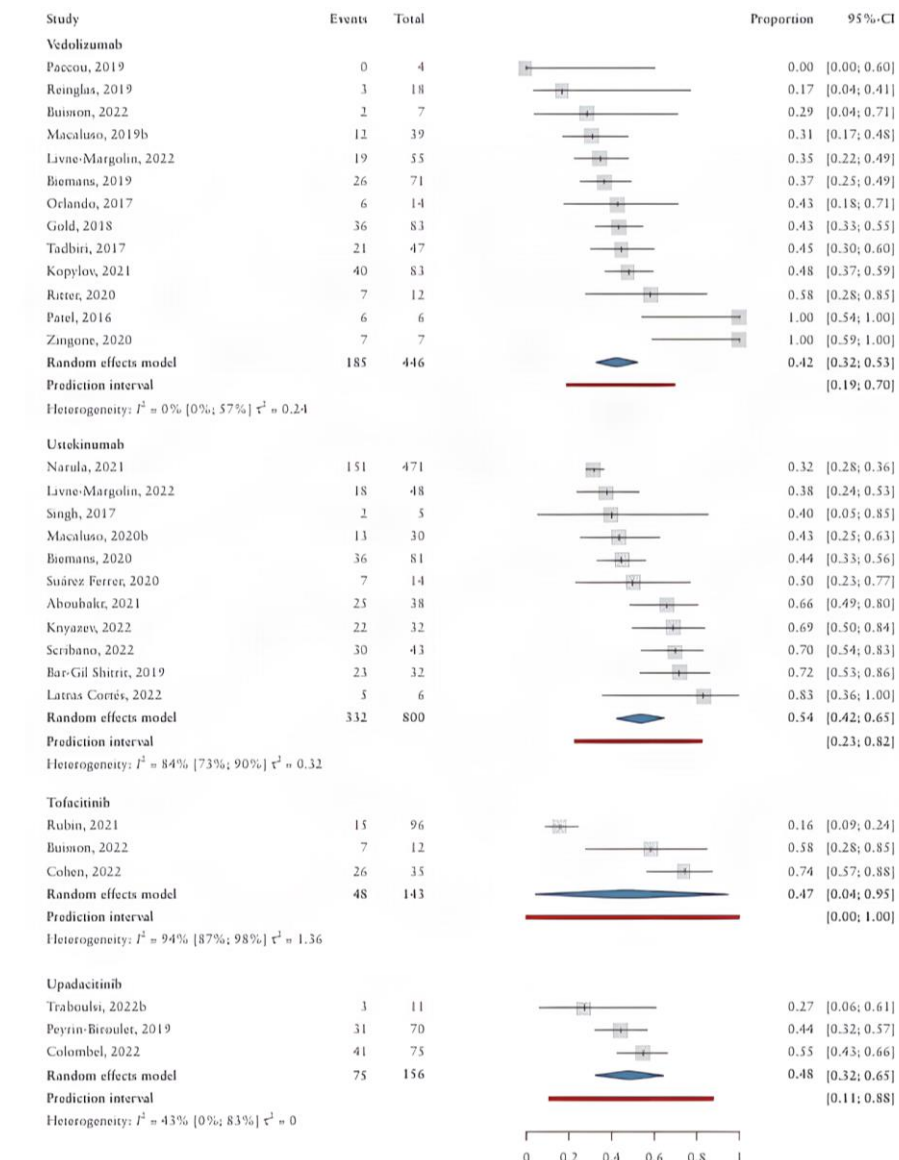


Figure 5. Proportion of improving joint manifestations with subgroup analysis based on advanced therapy.

Subgroup analyses demonstrated that spondyloarthritis improved in 42% of patients receiving VDZ and in 55% of those treated with UST, while improvement was reported in 15 of 96 patients treated with TOFA. Arthralgia improved in 40% and 52% of patients treated with VDZ and UST, respectively ($p=0.039$), with similar trends observed in cohorts receiving JAK inhibitors. Peripheral joint involvement showed relatively high response rates (68% with VDZ), whereas axial manifestations improved less frequently (27% with VDZ and 10% with UST).

Worsening of joint manifestations was significantly more common in the VDZ group compared with the UST group (18% vs 5%, $p=0.032$). In contrast, no statistically significant difference was observed in the worsening of arthralgia between treatment groups. Available data on axial and peripheral joint deterioration were limited but suggested that worsening may occur in a subset of patients, particularly during VDZ therapy (Figure 6.).

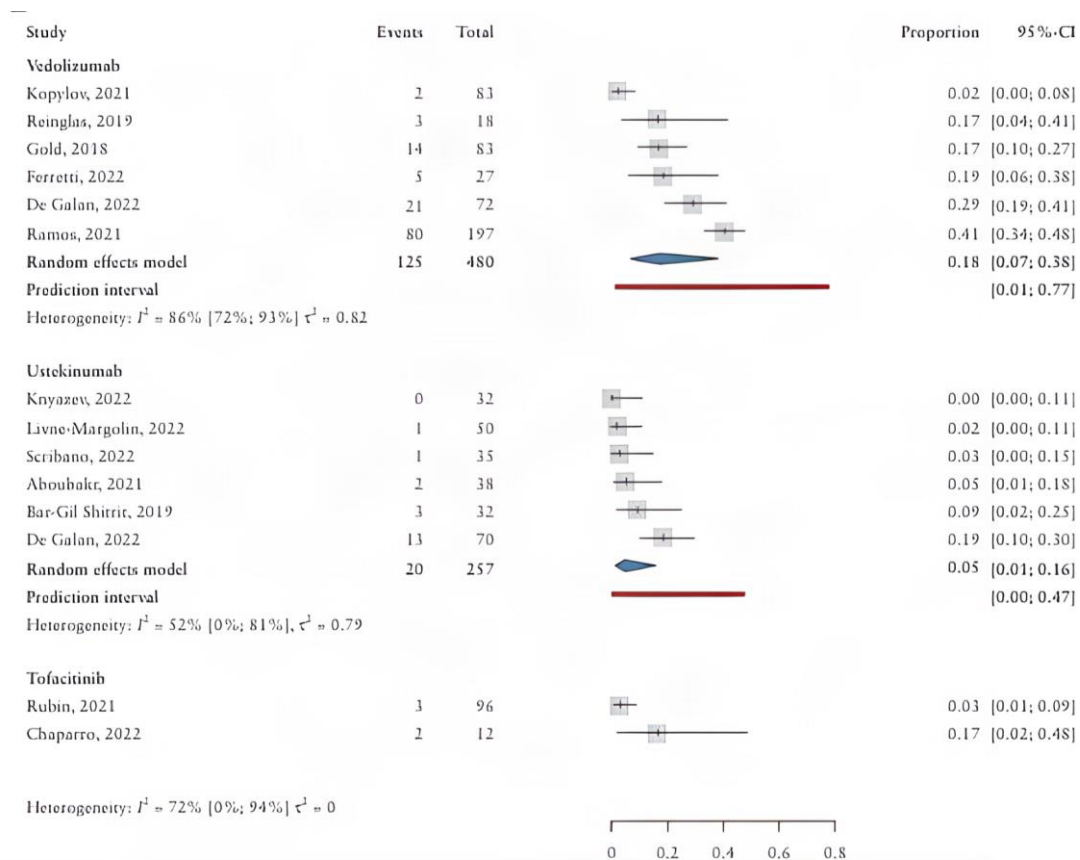


Figure 6. *Proportion of deteriorating joint manifestations with subgroup analysis based on advanced therapy.*

With regard to cutaneous manifestations, no significant difference in improvement rates was identified between VDZ (50%) and UST (61%) ($p=0.469$). EN demonstrated relatively high response rates (62–70%), whereas improvement in PG was less pronounced (25% with VDZ). Worsening skin manifestations were reported in 14% of patients treated with VDZ, while no deterioration was observed in the UST group (Figure 7.A and Figure 7.B).

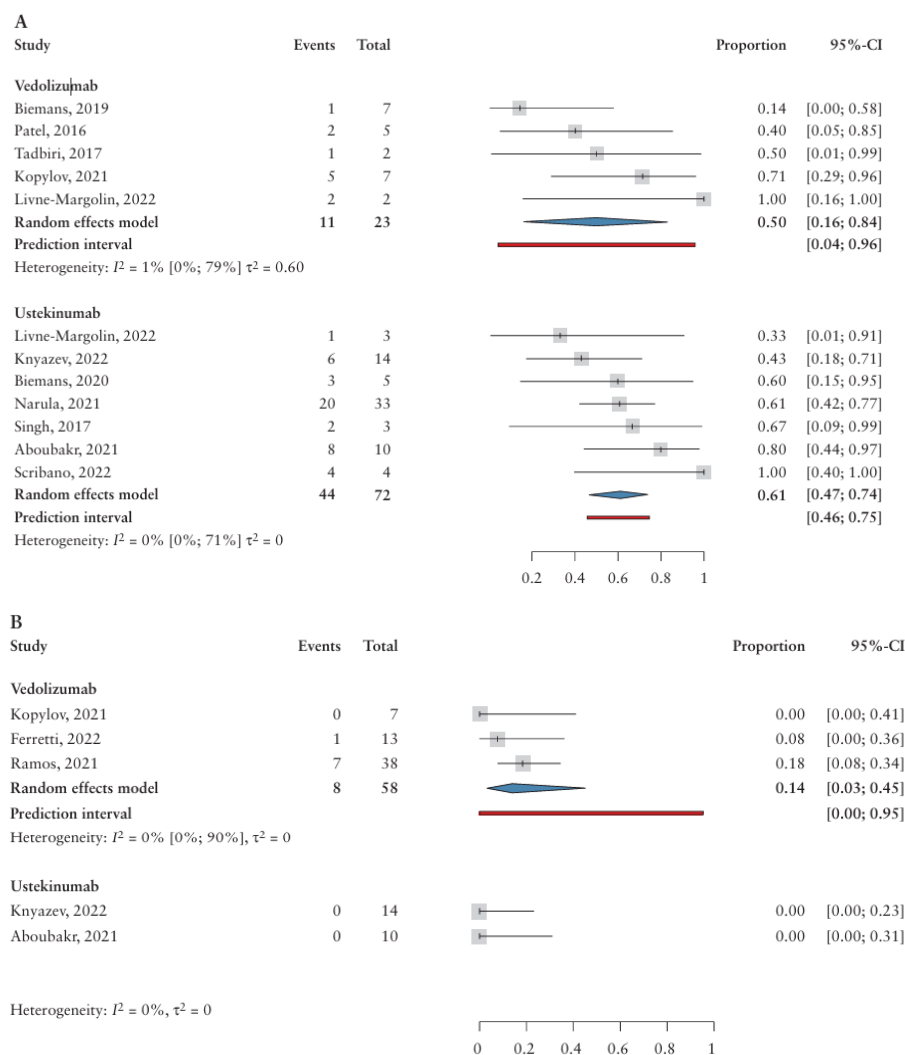


Figure 7. *[A] Proportion of improving skin manifestations with subgroup analysis based on advanced therapy. [B] Proportion of deteriorating skin manifestations with subgroup analysis based on advanced therapy.*

Ocular manifestations improved in 59% of patients receiving UST, with no reported cases of deterioration. Stomatitis showed improvement in 31% of VDZ-treated patients, although sporadic worsening was also described. In patients with PSC, improvement based on liver enzyme changes was observed in 17% of cases, whereas 27% experienced deterioration during VDZ treatment. Limited data from the two TOFA-treated cohorts indicated variable outcomes.

8.1.3.2. Recurrence of EIMs

During VDZ therapy, recurrence of joint manifestations was reported in 44% of patients. Specifically, based on the available evidence from three studies, peripheral spondyloarthritis recurred in 62% of cases.

8.1.4. Risk of Bias Assessment

Among the included studies, one was assessed as having a low risk of bias, 33 as having a moderate risk, and 27 as having a high risk. A low risk of bias was identified when all relevant confounding factors were adequately measured and reported, and when no selective reporting of EIMs was observed. The most common reason for a moderate risk of bias was that potential confounding factors were acknowledged but not properly addressed in the analysis. A high risk of bias was primarily associated with insufficient information on key confounding factors, such as concomitant treatments. Additional contributors to high risk included unclear definitions of EIMs and uncertainty regarding the methods used to determine maximum event values in the statistical analyses (Appendix Table 1).

8.1.5. Quality of Evidence

The quality of the evidence was further assessed using the GRADE framework. Across all examined outcomes, the certainty of evidence was rated as very low. This can be explained by several factors: first, most of the included studies were judged to have a moderate to high risk of bias; second, substantial imprecision due to small sample sizes; and third, considerable inconsistency, as reflected by wide confidence intervals. In

addition, some degree of indirectness was identified, since EIMs were not evaluated as primary outcomes in several studies.

8.2. Study II.

8.2.1. Study Population

Between 1 January 2010 and 31 December 2020, a total of 1,980 patients diagnosed with IBD were registered in the HUPIR database. Of these, 1,590 patients met the inclusion criteria, comprising 951 with CD, 545 with UC, and 94 with IBD-U.

Among patients with CD, 223 individuals (23%) presented with EIMs) at the time of diagnosis, while 685 (72%) did not develop any EIMs during the follow-up period. In the UC cohort, 71 patients (13%) had EIMs at diagnosis, whereas 447 (82%) remained free of EIMs throughout follow-up.

The mean duration of follow-up in the CD group was 3.3 years for patients with EIMs and 3.2 years for those without EIMs. In the UC group, the corresponding mean follow-up times were 3.7 years and 3.3 years, respectively.

BT was administered to a substantial proportion of patients (CD: 294, UC: 75, IBD-U: 12), with the majority receiving anti-TNF agents. A smaller subset of patients was treated with VDZ (10.5%) or UST (2.9%), primarily as second-line therapies.

Baseline demographic and clinical characteristics of the study population are summarized in Tables 2 and 3.

Table 2. 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, localization, 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).

Abbreviations: 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-Pediatric Crohn's Disease Activity Index.

Table 3. 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 ($p < 0.05$).

Abbreviations: 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.

8.2.2. Main Outcomes

8.2.2.1. EIMs at Diagnosis

A total of 309 patients from the registry were included, accounting for 340 EIM events. Musculoskeletal manifestations were the most frequent, affecting 159 patients (CD: 115,

UC: 37, IBD-U: 7). Aphthous stomatitis was documented in 82 cases (CD: 66, UC: 13, IBD-U: 3). PSC was identified in 45 patients (CD: 18, UC: 23, IBD-U: 4), while EN occurred in 44 patients (CD: 36, UC: 6, IBD-U: 2). PG was diagnosed in seven patients (CD: 6, UC: 1), and episcleritis was observed in three patients with CD.

Overall, EIMs were significantly more prevalent in CD than in UC (25.0% vs 14.0%, $p<0.00001$). No association was found between EIM occurrence and either age or sex. Among UC patients, pancolitis was associated with a higher likelihood of EIM development compared with distal colitis ($p=0.019$). Similarly, CD patients with ileocolonic involvement exhibited EIMs more frequently than those with isolated colonic or ileocaecal disease ($p<0.001$). In addition, pediatric CD patients with EIMs were less likely to present with a stricturing phenotype ($p<0.001$).

8.2.2.2. *EIMs during Follow-up*

Seventy-seven patients who developed EIMs during follow-up were excluded from further analyses due to the limited sample size (CD: 43 [55.8%], UC: 27 [35.1%], IBD-U: 7 [9.1%]). Within this subgroup, PSC was diagnosed in nine patients (CD: 1, UC: 7, IBD-U: 1), EN in seven (CD: 3, UC: 2, IBD-U: 1), and PG in one UC patient. Joint manifestations were reported in 51 patients (CD: 30, UC: 15, IBD-U: 6), while aphthous stomatitis occurred in nine CD patients. Notably, 93.5% of these EIMs emerged within two years of IBD diagnosis.

8.2.2.3. *Disease Course in Patients with CD*

- **Gastrointestinal Relapse**

During follow-up, 473 CD patients experienced relapse, including 116 (56.3%) with EIMs and 357 (52.2%) without. Kaplan–Meier analysis demonstrated no significant difference in relapse probability between the groups ($p=0.290$). This was confirmed by Cox regression, which showed no significant association between EIM status and relapse risk (HR 0.892, 95% CI 0.690–1.153; $p=0.383$). However, ileocolonic involvement was independently associated with an increased relapse risk (HR 1.374; 95% CI 1.033–1.828; $p=0.029$).

- Steroid Dependency/Refractoriness

At diagnosis, 34 CD patients with EIMs (16.5%) and 65 without EIMs (9.5%) were classified as steroid-dependent or steroid-refractory. Kaplan–Meier analysis showed that these outcomes occurred significantly earlier in patients with EIMs ($p=0.0047$). In multivariable Cox analysis, EIM presence was associated with a 71% higher hazard of developing steroid dependency or refractoriness (HR 1.710; 95% CI 1.040–2.790; $p=0.033$).

- Biological Therapy

BT was started in 89 CD patients with EIMs (43.2%) and 205 without EIMs (29.9%). Patients with EIMs required BT significantly earlier ($p=0.00049$). Cox regression confirmed a lower hazard of BT initiation in patients without EIMs (HR 0.597; 95% CI 0.445–0.803; $p<0.001$).

As BT may be initiated for EIMs rather than intestinal disease activity-particularly in joint involvement-subgroup analyses were performed, however the reason for BT was not included in the registry survey, that is why we performed a separate analysis. Among 214 CD patients receiving BT, 24 (11.2%) had joint manifestations and 44 (20.6%) had other EIMs. Kaplan–Meier analysis indicated that EIMs, especially non-joint manifestations at diagnosis, were associated with earlier BT initiation ($p<0.0001$), (Figure 8.). However, Cox regression showed no significant differences between patients without EIMs and those with joint involvement (HR 0.759; $p=0.224$), nor between joint and non-joint EIM subgroups (HR 1.483; $p=0.130$). Perianal disease and granuloma presence were significant predictors of BT requirement (HR 3.108; $p=0.003$ and HR 1.410; $p=0.020$, respectively).

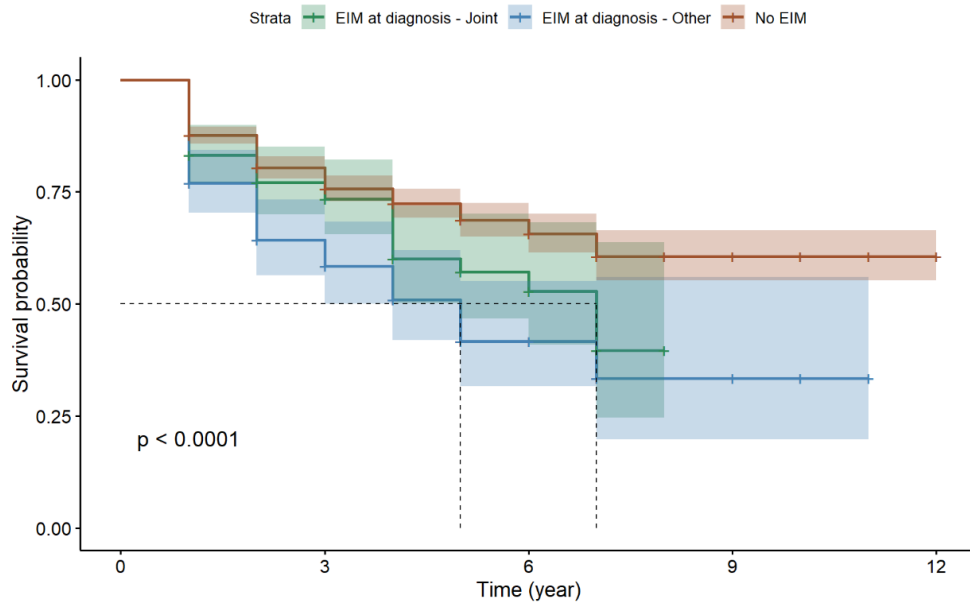


Figure 8. Kaplan-Meier analysis of biological therapy-free survival in Crohn's disease patients stratified by the type of extraintestinal manifestation. EIM-extraintestinal manifestation

- Surgical Procedures

Intestinal resection was performed in 10 patients with EIMs (4.9%) and 98 without EIMs (14.3%). Kaplan–Meier analysis showed that patients without EIMs underwent surgery earlier ($p=0.00037$). Multivariable Cox regression indicated a more than threefold higher hazard of surgery in patients without EIMs (HR 3.2; 95% CI 1.572–6.472; $p=0.001$). Stricturing and penetrating phenotypes, as well as prior BT, were strong predictors of surgery (HR 2.586; $p<0.001$ and HR 3.071; $p=0.008$, respectively). Given the relationship between BT and surgical outcomes, further stratified analysis ($n=891$) examined surgery-free survival. Patients without EIMs who received BT had the lowest surgery-free survival ($p=0.00016$) (Figure 9.). Intermediate risk was observed in patients with EIMs receiving BT and in those without EIMs not receiving BT. The most favorable outcomes were seen in patients with EIMs who did not require BT.

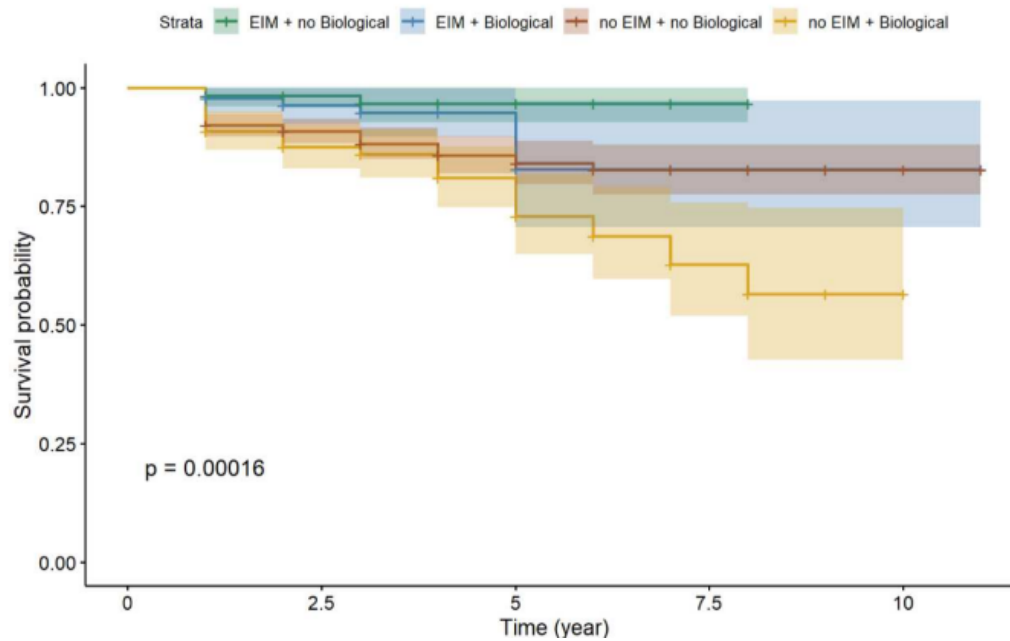


Figure 9. *Kaplan–Meier analysis of resection-free survival in Crohn’s disease patients stratified by biologic therapy. EIM-extraintestinal manifestation*

Kaplan-Meier survival curves are presented in Figure 10., whereas the variables included in the Cox regression analysis, along with their corresponding HRs, are detailed in Table 4.

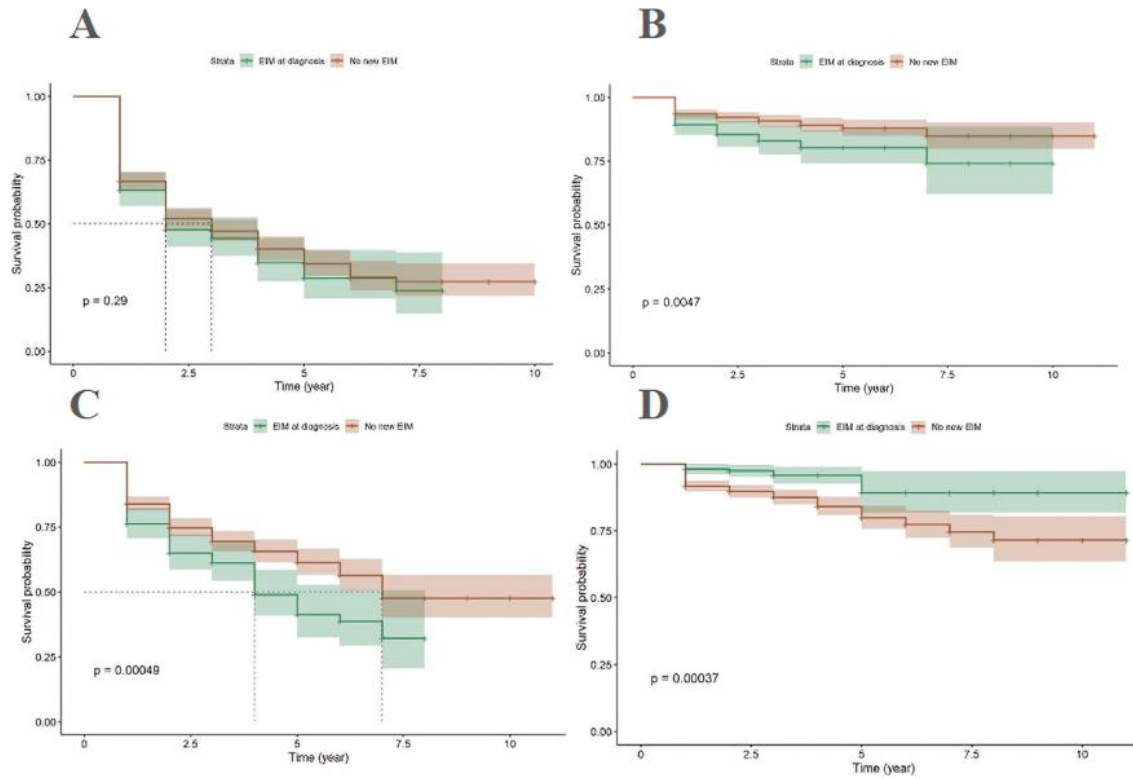


Figure 10. [A] Kaplan-Meier analysis of relapse-free survival in Crohn's disease patients. [B] Kaplan-Meier analysis of steroid dependence-free survival in Crohn's disease patients. [C] Kaplan-Meier analysis of biological therapy-free survival in Crohn's disease patients. [D] Kaplan-Meier analysis of resection-free survival in Crohn's disease patients.

Table 4. HRs of the multivariable Cox regression analyses in patients with CD

	Gastrointestinal relapse	Biological therapy	Surgery	Steroid dependence
Non-EIM	0.892 (0.690–1.153)	0.597 (0.445–0.803)*	3.190 (1.572–6.472)*	0.586 (0.358–0.958)*
Age	1.004 (0.969–1.041)	0.991 (0.948–1.035)	1.085 (0.996–1.181)	1.003 (0.929–1.082)

Female sex	0.990 (0.792–1.237)	0.947 (0.717–1.252)	1.102 (0.702–1.731)	1.139 (0.713–1.818)
Family history	1.022 (0.768–1.358)	0.952 (0.662–1.370)	NA	0.892 (0.465–1.710)
Localization (L3)	1.374 (1.033–1.828)*	1.161 (0.818–1.649)	0.718 (0.439–1.173)	1.718 (0.878–3.359)
Paris phenotype	1.312 (0.907–1.897)	1.299 (0.836–2.018)	2.586 (1.519–4.403)*	1.190 (0.539–2.630)
Perianal involvement	0.793 (0.418–1.507)	3.108 (1.458–6.625)*	2.854 (0.966–8.430)	1.282 (0.579–2.842)
CRP	1.003 (1.000–1.006)*	1.004 (1.001–1.008)*	1.003 (0.998–1.009)	1.004 (0.999–1.010)
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).

Values with * indicate statistically significant results (p<0.05).

Abbreviations: HR-hazard ratio; CD-Crohn's disease; CI-confidence interval; CRP-C-reactive protein; EIM-extraintestinal manifestation; L3-ileocolonic disease, NA-not applicable.

8.2.2.4. Disease Course in Patients with UC

- Gastrointestinal Relapse

Relapse occurred in 322 UC patients, including 40 with EIMs (62.5%) and 282 without (63.2%). Kaplan–Meier analysis showed no difference between groups ($p=0.600$), which was supported by Cox regression (HR 0.990; 95% CI 0.684–1.432; $p=0.956$).

- Steroid Dependency/Refractoriness

Steroid dependency or refractoriness was observed in 11 UC patients with EIMs (17.2%) and 67 without (15.0%). No difference in time-to-event was found ($p=0.890$), and Cox analysis confirmed the lack of association (HR 1.215; 95% CI 0.597–2.473; $p=0.591$).

- Biological Therapy

BT was administered to 15 UC patients with EIMs (23.4%) and 60 without (13.4%). Although there was a trend toward earlier BT use in patients with EIMs, this did not reach statistical significance ($p=0.081$). Cox regression similarly showed a non-significant reduction in BT requirement among patients without EIMs (HR 0.6; $p=0.146$).

- Surgical Procedures

Colectomy was performed in five patients with EIMs (7.8%) and 11 without (2.5%). Kaplan–Meier analysis demonstrated earlier surgery in patients with EIMs ($p=0.032$). However, this association did not remain significant in Cox regression (HR 0.323; 95% CI 0.099–1.051; $p=0.060$). Kaplan-Meier survival curves are presented in Figure 11., whereas the variables included in the Cox regression analysis, along with their corresponding HRs, are detailed in Table 5.

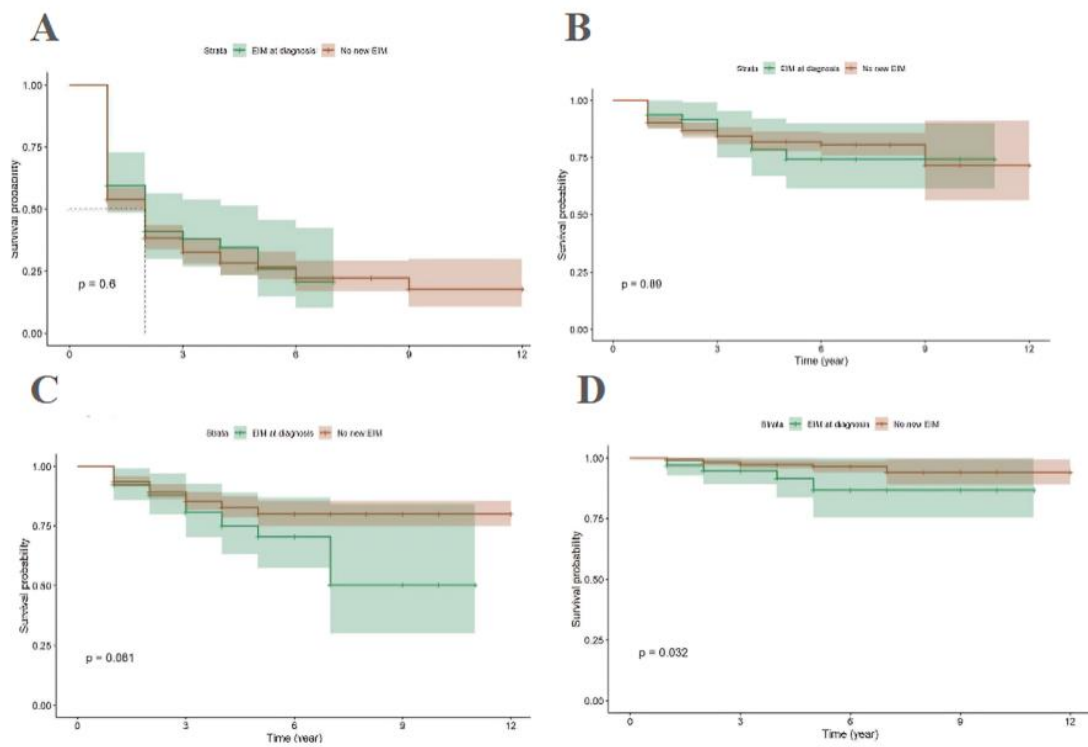


Figure 11. [A] Kaplan Meier analysis of relapse-free survival in ulcerative colitis patients. [B] Kaplan Meier analysis of steroid dependence-free survival in ulcerative colitis patients. [C] Kaplan Meier analysis of biological therapy-free survival in ulcerative colitis patients. [D] Kaplan Meier analysis of resection-free survival in ulcerative colitis patients.

Table 5. HRs of the multivariable Cox regression analyses in patients with UC

	Gastrointestinal Relapse	Biological therapy	Surgery	Steroid dependence
Non-EIM	0.990 (0.684–1.432)	0.621 (0.327–1.180)	0.323 (0.099–1.051)	1.215 (0.597–2.473)
Age	1.007 (0.973–1.042)	0.987 (0.918–1.062)	1.078 (0.906–1.282)	0.983 (0.919–1.051)
Female sex	0.997	0.989	1.009	1.091

	(0.783–1.269)	(0.597–1.639)	(0.353–2.887)	(0.675–1.763)
Family history	0.955 (0.704–1.296)	1.008 (0.518–1.959)	0.695 (0.153–3.151)	0.895 (0.464–1.727)
Localization (E4)	0.573 (0.388–0.846)*	0.714 (0.274–1.860)	0.576 (0.101–3.274)	2.242 (0.654–7.695)
PUCAI	1.012 (1.005–1.019)*	1.023 (1.008–1.039)*	1.001 (0.970–1.034)	1.030 (1.015–1.044)*
CRP	1.001 (0.996–1.006)	1.010 (1.003–1.017)*	1.011 (1.002–1.021)*	1.008 (1.001–1.015)*

Results are expressed as HR (95% CI).

Values with * indicate statistically significant results ($p < 0.05$).

Abbreviations: HR- hazard ratio; UC-ulcerative colitis; CI-confidence interval; CRP-C-reactive protein; PUCAI-Pediatric Ulcerative Colitis Activity Index; EIM-extraintestinal manifestation; E4-pancolitis.

9. DISCUSSION

9.1. Summary of Findings

Study I. In our first study, we aimed to provide a comprehensive overview of the occurrence and clinical course of EIMs during advanced therapies. Overall, the proportion of all new EIMs, as well as each individual EIM, remained low. This trend was consistently observed across all therapeutic subgroups in the subgroup analyses. Notably, similar rates of newly emerging EIMs were identified in patients receiving VDZ and UST, while the lowest occurrence was seen with TOFA, although conclusions regarding TOFA are limited due to the small number of available studies.

When evaluating pre-existing EIMs, no statistically significant differences were observed between VDZ and UST in terms of improvement or worsening, with the exception of joint manifestations. However, given the lack of direct head-to-head comparisons and the substantial heterogeneity among studies, these findings should be interpreted with caution. Evidence regarding TOFA remains scarce but suggests a potentially favourable effect on EIM outcomes.

Joint manifestations have been previously reported in association with both VDZ and UST therapy. Despite the systemic mode of action of UST in contrast to the gut-selective mechanism of VDZ and the established efficacy of UST in psoriatic arthritis, our analysis did not demonstrate any meaningful difference between the two agents in the development of new articular symptoms. These findings are in line with an earlier systematic review suggesting that VDZ does not increase and may even reduce the risk of new EIMs due to better disease control (101). It is also important to consider that the emergence of rheumatic symptoms during the induction period may be influenced by corticosteroid tapering rather than representing true drug-related adverse effects, although this could not be directly assessed in our analysis (102).

Spondyloarthritis represents a heterogeneous spectrum within IBD-related joint involvement. Although separate analyses of axial and peripheral disease, as well as arthralgia, were feasible, the limited available data indicate no clear differences between treatment groups regarding newly developed joint manifestations.

In contrast, differences became apparent when analyzing the course of pre-existing joint EIMs. Patients treated with VDZ showed lower rates of improvement and a higher proportion of worsening compared to those receiving UST.

Previous literature suggests that UST may be effective in peripheral arthritis but less so in axial spondyloarthritis, despite shared pathogenic pathways such as Interleukin-23/T helper 17 signalling (73,103). At the same time, control of intestinal inflammation itself may contribute to improvement in certain joint manifestations, which provides a rationale for the use of VDZ, particularly in peripheral disease linked to intestinal activity (104). In our analysis, VDZ did not appear inferior overall; however, it was associated with less favourable outcomes in terms of improvement and worsening rates across most joint subtypes.

Regarding cutaneous EIMs, no substantial differences were identified between VDZ and UST. Our findings also suggest comparable outcomes between the two therapies in conditions that follow intestinal inflammation such as EN. In contrast to some earlier reports, we did not observe clear inferiority of VDZ in this context, although the available data were limited (104). For PG, which is less closely linked to intestinal disease activity, both treatments showed similar outcomes; however, the small number of cases highlights the importance of individualized therapeutic decision-making. A plausible hypothesis is that EIMs that closely parallel the course of intestinal disease may be more likely to improve as a consequence of effective control of gut inflammation. In contrast, manifestations that evolve independently of intestinal disease activity may be less responsive to gut-selective therapies such as VDZ, potentially requiring treatment approaches with broader systemic immunomodulatory effects.

PSC remains a challenging condition without effective disease-modifying therapy. The studies included in our analysis suggested only modest and inconsistent biochemical improvement during VDZ treatment (81,94). This is somewhat surprising given the strong biological rationale for VDZ in hepatobiliary manifestations, particularly the involvement of the $\alpha 4\beta 7$ integrin–MAdCAM-1 pathway in hepatic lymphocyte trafficking in patients with IBD.

Study II. In our second study, based on a prospective pediatric registry (HUPIR), we examined the prevalence of EIMs and their association with the clinical course of IBD.

We found that pediatric patients with UC and concomitant EIMs had a higher likelihood of requiring surgical intervention compared to those without EIMs, indicating a more severe disease trajectory. In CD, the presence of EIMs was associated with an increased need for BT, although, interestingly, the rate of intestinal surgery was lower in this group.

At diagnosis, approximately one-fifth of our patients presented with EIMs. EIMs were more frequently observed in CD than in UC, in agreement with existing literature (4,105). During follow-up, however, the number of newly diagnosed EIMs was relatively low compared to earlier studies (13,105,106). The reason for this may have been underreporting of cases.

Disease extent and localization appeared to be associated with EIM risk. In UC, pancolitis was associated with a higher likelihood of EIM development compared to limited disease (105). In CD, ileocolonic involvement was linked to increased EIM prevalence, supporting the concept of a location-dependent risk profile, although previous studies have reported conflicting findings (4,11,13,105).

In CD, the presence of EIMs did not significantly affect relapse rates but was associated with earlier initiation of BT and increased corticosteroid dependence or refractoriness. This observation aligns with prior studies suggesting that EIMs themselves may drive treatment escalation (4,106,107). However, findings regarding the overall need for BT remain inconsistent across the literature (13,108).

A particularly notable finding in our cohort was the lower rate of intestinal surgery among CD patients with EIMs, which contrasts with previous reports (4,12). One possible explanation is the earlier introduction of BT in this group, although further analyses suggest that this alone does not fully account for the difference. Another possibility is that the disease localization may also play a role, as colonic involvement—associated with a lower surgical risk—was more common among patients with EIMs. Additionally, stricturing and penetrating disease phenotypes were more prevalent in patients without EIMs, which may partly explain their higher surgical rates in our cohort. In the

multivariate analysis, BT was associated with an increased risk of surgery rather than a protective effect. The reason for that could be that patients requiring BT typically have a more severe disease course and may remain at increased risk of surgery despite advanced treatment.

In UC, the presence of EIMs was consistently associated with indicators of a more severe disease course, including an increased need for colectomy. Although EIMs were not independently associated with earlier initiation of BT in multivariate analysis, multiple complementary analyses suggested a trend towards more intensive treatment in this subgroup. This discrepancy may be partly explained by the limited number of events, which may have restricted the power of the multivariable model to identify an independent association. Importantly, EIMs remained an independent predictor of colectomy, supporting their role as a marker of disease severity.

Finally, our analysis suggested that different types of EIMs may be associated with distinct prognostic implications. In particular, joint manifestations may identify a subgroup of patients at higher risk of an aggressive disease course, however the limited number of events prevented more detailed subgroup analyses. This observation is supported by previous cohort studies demonstrating an association between articular EIMs and worse clinical outcomes (109).

9.2. International Comparisons

Study I. Our findings are broadly consistent with previously published evidence regarding the occurrence of EIMs during advanced therapies, however, to our knowledge, this is the first meta-analysis specifically designed to investigate this question. Earlier systematic reviews, such as that by Chateau et al. (101), have reported that the overall incidence of newly developed EIMs remains relatively low in patients receiving biologics. This is in line with our results, where similarly low rates were observed across all treatment groups, with no significant difference between VDZ and UST. Furthermore, more recently published studies have also reported findings consistent with ours (110,111).

With respect to joint manifestations, the literature remains heterogeneous. Although UST has demonstrated efficacy in psoriatic arthritis due to its systemic mechanism of action, previous comparative studies have described the occurrence of new articular symptoms in patients treated with both VDZ and UST. In agreement with earlier studies, the frequency of newly developed joint EIMs did not show a significant difference between these therapies in our analysis (73,80).

Our observations regarding the course of pre-existing joint manifestations are also supported by prior literature. Several cohort studies have indicated that UST may be beneficial in peripheral arthritis but less effective in axial spondyloarthritis, despite shared pathogenic pathways, as discussed by Feagan et al. (98) and Deodhar et al. (112). At the same time, the importance of intestinal inflammation in driving peripheral joint symptoms has been emphasized by Romano et al. (104), reinforcing the notion that EIMs closely linked to intestinal disease activity may still respond to gut-selective therapies such as VDZ. Nevertheless, our findings—showing lower improvement and higher worsening rates in the VDZ group—are consistent with earlier comparative analyses, including those by Livne-Margolin et al. (80), although these differences did not consistently reach statistical significance. A recent meta-analysis (113), addressing the same research question, reached the same conclusion, further supporting our findings.

Regarding cutaneous EIMs, our results are in line with previous cohort studies. However, it is important to note that cutaneous EIMs were rare across the included cohorts; therefore, both the previous studies and our meta-analysis are limited in their ability to support definitive conclusions. Both Ramos et al. (83) and the OBSERV-IBD study group (89) reported that worsening of pre-existing skin manifestations was uncommon, with most cases remaining stable following VDZ initiation. Similarly, Livne-Margolin et al. (80) found no significant difference between VDZ and UST in terms of deterioration of cutaneous EIMs. While Romano et al. (104) suggested that UST may be more effective in EN, our findings did not confirm this difference, likely due to the limited number of available cases. In the case of PG which is less closely linked to intestinal disease activity, previous reports have demonstrated benefit with UST; however, our results suggest comparable outcomes between therapies, highlighting the need for individualized treatment decisions.

PSC as an EIM in IBD, remains a therapeutic challenge. Consistent with earlier reports, such as those by Christensen et al. (94) and Lynch et al. (81), our findings indicate that VDZ has only a modest and often non-sustained effect on biochemical markers of PSC. Nevertheless, VDZ may still represent a valuable option in patients with IBD and PSC, particularly after liver transplantation, as it allows control of intestinal inflammation without intensifying systemic immunosuppression. Emerging evidence, including recent findings by Schregel et al. (114), suggests that TOFA may improve laboratory parameters such as alkaline phosphatase, which is also reflected in our results, although further research is needed.

Study II. Our findings regarding the prevalence and clinical impact of EIMs in pediatric IBD are largely in agreement with previously published studies. The proportion of patients presenting with EIMs at diagnosis in our cohort is comparable to earlier reported pediatric data (105,115,116). However, the proportion of newly developed EIMs during follow-up in our study was lower than that described in previous cohorts, which may be explained by differences in EIM definition, follow-up duration, study design, or evolving therapeutic strategies (13,105,106).

Consistent with earlier reports, we found that EIMs were more frequently observed in CD than in UC (4,105,106,108,117). The association between disease extent and EIM risk also aligns with prior findings. In UC, pancolitis was associated with EIMs in several studies (105,108,118), which is consistent with our observations. In CD, the relationship between disease localization and EIMs remains controversial; while some studies (13,105,108) did not find a significant association, others, including Vavricka et al. (4) and Duricova et al. (11), reported upper gastrointestinal involvement as a potential risk factor, supporting the concept of a localization-dependent risk profile.

In CD, our finding that patients with EIMs required earlier and more frequent BT is in line with studies by Greuter et al. (106) and Alizadeh et al. (107), who also reported increased use of biologics in this subgroup. This may be partly explained by the observation of Vavricka et al. (4) that BT is often initiated due to EIMs themselves. However, not all studies are consistent; for example, Jansson et al. (13) and Vegh et al. (108) did not observe a significantly increased need for biologics, likely reflecting differences in study populations and treatment availability.

Interestingly, the lower rate of intestinal surgery among CD patients with EIMs in our cohort contrasts with findings from studies by Vavricka et al. (4) and the meta-analysis by Attauabi et al. (12), both of which reported higher surgical risks in patients with EIMs. This discrepancy may be explained by differences in disease phenotype. Consistent with our findings, data from the CEDATA registry (119) demonstrated that colonic disease, which is generally associated with a lower risk of intestinal resection, was more frequently observed in patients with EIMs, whereas stricturing and penetrating disease phenotypes were more common among patients without EIMs.

In UC, our results demonstrating an increased need for colectomy in patients with EIMs are consistent with pediatric cohorts reported by Duricova et al. (11) and Jansson et al. (13), as well as the meta-analysis by Attauabi et al. (12). Although pancolitis was more frequently observed among patients with EIMs in our cohort, and is a recognized predictor of colectomy, multivariable analysis confirmed that EIMs were independently associated with an increased risk of colectomy after adjustment for potential confounders. In contrast, some adult studies, such as those by Vavricka et al. (4) and Vegh et al. (108), did not find a significant association, which may reflect differences in patient populations and treatment strategies. Importantly, our multivariate analysis identified EIMs as an independent predictor of colectomy, a finding also reported by Parragi et al. (120), further supporting their prognostic relevance. Furthermore, pancolitis was more common among patients with EIMs in our cohort, and pancolitis is a recognized predictor of colectomy.

Finally, different EIM subtypes may carry distinct prognostic implications. For example, Hiller et al. (109) reported that joint manifestations were associated with a more severe disease course. However, due to the limited number of events in our analysis, further research is required to better define the prognostic impact of specific EIM categories.

9.3. Strengths

Study I. To the best of our knowledge, this is the first meta-analysis specifically comparing the effects of different non-TNF inhibitor therapies on EIMs in IBD. A further strength is the inclusion of a relatively large number of studies originating from more than 14 countries, enhancing the generalizability and international relevance of the findings.

Importantly, all included studies were published recently, ensuring that the analysis reflects current therapeutic strategies and clinical practice. In addition, this meta-analysis provides a comprehensive evaluation of multiple types of EIMs across different organ systems. The application of detailed subgroup analyses allowed for a more nuanced understanding of treatment effects across therapies and manifestations. Finally, the study is strengthened by the use of a rigorous methodological approach, including systematic data collection and analysis, which supports the robustness and reliability of the results.

Study II. The primary strength of this study lies in its large overall sample size from a nationwide, prospective database with long-term follow-up and the careful selection of patients, which together ensure robust and reliable findings. In addition, this registry reflects real-world clinical practice and enhances the generalizability of the results. Another key strength is that only patients who met the ECCO-defined criteria for EIMs were included, thereby ensuring a high level of consistency and standardization. Furthermore, we performed detailed statistical analyses using Cox proportional hazards regression models to identify factors associated with long-term outcomes. We also analyzed patients with CD and UC separately, allowing for disease-specific evaluation and reducing potential bias arising from the heterogeneity of IBD subtypes. Also, the study focused on clinically relevant outcomes, thereby increasing the practical applicability and clinical significance of the findings.

9.4. Limitations

Study I. This study has several limitations that should be considered when interpreting the results. First, the majority of the included studies were retrospective cohort studies, frequently involving a relatively low number of patients with EIMs, which may limit the robustness of the findings.

In addition, direct head-to-head comparisons between different advanced therapies were largely lacking, restricting the ability to draw definitive conclusions regarding comparative effectiveness. The heterogeneity of follow-up durations across studies may also have influenced the observed cumulative incidence and course of EIMs.

Furthermore, the assessment and reporting of EIMs were not standardized among the included studies, potentially introducing variability and reporting bias. Although EIMs comprise a heterogeneous spectrum of clinically and biologically distinct disorders, subgroup analyses according to individual EIM types could not be performed because of limited statistical power and incomplete data. Finally, detailed data on concomitant medications were not consistently available, and it was not possible to determine whether advanced therapies were used as first- or second-line treatments, both of which may have impacted the outcomes.

Study II. One limitation of the present study is that it constitutes a post hoc analysis based on data derived from a prospective registry. Consequently, certain relevant information, such as the specific indications for therapy, were lacking, which may limit the interpretation of some findings. Furthermore, some subgroups included relatively low patient numbers, and no separate analyses were performed for the different types of EIMs, which might have provided more detailed insights. The relatively low number of surgical events, particularly colectomies in UC, may have limited statistical power.

10. CONCLUSIONS, THESES

Study I. The available evidence indicates that the proportion of newly developing EIMs remains relatively low among patients receiving advanced therapies. Among newly developing EIMs, joint manifestations were the most frequently reported. Moreover, our findings imply that the presence of pre-existing EIMs should not, in itself, lead to deprioritizing VDZ as a treatment option. Better control of intestinal inflammation may contribute to the improvement of certain EIMs that closely parallel intestinal disease activity, thereby providing indirect benefits beyond the gastrointestinal manifestations of the disease. An exception may be considered in cases involving articular manifestations, where greater caution in therapeutic decision-making may be warranted. Overall, worsening of pre-existing EIMs during treatment was uncommon in both groups. While no significant differences were observed between VDZ and UST regarding the development of new EIMs, improvement of existing manifestations appeared to be more frequent among patients receiving UST.

Study II. The prevalence of EIMs at the time of diagnosis (CD: 25%, UC: 14%) was comparable to that reported in previous international cohorts. Joint manifestations were the most common type of EIM, consistent with the existing literature. Moreover, patients with CD who present with EIMs at diagnosis tend to require earlier initiation of BT, while undergoing surgical interventions less frequently; importantly, this difference is not explained by the earlier use of biological treatment. In contrast, in patients with UC, the presence of EIMs at diagnosis appears to be a clear predictor of a more severe disease course.

11. IMPLICATIONS FOR PRACTICE

Study I. Although non-gut-selective therapies are generally preferred in patients with EIMs due to their systemic effects, the findings of the present study suggest that VDZ may also represent a viable therapeutic option in selected patients with concomitant EIMs. In particular, it may be considered in vulnerable patient populations who could benefit from its favourable safety profile, as well as in patients whose EIMs closely follow the intestinal disease activity. However, the available data warrant caution in the case of joint manifestations.

Study II. The results further indicate that the presence of EIMs may be associated with a more complex disease course in IBD. In patients with UC, the presence of EIMs at diagnosis was associated with a less favourable disease course. Therefore, incorporating EIM status into clinical risk assessment may improve early identification of patients at increased risk of adverse outcomes and facilitate timely therapeutic decision-making. In CD, the prognostic significance of EIMs is less well established. However, patients presenting with EIMs required BT earlier during the disease course, suggesting a potentially more aggressive disease phenotype. Furthermore, among patients with EIMs, the need for BT was identified as a predictor of subsequent surgery. Incorporating the presence of EIMs into clinical risk assessment may support more individualized follow-up and management strategies.

12. IMPLICATIONS FOR RESEARCH

In light of the current lack of robust evidence, well-designed comparative randomized clinical trials are required to more precisely address the comparative effectiveness of different advanced therapies for the treatment of EIMs in patients with IBD. In addition, further prospective studies with extended follow-up periods and stratified analyses according to different types of EIMs are warranted to better elucidate the relationship between therapeutic strategies and EIM outcomes. The establishment of prospective registries incorporating detailed documentation of EIMs and advanced therapeutic regimens would also provide valuable real-world evidence. Furthermore, the adoption of a standardized definition of EIMs, as outlined by ECCO, is strongly recommended for future registries and clinical studies in order to enhance methodological consistency and improve comparability across research efforts.

13. IMPLICATIONS FOR POLICY MAKERS

The findings of the present studies have several implications for healthcare policy and clinical guideline development in IBD. First, given the heterogeneous clinical presentation and the potential prognostic relevance of EIMs, healthcare systems should support structured monitoring strategies for patients with EIMs to enable earlier identification of patients at risk for a more complicated disease course. Clinical guidelines should also emphasize the prognostic significance of EIMs present at diagnosis. In UC, the presence of EIMs at diagnosis may identify patients at increased risk of BT initiation and colectomy and in CD, EIMs at diagnosis are associated with an earlier need for BT. Second, therapeutic decision-making frameworks and reimbursement policies should consider that gut-selective therapies, such as VDZ, may represent a safe and appropriate treatment option for selected patients with concomitant EIMs, particularly for vulnerable patient populations in whom safety considerations are of particular importance. Finally, policymakers and research funding bodies should promote the development of prospective registries and high-quality comparative clinical studies with standardized definitions of EIMs, as recommended by the ECCO, in order to generate more robust evidence, improve the comparability of future research, and assess the impact of emerging advanced therapies on individual EIMs. Particular emphasis should be placed on collecting data separately for specific EIMs, given the heterogeneity of these manifestations and the current lack of EIM-specific evidence.

14. FUTURE PERSPECTIVES

The findings of this thesis have important implications for both clinical practice and future research. From a clinical perspective, although non-gut-selective therapies are generally preferred in patients with EIMs, vedolizumab may also represent a viable option in selected cases, particularly in vulnerable patient populations due to its favourable safety profile. Furthermore, the presence of EIMs should be considered in clinical decision-making, as it may indicate a more complex disease course and justify closer monitoring and individualized management strategies.

From a research perspective, further well-designed comparative randomized clinical trials are needed to better evaluate the effects of different advanced therapies on specific types of EIMs. More data are also needed for each EIM separately, as the available evidence remains limited for individual manifestations. Prospective studies with longer follow-up and stratification according to EIM subtypes are also warranted. The development of large, prospective registries with standardized definitions-such as those proposed by ECCO would improve data quality and comparability. Ultimately, integrating these approaches may lead to more precise, evidence-based management of IBD and its EIMs.

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17. ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor, Dr. Müller Katalin Eszter, for her invaluable guidance and continuous support throughout this work. Her expertise, encouragement, and willingness to share her knowledge have greatly contributed to my academic development and to the completion of this thesis.

I am also deeply grateful to all collaborators and colleagues who contributed to this research, as well as to the patients and families who participated in the study.

I would like to thank my family and friends for their unwavering support, encouragement, and understanding during this journey. I am especially grateful to my mother for her constant love, motivation, and belief in me, which have been a strong foundation throughout my life.

Finally, I would like to express my deepest gratitude to my husband for his endless patience, support, and encouragement. His presence and understanding have meant more to me than words can express, both during my academic journey and in everyday life.

APPENDIX

Artificial Intelligence disclosure: The AI tool (OpenAI GPT-5.6 Luna) was used exclusively for language correction and stylistic editing. The content, ideas, and academic arguments are entirely my own, AI was used only to improve the linguistic quality and phrasing of the text.

Appendix Table 1. Risk of bias assessment using the QUIPS tool

Author	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall*
Aboubakr a	Moderate	No information	Moderate	Low	Moderate	Low	High
Aboubakr b	Moderate	No information	Moderate	Low	Moderate	Low	High
Aboubakr c	Moderate	No information	Moderate	Low	Moderate	Low	High
Anjur	Low	Moderate	Low	High	High	Moderate	High
Bacaksiz	Moderate	No information	Low	Low	Moderate	Moderate	High
Bar-Gil Shitrit a	Low	Moderate	Moderate	Moderate	High	Moderate	High
Bar-Gil Shitrit b	Low	Moderate	Moderate	Moderate	High	Moderate	High
Baumgart	Low	Low	Low	Low	Moderate	Low	Moderate
Biemans2020a	Low	Low	Low	Low	Moderate	Low	Moderate
Biemans2020b	Low	Low	Low	Low	Moderate	Low	Moderate
Biemans2019a	Low	Low	Low	Low	Moderate	Low	Moderate
Biemans2019b	Low	Low	Low	Low	Moderate	Low	Moderate
Bor	Low	No information	Low	Low	Moderate	Moderate	Moderate

Buisson a	Low	No information	Low	Low	Moderate	Low	Moderate
Buisson b	Low	No information	Low	Low	Moderate	Low	Moderate
Cai	Low	No information	Low	Low	Moderate	Moderate	Moderate
Caron	Low	No information	Low	Moderate	Moderate	Low	Moderate
Chaparro a	Low	No information	Low	Moderate	Moderate	Moderate	High
Chaparro b	Low	No information	Low	Moderate	Moderate	Moderate	High
Christensen	Low	Low	Low	Low	Moderate	Low	Moderate
Cohen a	Low	No information	Low	Low	Moderate	Low	Moderate
Cohen b	Low	No information	Low	Low	Moderate	Low	Moderate
Colombel	Low	No information	Low	Moderate	Moderate	Moderate	High
Conrad	Low	Low	Low	Low	Moderate	Low	Moderate
De Galan a	Low	No information	Low	Low	Moderate	Low	Moderate
De Galan b	Low	No information	Low	Low	Moderate	Low	Moderate
Di Ruscio a	Low	No information	Low	Low	Moderate	Low	Moderate
Di Ruscio b	Low	No information	Low	Low	Moderate	Low	Moderate

Diaz	Low	No information	Low	Low	Moderate	Low	Moderate
Drvarov	Moderate	No information	Low	Low	High	Moderate	High
Dubinsky	Low	No information	Low	Low	Moderate	Low	Moderate
Dupré	Low	No information	Low	Low	Moderate	Low	Moderate
Fages	Moderate	No information	Low	Moderate	Moderate	Moderate	High
Favale	Low	No information	Low	Low	Moderate	Low	Moderate
Feagan	Low	No information	Low	Low	Moderate	Low	Moderate
Ferretti a	Low	No information	Low	Low	Moderate	Low	Moderate
Ferretti b	Low	No information	Low	Low	Moderate	Low	Moderate
Galindo a	Low	No information	Low	Low	High	Low	High
Galindo b	Low	No information	Low	Moderate	High	Low	High
Galindo c	Low	No information	Low	Moderate	High	Low	High
Gold a	Moderate	No information	Low	Low	High	Moderate	High
Gold b	Moderate	No information	Low	Low	High	Moderate	High

Gold c	Moderate	No information	Low	Low	High	Moderate	High
Iborra a	Low	No information	Low	Low	Moderate	Low	Moderate
Iborra b	Low	No information	Low	Low	Moderate	Low	Moderate
Knyazev	Low	Low	Low	Low	Moderate	Moderate	Moderate
Kokkotis a	Moderate	No information	Low	Low	High	Moderate	High
Kokkotis b	Moderate	No information	Low	Low	High	Moderate	High
Kopylov a	Moderate	No information	Low	Low	High	Moderate	High
Kopylov b	Moderate	No information	Low	Low	High	Moderate	High
Latras Cortés	Low	No information	Low	Low	High	Low	High
Lewis	Low	Moderate	Low	Low	Moderate	Moderate	High
Livne-Margolin a	Low	No information	Low	Low	Moderate	Low	Moderate
Livne-Margolin b	Low	No information	Low	Low	Moderate	Low	Moderate
Livne-Margolin c	Low	No information	Low	Low	Moderate	Low	Moderate
Lynch a	Low	No information	Low	Moderate	High	Low	High
Lynch b	Low	No information	Low	Moderate	High	Low	High
Macaluso2019	Low	Moderate	Low	Low	Moderate	Moderate	High

Macaluso2020	Moderate	Moderate	Low	Low	High	Moderate	High
Narula a	Low	No information	Low	Low	Moderate	Low	Moderate
Narula b	Low	No information	Low	Low	Moderate	Low	Moderate
Orlando a	Low	Moderate	Low	Low	Moderate	Moderate	High
Orlando b	Low	Moderate	Low	Low	Moderate	Moderate	High
Paccou a	Moderate	No information	Low	Low	High	Moderate	High
Paccou b	Moderate	No information	Low	Low	High	Moderate	High
Patel a	Moderate	No information	Low	Low	Moderate	Low	Moderate
Patel b	Moderate	No information	Low	Low	Moderate	Low	Moderate
Peyrin-Biroulet	Moderate	No information	Low	Low	Moderate	Low	Moderate
Ramos	Low	No information	Low	Low	Moderate	Low	Moderate
Reinglas a	Low	No information	Low	Low	Moderate	Low	Moderate
Reinglas b	Low	No information	Low	Low	Moderate	Low	Moderate
Reinglas c	Low	No information	Low	Low	Moderate	Low	Moderate
Ritter a	Moderate	No information	Low	Low	High	Low	High
Ritter b	Moderate	No information	Low	Low	High	Low	High

Rubin a	Low	No information	Low	Low	Low	Low	Low
Rubin b	Low	No information	Low	Low	Low	Low	Low
Rubin c	Low	No information	Low	Low	Low	Low	Low
Scribano a	Low	No information	Low	Low	Moderate	Low	Moderate
Scribano b	Low	No information	Low	Low	Moderate	Low	Moderate
Scribano c	Low	No information	Low	Low	Moderate	Low	Moderate
Sedano	Low	No information	Low	Low	Moderate	Low	Moderate
Shelton	Low	No information	Low	Low	Moderate	Low	Moderate
Singh	Moderate	No information	Low	Low	High	Moderate	High
Stallmach	Low	No information	Low	Low	Moderate	Low	Moderate
Suárez Ferrer a	Moderate	No information	Low	Low	High	Moderate	High
Suárez Ferrer b	Moderate	No information	Low	Low	High	Moderate	High
Tadbiri a	Low	No information	Low	Low	Moderate	Low	Moderate
Tadbiri b	Low	No information	Low	Low	Moderate	Low	Moderate
Tauqir	Moderate	Moderate	Low	Low	High	High	High

Traboulsi	Low	No information	Low	Low	Moderate	Moderate	Moderate
Truyens	Moderate	No information	Low	Low	High	Low	High
Tse a	Moderate	No information	Low	Low	High	Moderate	High
Tse b	Moderate	No information	Low	Low	High	Moderate	High
Tzadok	Moderate	No information	Low	Low	High	Moderate	High
Williamson	Moderate	Moderate	Low	Low	Moderate	Low	High
Zingone a	Low	No information	Low	Low	Moderate	Low	Moderate
Zingone b	Low	No information	Low	Low	Moderate	Low	Moderate
Zingone c	Low	No information	Low	Low	Moderate	Low	Moderate

Appendix Table 2. Investigation of quality of the evidence (GRADE)

Question: Course of extraintestinal manifestations in vedolizumab treated patients

№ of studies	Certainty assessment						Effect			Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)	
New extraintestinal manifestations										
31 ^{5,6,8–10,13,16–22,24–28,31,35,40,42,45,46,50,52,54,55,57,59,61}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	941	7090	event rate 11.0% (0.08 to 0.15)	⊕○○○ Very low
Improvement of pre-existing joint manifestations										
13 ^{6,9,28,32,35,38,40–42,45,46,54,61}	observational studies	serious ^a	serious ^b	serious ^c	serious ^e	none	185	466	event rate 42.0%	⊕○○○ Very low

									(0.32 to 0.53)	
Worsening of pre-existing joint manifestations										
6 ^{17,26,28,32,44,45}	observation al studies	serious ^a	serious ^b	not serious	serious ^c	none	125	480	event rate 18.0% (0.07 to 0.38)	⊕○○○ Very low
Improvement of pre-existing skin manifestations										
5 ^{6,32,35,42,54}	observation al studies	serious ^a	serious ^b	serious ^c	very serious ^f	none	11	23	event rate 50.0% (0.16 to 0.84)	⊕○○○ Very low
Worsening of pre-existing skin manifestations										

3 ^{26,32,44}	observation al studies	serious ^a	serious ^b	not serious	very serious ^f	none	8	58	event rate 14.0% (0.03 to 0.45)	⊕○○○ Very low
New joint manifestations										
28 ^{5,6,9,10,13,17–22,24– 28,31,35,40,42,45,46,50,52,54,55,57,61}	observation al studies	serious ^a	serious ^b	serious ^c	serious ^d	none	748	6406	event rate 9.0% (0.06 to 0.13)	⊕○○○ Very low
New skin manifestations										
11 ^{5,6,16,19,21,25–27,35,50,57}	observation al studies	serious ^a	serious ^b	serious ^c	serious ^d	publication bias strongly suspected ^g	55	4474	event rate 1.0% (0.01	⊕○○○ Very low

									to 0.02)	
New ocular manifestations										
86,19,21,25,27,35,54,57	observation al studies	serious ^a	serious ^b	not serious	very serious ^d	none	44	4109	event rate 1.0% (0 to 0.02)	⊕○○○ Very low
New spondyloarthritis										
75,6,18–20,24,61	observation al studies	serious ^a	serious ^b	not serious	very serious ^f	none	72	762	event rate 6.0% (0.02 to 0.19)	⊕○○○ Very low
New arthralgia										

25 ^{5,6,9,10,13,17,19,21,22,24–28,31,35,40,42,45,46,50,52,54,55,57}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	676	6024	event rate 9.0% (0.06 to 0.13)	⊕○○○ Very low
New peripheral joint involvement										
3 ^{18,20,27}	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	59	718	event rate 12.0% (0.01 to 0.77)	⊕○○○ Very low
New erythema nodosum										
8 ^{5,6,16,19,21,25,27,35}	observational studies	serious ^a	serious ^b	not serious	serious ^d	publication bias strongly suspected ^g	36	3516	event rate 1.0% (0.01	⊕○○○ Very low

									to 0.02)	
New pyoderma gangrenosum										
6 ^{6,19,21,25,27,50}	observation al studies	serious ^a	serious ^b	not serious	serious ^d	none	10	3302	event rate 0.0% (0 to 0.02)	⊕○○○ Very low
New stomatitis										
3 ^{6,21,25}	observation al studies	serious ^a	serious ^b	not serious	serious ^d	none	68	2585	event rate 3.0% (0.01 to 0.09)	⊕○○○ Very low
Improvement of pre-existing spondyloarthritis										

5 ^{6,32,35,41,61}	observation al studies	serious ^a	serious ^b	not serious	very serious ^f	none	31	61	event rate 42.0% (0.02 to 0.95)	⊕○○○ Very low
Improvement of pre-existing arthralgia										
11 ^{6,9,28,32,35,38,40,42,45,46,54}	observation al studies	serious ^a	serious ^b	serious ^c	serious ^d	none	154	385	event rate 40.0% (0.35 to 0.46)	⊕○○○ Very low
Improvement of pre-existing peripheral joint involvement										
3 ^{32,41,61}	observation al studies	serious ^a	serious ^b	serious ^c	very serious ^f	none	15	22	event rate 68.0% (0.23	⊕○○○ Very low

									to 0.94)	
Improvement of pre-existing axial joint involvement										
4 ^{32,35,41,61}	observation al studies	serious ^a	serious ^b	serious ^c	very serious ^f	none	9	19	event rate 27.0% (0 to 1)	⊕○○○ Very low
Worsening of pre-existing arthralgia										
5 ^{17,26,28,32,45}	observation al studies	serious ^a	serious ^b	serious ^c	not serious	none	44	254	event rate 14.0% (0.05 to 0.34)	⊕○○○ Very low
Improvement of pre-existing erythema nodosum										

5 ^{6,32,35,42,54}	observation al studies	serious ^a	serious ^b	not serious	very serious ^f	none	9	15	event rate 62.0% (0.13 to 0.94)	⊕○○○ Very low
Improvement of pre-existing pyoderma gangrenosum										
3 ^{6,35,42}	observation al studies	serious ^a	serious ^b	not serious	very serious ^f	none	2	8	event rate 25.0% (0.01 to 0.92)	⊕○○○ Very low
Improvement of pre-existing stomatitis										
4 ^{6,32,42,54}	observation al studies	serious ^a	serious ^b	serious ^c	very serious ^f	none	4	31	event rate 31.0%	⊕○○○ Very low

									(0 to 0.99)	
Improvement of pre-existing primary sclerosing cholangitis										
5 ^{11,32,36,58,60}	observational studies	serious ^a	serious ^b	not serious	very serious ^f	none	35	211	event rate 17.0% (0.08 to 0.33)	⊕○○○ Very low
Worsening of pre-existing primary sclerosing cholangitis										
3 ^{32,36,58}	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	49	146	event rate 27.0% (0.05 to 0.71)	⊕○○○ Very low
Recurrence of joint involvement										

4 ^{18,31,41,61}	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	26	59	event rate 44.0% (0.25 to 0.64)	⊕○○○ Very low
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Explanations

- a. Serious risk of bias because of confounding factors.
- b. The confidence intervals (CI) varied widely, some studies reported higher proportions where the CI-s did not overlap.
- c. Assessment of extraintestinal manifestations is not a primary outcome in all studies.
- d. Confidence intervals are wide.
- e. The imprecision is serious because of the small number of patients.
- f. The imprecision is very serious because of the very small sample size.
- g. The funnel plot assessment showed publication bias.

Appendix Table 3. Investigation of quality of the evidence (GRADE)

Question: Course of extraintestinal manifestations in ustekinumab treated patients

№ of studies	Certainty assessment						Effect			Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)	
New extraintestinal manifestations										
11 ^{2,7,17,23,29,35,39,48,49,53,57}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	175	2478	event rate 6.0% (0.03 to 0.11)	⊕○○○ Very low
New joint manifestations										
9 ^{2,7,17,35,39,48,49,53,57}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	135	1596	event rate 6.0% (0.03 to 0.14)	⊕○○○ Very low
New skin manifestations										

67,23,35,39,48,57	observational studies	serious ^a	serious ^b	not serious	serious ^d	none	9	1691	event rate 1.0% (0 to 0.02)	⊕○○○ Very low
New ocular manifestations										
47,35,39,57	observational studies	serious ^a	serious ^b	not serious	serious ^d	none	10	1510	event rate 1.0% (0 to 0.05)	⊕○○○ Very low
Improvement of pre-existing joint manifestations										
111,4,7,30,33,35,38,39,48,51,53	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	332	800	event rate 54.0% (0.42 to 0.65)	⊕○○○ Very low
Worsening of pre-existing joint manifestations										
61,4,17,30,35,48	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	20	257	event rate 5.0% (0.01 to 0.16)	⊕○○○ Very low

Improvement of pre-existing skin manifestations										
7 ^{1,7,30,35,39,48,51}	observational studies	serious ^a	serious ^b	serious ^c	very serious ^e	none	44	72	event rate 61.0% (0.47 to 0.74)	⊕○○○ Very low
New arthralgia										
8 ^{7,17,35,39,48,49,53,57}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	133	1575	event rate 6.0% (0.02 to 0.16)	⊕○○○ Very low
New erythema nodosum										
5 ^{7,23,35,39,48}	observational studies	serious ^a	serious ^b	not serious	serious ^d	none	7	1358	event rate 1.0% (0 to 0.04)	⊕○○○ Very low
Improvement of pre-existing spondyloarthritis										

4 ^{33,35,38,48}	observational studies	serious ^a	serious ^b	serious ^c	very serious ^e	none	18	33	event rate 55.0% (0.28 to 0.78)	⊕○○○ Very low
Improvement of pre-existing arthralgia										
10 ^{1,4,7,30,35,38,39,48,51,53}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	314	767	event rate 52.0% (0.4 to 0.64)	⊕○○○ Very low
Improvement of pre-existing axial joint involvement										
3 ^{35,38,48}	observational studies	serious ^a	serious ^b	not serious	very serious ^e	none	3	9	event rate 10.0% (0 to 1)	⊕○○○ Very low
Worsening of pre-existing arthralgia										
6 ^{1,4,17,30,35,48}	observational studies	serious ^a	serious ^b	serious ^c	very serious ^e	none	20	257	event rate 5.0%	⊕○○○ Very low

									(0.01 to 0.16)	
Improvement of pre-existing erythema nodosum										
3 ^{7,39,48}	observational studies	serious ^a	serious ^b	not serious	very serious ^c	none	26	37	event rate 70.0% (0.33 to 0.92)	⊕○○○ Very low
Improvement of pre-existing ocular manifestations										
4 ^{1,7,35,39}	observational studies	serious ^a	serious ^b	not serious	very serious ^c	none	20	34	event rate 59.0% (0.32 to 0.81)	⊕○○○ Very low

Explanations

- a. Serious risk of bias because of confounding factors.
- b. The confidence intervals (CI) varied widely, some studies reported higher proportions where the CI-s did not overlap.
- c. Assessment of extraintestinal manifestations is not a primary outcome in all studies.

- d. Serious imprecision because of the small number of patients.
- e. Very serious imprecision because of the very small sample size.

Appendix Table 4. Investigation of quality of the evidence (GRADE)

Question: Course of extraintestinal manifestations in tofacitinib treated patients

№ of studies	Certainty assessment						Effect			Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)	
New extraintestinal manifestations										
3 ^{9,12,47}	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	31	1258	event rate 3.0% (0 to 0.15)	⊕○○○ Very low
Improvement of pre-existing joint manifestation										
3 ^{9,14,47}	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	48	143	event rate 47.0% (0.04 to 0.95)	⊕○○○ Very low

Explanations

- a. Serious risk of bias because of confounding factors.
- b. The confidence intervals (CI) varied widely, some of the studies reported higher proportions where the CI-s did not overlap.
- c. Serious imprecision because of the very small sample size.

Appendix Table 5. Investigation of quality of the evidence (GRADE)

Question: Course of extraintestinal manifestations in upadacitinib treated patients

№ of studies	Certainty assessment						Effect			Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)	
Improvement of pre-existing joint manifestations										
3 ^{15,43,56}	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	75	156	event rate 48.0% (0.32 to 0.65)	⊕○○○ Very low

Explanations

- a. Serious risk of bias because of confounding factors.
- b. Confidence intervals are wide.
- c. Assessment of EIMs is not necessarily a primary outcome.
- d. Serious imprecision because of the very small sample size.

Beyond the Gut: A Systematic Review and Meta-analysis of Advanced Therapies for Inflammatory Bowel Disease-associated Extraintestinal Manifestations

Ágnes Eszter Tímár,^{a,b} Andrea Párniczky,^{a,b} Kinga Anna Budai,^{b,c} Márk Viktor Hernádfői,^{b,d} Emese Kasznár,^b Péter Varga,^{b,e} Péter Hegyi,^{b,f,g} Szilárd Váncsa,^{b,f,g} Réka Tóth,^b Dániel Sándor Veres,^{b,h} Miklós Garami,^{b,i} Katalin Eszter Müller^{a,b,j}

^aHeim Pál National Pediatric Institute, Budapest, Hungary

^bCentre for Translational Medicine, Semmelweis University, Budapest, Hungary

^cUniversity Pharmacy Department of Pharmacy Administration, Semmelweis University, Budapest, Hungary

^dBethesda Children's Hospital, Budapest, Hungary

^eDepartment of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary

^fInstitute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary

^gInstitute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary

^hDepartment of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary

ⁱPediatric Center, Semmelweis University, Budapest, Hungary

^jDepartment of Family Care Methodology, Faculty of Health Sciences, Semmelweis University, Budapest, Hungary

Corresponding author: Katalin Eszter Müller, MD, PhD, Heim Pál National Pediatric Institute, H-1089 Budapest, Üllői út 86, Hungary. Tel: +36-1-459-9100/1214;

E-mail: muller.katalin.eszter@gmail.com

Abstract

Background and Aims: Extraintestinal manifestations are frequent in patients with inflammatory bowel disease and have a negative impact on quality of life. Currently, however, there is no evidence available to determine which drug should be recommended for these patients beyond anti-tumour necrosis factor (anti-TNF) treatment. We aimed to analyse the frequency of new extraintestinal manifestations and the behaviour of pre-existing extraintestinal manifestations during advanced therapy.

Methods: We conducted a systematic search on November 15, 2022, and enrolled randomized controlled trials, cohorts, and case series reporting the occurrence and behaviour of extraintestinal manifestations in patients with inflammatory bowel disease receiving advanced therapy [non-TNF inhibitor biologicals and JAK inhibitors]. Proportions of new, recurring, worsening, and improving extraintestinal manifestations were calculated with 95% confidence intervals [CIs]. The risk of bias was assessed with the QUIPS tool.

Results: Altogether, 61 studies comprising 13,806 patients reported eligible data on extraintestinal manifestations. The overall proportion of new extraintestinal manifestations was 8% [95% CI, 6–12%] during advanced therapy. There was no significant difference between the frequency of new extraintestinal manifestations during vedolizumab and ustekinumab therapy [11%, 95% CI, 8–15% vs 6%, 95% CI, 3–11%, $p = 0.166$]. The improvement of pre-existing manifestations was comparable between vedolizumab- and ustekinumab-treated patients, except for joint involvement [42%, 95% CI, 32–53% vs 54%, 95% CI, 42–65%, $p = 0.029$].

Conclusion: The proportion of new extraintestinal manifestations was low during advanced therapy. Furthermore, the improvement of pre-existing manifestations was comparable between advanced therapies, except for pre-existing joint manifestations.

Key Words: Extraintestinal manifestations; biological products; inflammatory bowel disease

1. Introduction

Inflammatory bowel disease [IBD], encompassing Crohn's disease [CD] and ulcerative colitis [UC], is a chronic, relapsing–remitting disorder of the gastrointestinal tract.¹

IBD mainly affects the intestines, but it can induce immune-mediated conditions outside of the gastrointestinal system. Extraintestinal manifestations [EIMs] most frequently occur in joints, eyes, skin, and liver. The reported pooled prevalence of EIMs varies between 10 and 25% at the time of IBD diagnosis.^{2–4} However, approximately half of the patients experience at least one EIM during the disease course.⁵

The presence of EIMs contributes significantly to morbidity and reduced quality of life, being often more debilitating to the patients than the IBD itself. Hence, it is highly important to consider them when deciding on therapy.^{4,6–8} Some EIMs (e.g. erythema nodosum [EN], aphthous stomatitis) follow the intestinal disease activity, tending to occur during intestinal flare-ups, and usually improve when the intestinal inflammation is appropriately controlled. However, some EIMs (e.g. pyoderma gangrenosum [PG] and primary sclerosing cholangitis [PSC]) are independent of the intestinal disease activity. Therefore, the successful treatment of intestinal inflammation will not always be sufficient to control all EIMs.⁴

The advent of anti-tumour necrosis factor-alpha [anti-TNF] drugs has revolutionized the management of IBD. These drugs have also been indicated in most EIMs [axial and peripheral arthritis, ocular manifestations].⁵ However, approximately one-third of patients experience loss of response and hence require advanced therapy.⁹ Currently, there are several novel drugs [e.g. biologicals, small molecules] with promising results regarding IBD treatment beyond anti-TNFs. Guidelines mostly recommend these new agents as second-line therapies.^{10,11} It is a burning question for IBD experts what to prioritize when choosing new medications. The choice of advanced therapy is based on potential side effects, rapidity of action, concomitant diseases and medications, and presence of EIMs. Furthermore, patient adherence and preference, availability, and cost may also influence the final decision.¹²

The problem of EIMs, however, may be more complex. Usually, vedolizumab [VDZ], a gut-selective alpha4-beta7 integrin antagonist, is considered less beneficial in case of EIMs. Moreover, Dubinsky *et al.* have suggested that VDZ may increase the risk for *de novo* EIMs.¹³

Still, patients with EIMs that follow the disease activity may respond to VDZ. Therefore, it remains an open question as to whether VDZ should be underprioritized in all type of EIMs. Additionally, newly occurring arthralgia has also been reported in psoriatic patients receiving ustekinumab [UST], a monoclonal antibody against the p40 subunit of IL-12 and IL-23.^{14,15} It is unclear whether tofacitinib [TOFA] or UST are effective in the control of all types of EIMs. The non-selective JAK inhibitor, TOFA, was approved for rheumatoid arthritis and psoriatic arthritis.¹⁶ UST, which is a monoclonal antibody against the p40 subunit of IL-12 and IL-23 is recommended in psoriatic arthritis.¹⁷ Furthermore, UST may be effective for peripheral arthritis and skin manifestation EIMs but not in axial spondyloarthritis [SpA].¹⁸

Here we aimed to analyse the frequency of new EIMs and the improvement and deterioration of pre-existing EIMs in IBD patients receiving various advanced therapies.

2. Materials and Methods

Our systematic review and meta-analysis was reported according to the recommendations of the PRISMA 2020 [Preferred Reporting Items in Systematic Reviews and Meta-Analysis] statement,¹⁹ while following the Cochrane Handbook.²⁰ The study protocol was registered with the National Institute for Health Research PROSPERO system [CRD42022366812] and we adhered to it.

2.1. Eligibility criteria

The study population was defined as patients with IBD who were treated with advanced therapy, regardless of their age. Advanced therapy included non-TNF inhibitor [TNFi] biologics [VDZ, UST, mirikizumab, etrolizumab] or oral small molecules [TOFA, upadacitinib, filgotinib, ozanimod]. Our primary outcome was the frequency of new EIMs during advanced therapies. Secondary outcomes were improvement, resolution, or deterioration and reoccurrence of pre-existing EIMs in patients receiving advanced therapies. We included the following EIMs based on the 6th ECCO [European Crohn's and Colitis Organisation] scientific workshop: joint involvement, skin manifestations [EN, PG], liver diseases [PSC], and mucosal and ocular EIMs.⁵ Joint involvement is heterogeneous in IBD and can be

classified based on the presence or absence of inflammation [arthritis or arthralgia] and on the location [axial or peripheral]. Thus, we collected data on overall joint involvement and separately on SpA, peripheral and axial joint involvement, and arthralgia [defined as joint pain in the absence of clinical inflammatory arthritis]. Randomized controlled trials, non-randomized controlled trials and post-hoc analyses that assessed the frequency of EIMs during advanced therapy were included for the analysis. Similarly, prospective and retrospective cohort studies and case series reporting on EIMs occurring during advanced treatment were included. We also included conference abstracts which reported on EIMs observed during advanced therapy. Case reports were excluded.

2.2. Information sources

The systematic search was conducted on November 15, 2022, in four databases: EMBASE, MEDLINE [via PubMed], Cochrane Central Register of Controlled Trials [CENTRAL], and Web of Science. Citationchaser²¹ was used to identify relevant studies from the reference lists of the eligible studies and from the citing studies.

2.3. Search strategy

Our search query consisted of three domains, explaining IBD, the applied drug type, and EIMs. The detailed search key can be found [Supplementary Table S1](#). No limits were applied regarding the publication period. No language or other restrictions were applied during the search.

2.4. Selection process

The studies were imported into reference management software [EndNote 20, Clarivate Analytics]. After automatic and manual duplicate removal, three independent authors performed the title–abstract selection [ÁT, KB, and EK]. The full texts were screened by two investigators [ÁT, KB]. All disagreements were resolved by discussion with a third author [MH]. We calculated Cohen's kappa coefficient after each selection phase.

2.5. Data collection process

Two independent researchers [ÁT, KB] extracted data from the eligible studies in an Excel [Office 365, Microsoft] data collection form. Any questions and differences related to the data extraction were settled by discussion.

2.6. Data items

The following data were extracted from the studies: first author, year of publication, digital object identifier, study design, study period, country, number of participating centres, total number of patients, age of the population, sex distribution, IBD type, duration of IBD, concomitant treatment, proportion of bio-experienced patients, type and number of EIMs at inclusion, type and number of new EIMs, number of patients with worsening, improving/resolving EIM, recurring EIM, and follow-up time.

EIM designations from individual studies were grouped into 'domains' according to pathomechanisms and affected organs; we also analysed individual designations where possible. The four possible outcomes per domain were: new occurrence, recurrence, worsening, and resolution or improvement. The occurrence of new EIMs was also analysed, with all EIM types considered.

2.7. Study risk of bias assessment

Two investigators [ÁT, KB] independently performed the risk of bias assessment for each study using the Quality in Prognostic Studies [QUIPS] tool.²² Any disagreements were resolved by discussion with a third author [MH]. The overall risk of bias was categorized as ‘low’, ‘moderate’, or ‘high’. The six items of QUIPS were evaluated, and an overall bias assessment was conducted based on [1] study participation, [2] study attrition, [3] prognostic factor measurement, [4] outcome measurement, [5] study confounding, and [6] statistical analysis and reporting.

2.8. Certainty assessment

The quality of evidence was evaluated based on the criteria of Grading of the Recommendations Assessment, Development, and Evaluation [GRADE] method.²³ The certainty-level assessment was performed by two independent researchers [ÁT, KB], and disagreements were resolved by consensus and discussion with a third investigator [MH]. Each outcome was rated for the risk of bias, inconsistency, indirectness, imprecision, and publication bias. The final certainty of evidence was categorized as ‘very low’, ‘low’, ‘moderate’, or ‘high’.

2.9. Synthesis methods

Proportions were pooled with 95% confidence intervals [CIs] irrespective of follow-up time using a random effects model.

To meta-analyse the frequency of EIMs independently of treatment, we added together events and totals for patients from the same study receiving different treatments and pooled these proportions along with those from studies examining one treatment.

Only subgroup pools per drug with CIs and prediction intervals were reported from a mixed-effects model, without the overall pool. If there were fewer than three studies in a domain and subgroup, the study effects were visualized without pooling. Between-study heterogeneity and variance were described by Higgins and Thompson’s I^2 statistics²⁴ and τ^2 value. Meta-analysis findings were visualized on forest plots.

If multiple drugs had pooled proportions [i.e. if there were at least three studies in at least two subgroups], a ‘Cochran’s Q’ test for subgroup differences was performed at the 5% significance level.²⁵ If possible, a Q-test comparing only VDZ and UST was also performed. Some studies appeared in two subgroups. In such cases, we analysed each study in its original form, as well as applying a leave-one-out approach to both options. If there were more such studies, a multivariate meta-analysis was performed following Viechtbauer²⁶ with drugs as moderators and studies as outer factors. For further description, see the [Supplementary Material](#) [Detailed statistical methods].

Small study publication bias was assessed by visual inspection of funnel-plots and Peters test for proportions.²⁷ We assumed possible small study bias if the p -value was <10% [considering that the tests have limited diagnostic assessment below ten studies]. Funnel-plots with at least ten studies are shown in the [Supplementary Material](#) [Detailed statistical methods].

Due to the low total number of patients for many outcomes, a sensitivity analysis excluding totals below ten was performed. As a sensitivity analysis, we excluded studies published only as abstract and those with high risk of bias, provided that after the exclusion there were at least three studies remaining.

We reported the results as: point estimate [lower limit of 95% CI – upper limit of 95% CI]. All statistical analyses were made with R [R Core Team 2023, v4.2.3] using the meta²⁸ [v6.2.1] and dmetar²⁹ [v0.0.9000] packages for meta-analysis and influential analysis, and the metafor³⁰ [v4.0.0] package for multivariate analysis.

Additional details are available in the [Supplementary Material](#) [Detailed statistical methods].

2.10. Ethical approval

No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct, or interpretation of our study.

2.11. Data availability statement

All data relevant to the study are included in the study or have been uploaded as online supplementary information. The data supporting this systematic review and meta-analysis are from previously reported studies, which have been cited. The processed data are available in the paper and the [Supplementary Material](#).

3. Results

3.1. Study selection

During the systematic search, 13 544 records were identified, and after duplicate removal 10 987 studies were screened during the selection process. After title and abstract selection [Cohen’s kappa 0.82], we found 61 eligible studies during the full-text selection [Cohen’s kappa 0.85], out of which 55 were included in the quantitative analysis [[Figure 1](#)].

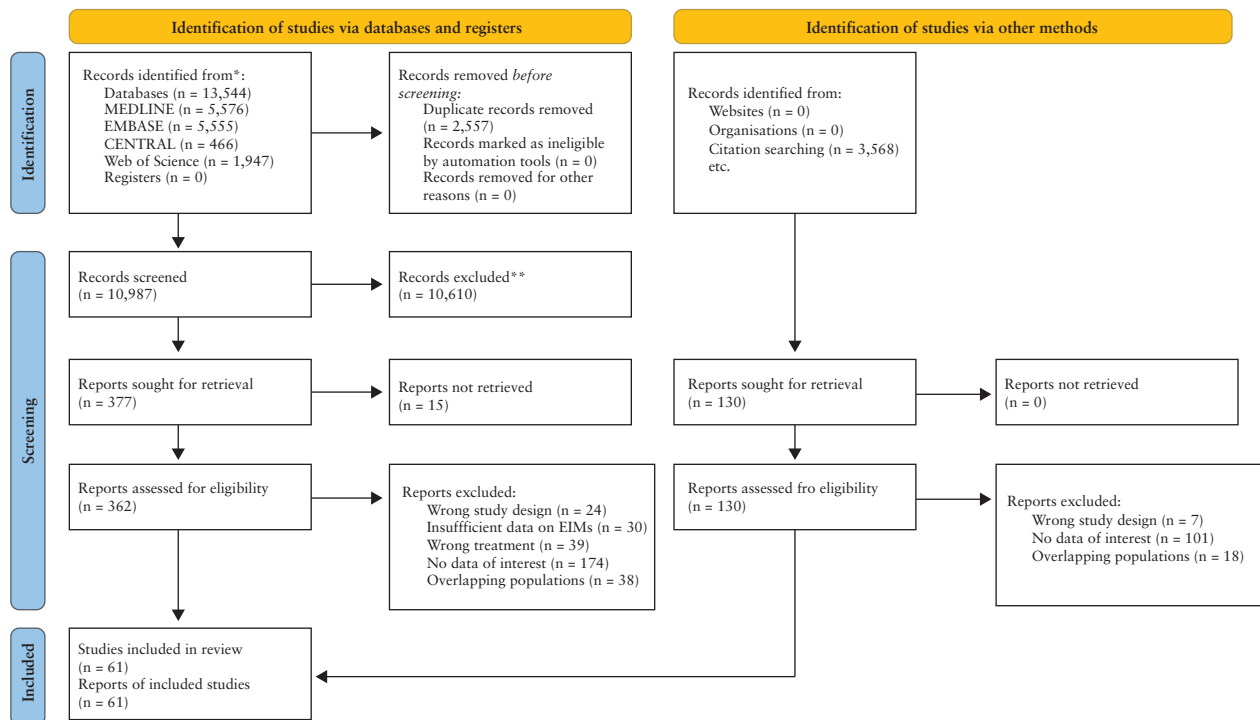
3.2. Study characteristics

All 61 eligible studies were published between 2015 and 2022. Among them, there were 22 single-centre studies and 31 multicentre studies. In eight cases, the number of centres was not reported. We included 26 conference abstracts,^{31–56} 26 retrospective cohorts,^{13,57–81} six prospective cohort studies,^{14,82–86} and three post-hoc analyses of randomized controlled trials.^{87–89} Thirteen studies were conducted in the USA, two in Canada, 26 in Europe, and four in the Middle East. Ten studies were international. The country of origin was missing in the remaining six studies. The number of participants ranged from five to 941 in the included studies. The studies investigated mucosal, joint, skin, ocular, and hepatic manifestations in patients treated mostly with VDZ or UST, in five studies with TOFA, and in three studies with upadacitinib. The follow-up times were heterogeneous [from 6 weeks to a median of 4 years]. Individual data of the included studies are shown in [Supplementary Table S2](#).

3.3. Risk of bias in studies

The detailed results of the risk of bias assessment are shown in [Supplementary Table S3](#). Among the included studies, the overall risk of bias was low in one study,⁸⁹ moderate in 33 studies, and high in 27 studies. The overall risk of bias was low when all important confounding factors were measured and provided, and there was no selective reporting regarding EIMs. The most frequent reason for moderate risk of bias was that possible confounding factors were mentioned, but they were not addressed and considered during the analysis. High risk of bias was usually due to a lack of information about

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

**Figure 1.** PRISMA 2020 flowchart representing the study selection process. EIMs, extraintestinal manifestations.

important confounding factors, such as concomitant treatment. Additional reasons for high risk were unclear definitions of EIMs and uncertainties regarding how the maximum values for events were calculated in the statistical analyses.

3.4. Results of syntheses

3.4.1. Occurrence of new EIMs during advanced therapy

A total of 42 studies, covering 10 826 patients with IBD treated with advanced therapy, reported the frequency of new EIMs. The proportion of new EIMs independently of the applied treatment was 8% [95% CI, 6–12%, $I^2 = 92\%$, 95% CI 90–94%], [Figure 2A]. The overall proportion of new EIMs after removing the studies labelled as high risk of bias and those papers that were only published in abstract form was 8% [95% CI, 5–12%, $I^2 = 93\%$, 95% CI 91–95%] [Table 1].

We also performed subgroup analyses based on the type of drug [VDZ, UST, TOFA]. The proportion of all new EIMs was 11% [95% CI, 8–15%, $I^2 = 90\%$, 95% CI 87–92%] in the VDZ group, 6% [95% CI, 3–11%, $I^2 = 87\%$, 95% CI 79–92%] in the UST group, and 3% [95% CI, 0–15%, $I^2 = 88\%$, 95% CI 66–96%] in the TOFA group. The difference among all three subgroups was statistically significant [$p = 0.013$]. However, the difference between the VDZ and UST subgroups was not significant [$p = 0.166$] [Figure 2B].

3.4.2. Proportion of new EIMs in different organ systems during advanced therapy

3.4.2.1. Joint manifestations

The overall proportion of new joint manifestations was 8% [95% CI, 5–11%, $I^2 = 93\%$, 95% CI 91–94%]. Upon exclusion of studies with high risk of bias and those that were only available in abstract form, the proportion of new joint manifestations was 7% [95% CI, 4–11%, $I^2 = 93\%$, 95% CI 91–95%]. The difference between VDZ and UST was

not significant regarding new joint involvement (9% [95% CI, 6–13%, $I^2 = 92\%$, 95% CI 90–94%] vs 6% [95% CI, 3–14%, $I^2 = 79\%$, 95% CI 60–89%], $p = 0.840$, respectively), although heterogeneity was considerable [Figure 3].

The frequency of new SpA was 6% [95% CI, 2–19%, $I^2 = 92\%$, 95% CI 86–95%] in patients treated with VDZ [Supplementary Figure S1].

There was no significant difference in the frequency of new arthralgia between VDZ and UST therapy (9% [95% CI, 6–13%, $I^2 = 92\%$, 95% CI 89–94%] vs 6% [95% CI, 2–16%, $I^2 = 82\%$, 95% CI 65–90%], $p = 0.926$, respectively) [Supplementary Figure S2].

The proportion of new peripheral arthropathy was 12% [95% CI, 1–77%, $I^2 = 98\%$, 95% CI 95–99%] in the VDZ subgroup [Supplementary Figure S3].

Diaz *et al.*⁶⁵ found one new axial joint involvement out of 71 patients, and Zingone *et al.*⁸¹ observed two in 103 patients during VDZ treatment. Axial joint involvement was reported in only one TOFA study, with one new case observed among 862 patients on TOFA. This outcome has not been investigated in UST-treated patients.

3.4.2.2. Skin manifestations

The frequency of new skin manifestations was 1% [95% CI, 1–2%, $I^2 = 51\%$, 95% CI 15–72%], and this was not changed after sensitivity analysis (1% [95% CI, 1–2%, $I^2 = 52\%$, 95% CI 11–74%]). The overall proportion of new skin lesions was the same in both the VDZ and UST subgroups (1% [95% CI, 1–2%, $I^2 = 48\%$, 95% CI 0–73%] vs 1% [95% CI, 0–2%, $I^2 = 54\%$, 95% CI 0–82%], $p = 0.375$, respectively).

The proportion of new EN was equal during VDZ and UST (1% [95% CI, 1–2%, $I^2 = 53\%$, 95% CI 0–78%] vs 1% [95% CI, 0–4%, $I^2 = 55\%$, 95% CI 0–84%], $p = 0.476$, respectively). New PG was reported in ten out of 3302 [0%,

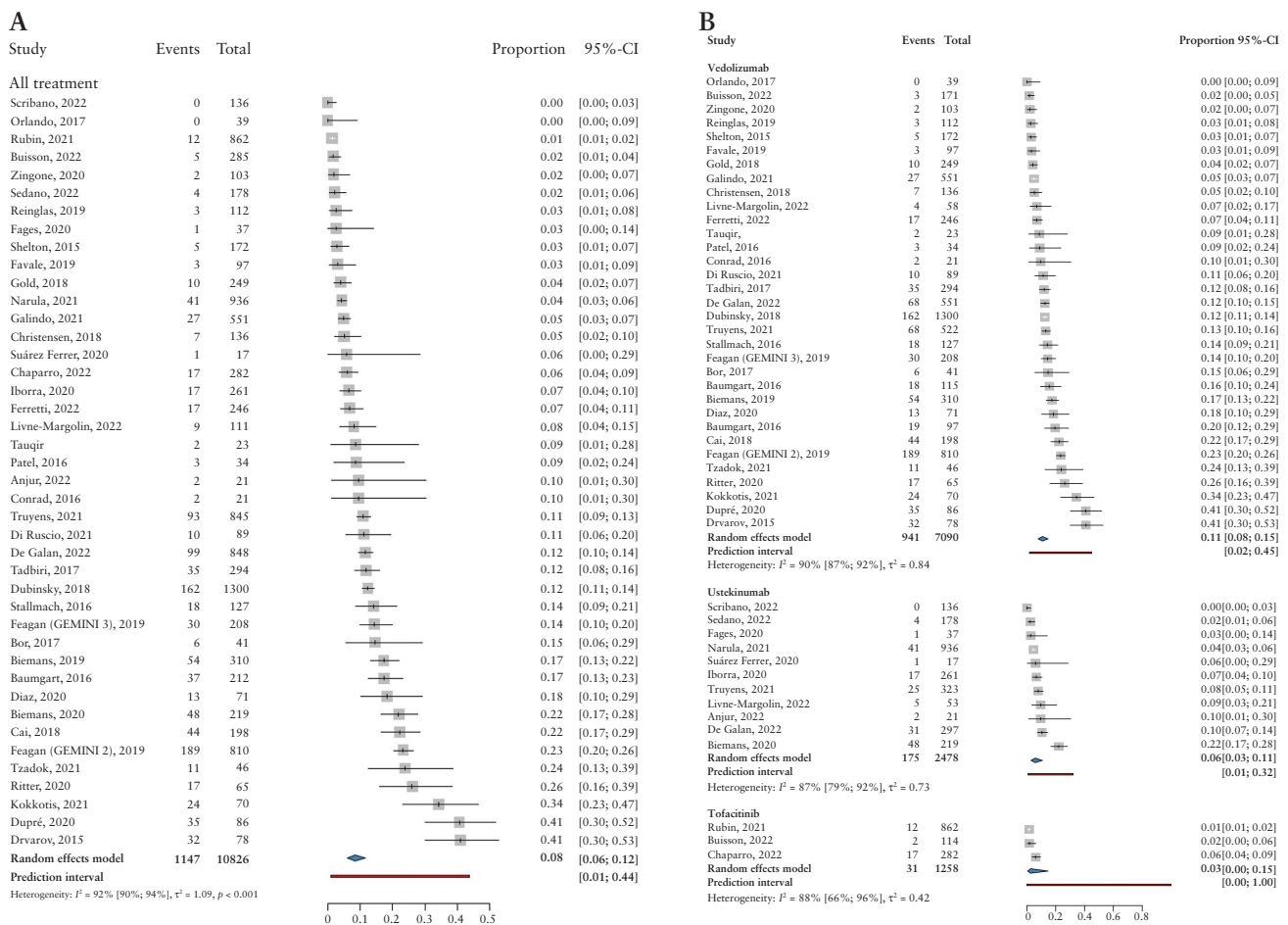


Figure 2. [A] Proportion of new extraintestinal manifestations [any type] during advanced therapy. [B] Proportion of new extraintestinal manifestations [any type] with subgroup analysis based on advanced therapy. CI, confidence interval.

Table 1. Proportion of different extraintestinal manifestations during advanced therapy

Type of extraintestinal manifestation	Proportion (%) [95% CI]	Heterogeneity [I^2] (%) [95% CI]	Proportion after sensitivity analysis (%) [95% CI]*
All new EIMs	8 [6–12]	92 [90–94]	8 [5–12]
New joint manifestation	8 [5–11]	93 [91–94]	7 [4–11]
New spondyloarthritis	4 [1–11]	93 [89–96]	2 [1–7]
New arthralgia	8 [5–11]	92 [89–94]	8 [5–12]
New peripheral arthropathy	4 [0–33]	97 [95–98]	1 [0–65]
New skin manifestation	1 [1–2]	51 [15–72]	1 [1–2]
New erythema nodosum	1 [0–2]	50 [8–73]	1 [0–2]
New pyoderma gangrenosum	0 [0–1]	43 [0–74]	0 [0–1]
New ocular manifestation	1 [0–2]	54 [13–76]	1 [0–2]
New stomatitis	2 [1–5]	90 [81–95]	2 [1–5]

*Studies with high-risk bias and published only in abstract form have been removed from the analyses. CI, confidence interval.

95% CI, 0–1%, $I^2 = 50\%$, 95% CI 0–79%] patients in the VDZ subgroup [Supplementary Figures S4 and S5].

3.4.2.3. Ocular manifestations

The overall proportion of new ocular manifestations was 1% [95% CI, 0–2%, $I^2 = 51\%$, 95% CI 5–75%], and after sensitivity analysis the frequency was also 1% [95% CI, 0–2%, $I^2 = 27\%$, 95% CI 0–65%]. The proportion of new ocular manifestations

was 1% in both the VDZ group and the UST group (1% [95% CI, 0–2%, $I^2 = 36\%$, 95% CI 0–71%] vs 1% [95% CI, 0–5%, $I^2 = 61\%$, 95% CI 0–87%], $p = 0.834$) [Figure 3].

3.4.2.4. Stomatitis

The proportion of new stomatitis was 3% [95% CI, 1–9%, $I^2 = 91\%$, 95% CI 80–96%] in the VDZ subgroup [Supplementary Figure S6].

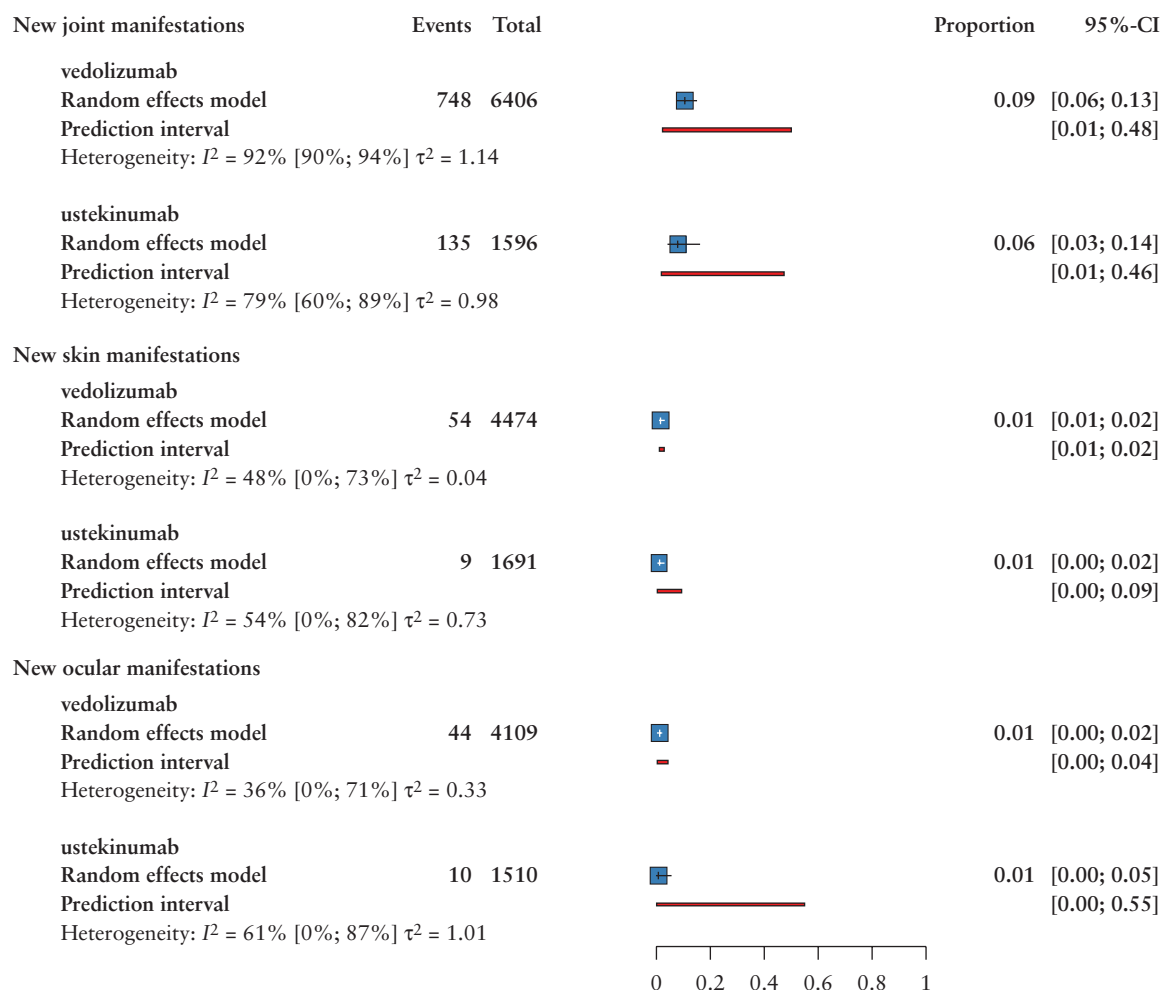


Figure 3. Proportion of new joint, skin, ocular manifestations with subgroup analysis based on advanced therapy. CI, confidence interval.

3.4.2.5. Liver manifestations

No studies have reported new cases of PSC during advanced therapy. Other liver EIMs, such as autoimmune hepatitis, were not reported in the included studies.

Table 1 provides an overview of the overall proportions of new EIMs in different organ systems regardless of the type of treatment.

3.4.3. Change in the activity of pre-existing EIMs

3.4.3.1. Improvement and deterioration of joint manifestations

An improvement of pre-existing joint manifestations was seen in 54% [95% CI, 42–65%, $I^2 = 84\%$, 95% CI 73–90%] in the UST subgroup, and 42% [95% CI, 32–53%, $I^2 = 0\%$, 95% CI 0–57%] in the VDZ group [$p = 0.029$]. The proportion of improved joint manifestation was similar in the JAK inhibitor subgroups (TOFA: 47% [95% CI, 4–95%, $I^2 = 94\%$, 95% CI 87–98%]; upadacitinib: 48% [95% CI, 32–65%, $I^2 = 43\%$, 95% CI 0–83%]) [Figure 4A].

The proportion of improving SpA was 42% [95% CI, 2–95%, $I^2 = 0\%$, 95% CI 0–79%] in the VDZ subgroup and 55% [95% CI, 28–78%, $I^2 = 0\%$, 95% CI 0–85%] in the UST subgroup, and 15/96 patients treated with TOFA reported improvement⁸⁹ [Supplementary Figure S7].

The proportion of improving arthralgia was 40% [95% CI, 35–46%, $I^2 = 0\%$, 95% CI 0–60%] in the VDZ subgroup

and 52% [95% CI, 40–64%, $I^2 = 84\%$, 95% CI 73–91%] in the UST subgroup [$p = 0.039$] [Supplementary Figure S8]. Furthermore, the rate of improving joint pain was 48% [95% CI, 32–65%, $I^2 = 43\%$, 95% CI 0–83%] in the upadacitinib subgroup, while 7/12 [Buisson *et al.*⁵⁸] and 26/32 patients [Cohen *et al.*⁶¹] treated with TOFA reported improvement.

The proportion of improvement in the case of peripheral joint involvement was 68% [95% CI, 23–94%, $I^2 = 0\%$, 95% CI 0–90%] in the VDZ subgroup [Supplementary Figure S9].

The proportion of improvement in axial joint involvement was 27% [95% CI, 0–100%, $I^2 = 0\%$, 95% CI 0–85%] in the VDZ subgroup and 10% [95% CI, 0–100%, $I^2 = 0\%$, 95% CI 0–90%] in the UST subgroup [Supplementary Figure 10].

Worsening of joint involvement was significantly more common in patients treated with VDZ compared to the UST group (18% [95% CI, 7–38%, $I^2 = 86\%$, 95% CI 72–93%] vs 5% [95% CI, 1–16%, $I^2 = 52\%$, 95% CI 0–81%], $p = 0.032$, respectively) [Figure 4B].

Worsening of arthralgia did not significantly differ between patients treated with VDZ and UST (14% [95% CI, 5–34%, $I^2 = 63\%$, 95% CI 3–86%] vs 5% [95% CI, 1–16%, $I^2 = 52\%$, 95% CI 0–81%], $p = 0.069$, respectively) [Supplementary Figure S11].

The deterioration of axial joint involvement was reported in two studies: Kopylov *et al.*⁴² did not observe any patients with worsening symptoms, whereas Ramos *et al.*⁷³ reported

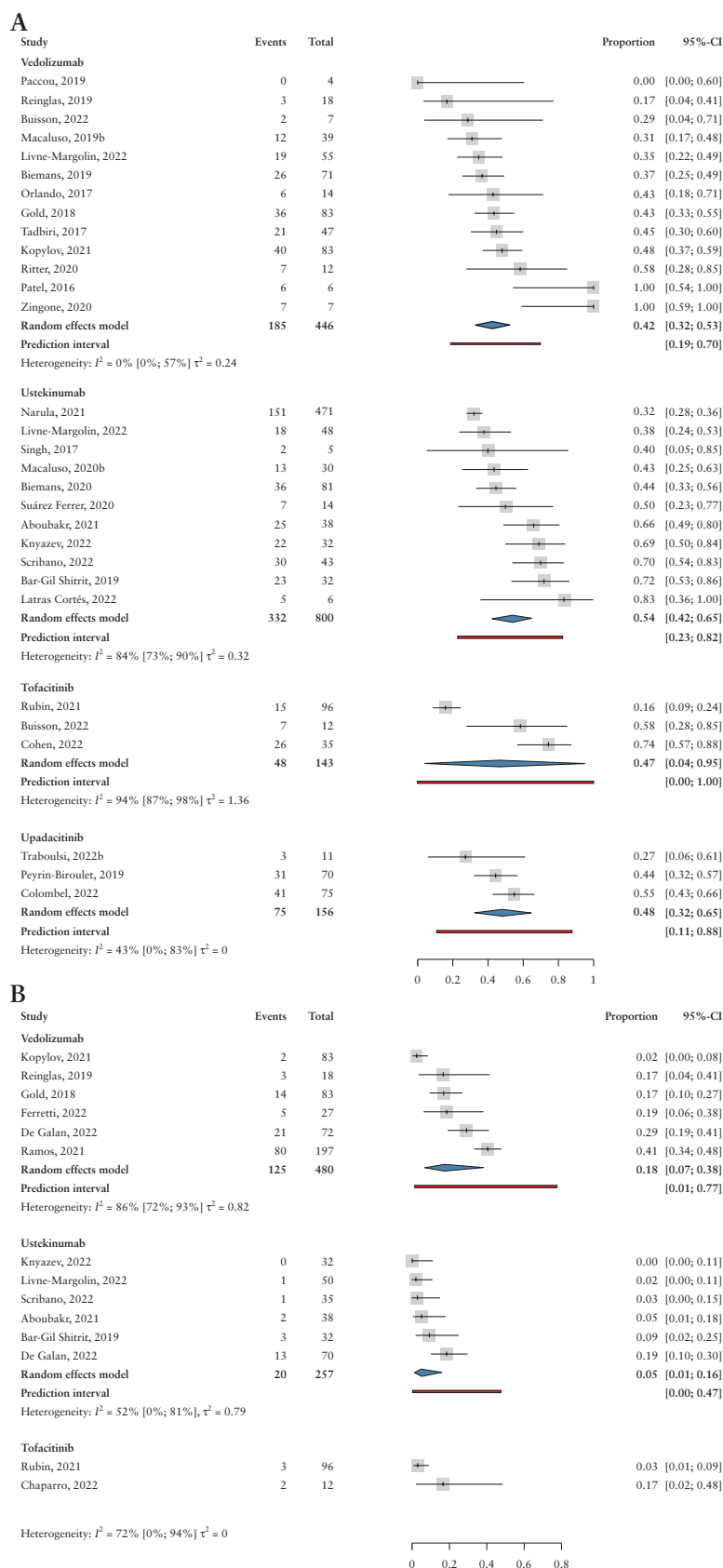


Figure 4. [A] Proportion of improving joint manifestations with subgroup analysis based on advanced therapy. [B] Proportion of deteriorating joint manifestations with subgroup analysis based on advanced therapy. CI, confidence interval.

that 21 out of 60 patients experienced deterioration during VDZ treatment.

Kopylov *et al.*⁴² found that one out of 20 patients experienced more severe symptoms and according to Ramos *et al.*⁷³ in 59 out of 137 cases the peripheral joint involvement deteriorated in patients treated with VDZ. Scribano *et al.*⁷⁵ documented one out of 35 UST-treated patients with worsening symptoms. Chaparro *et al.*³⁶ and Rubin *et al.*⁸⁹ investigated patients receiving TOFA and they found flare-up of peripheral joint manifestation in two out of 12 and in three out of 96 cases.

3.4.3.2. Change in pre-existing skin manifestations

Analysis showed no significant difference in the improvement of skin manifestations between VDZ and UST treatment (50% [95% CI, 16–84%, $I^2 = 1\%$, 95% CI 0–79%] vs 61% [95% CI, 47–74%, $I^2 = 0\%$, 95% CI 0–71%], $p = 0.469$, respectively) [Figure 5.A]. EN improved in 62% of patients [95% CI, 13–94%, $I^2 = 0\%$, 95% CI 0–79%] in the VDZ group and 70% [95% CI, 33–92%, $I^2 = 0\%$, 95% CI 0–90%] in the UST group [Supplementary Figure S12]. Improvement of PG was documented in 25% of the patients [95% CI, 1–92%, $I^2 = 0\%$, 95% CI 0–90%] in the VDZ subgroup [Supplementary Figure S13].

Worsening of pre-existing skin manifestations occurred in 14% [95% CI, 3–45%, $I^2 = 0\%$, 95% CI 0–90%] of the patients in the VDZ subgroup, while none of the patients receiving UST experienced deterioration [Figure 5B].

3.4.3.3. Ocular manifestations

In the UST subgroup, ocular symptoms improved in 59% of cases [95% CI, 32–81%, $I^2 = 0\%$, 95% CI 0–85%] [Supplementary Figure S14]. No worsening of symptoms was observed.

3.4.3.4. Stomatitis

Altogether 31% [95% CI, 0–99%, $I^2 = 0\%$, 95% CI 0–85%] of the patients in the VDZ group reported improvement [Supplementary Figure S15]. Moreover, two studies^{42,73} reported worsening cases in patients treated with VDZ [0/1 and 3/28].

3.4.3.5. Liver manifestations

The evaluation of improvement and worsening of PSC was based on changes in liver enzyme levels. In total, 17% [95% CI, 8–33%, $I^2 = 58\%$, 95% CI 0–84%] of the patients showed some improvement, whereas in 27% [95% CI, 5–71%, $I^2 = 75\%$, 95% CI 19–93%] of the cases, laboratory parameters deteriorated in the VDZ group. In the remaining two studies, TOFA was administered. Lewis *et al.*⁴⁴ described that five out of five PSC patients experienced some improvement, while Cohen *et al.*⁶¹ reported that one out of two patients had impairment in their results [Supplementary Figures S16 and S17].

3.4.4. Frequency of recurring EIMs

The proportion of recurring joint involvement was 44% [95% CI, 25–64%, $I^2 = 0\%$, 95% CI 0–85%] during VDZ treatment. Regarding peripheral SpA, three studies showed recurrence in 62% [95% CI, 7–97%, $I^2 = 0\%$, 95% CI 0–90%] of patients on VDZ [Supplementary Figures S18–S20].

3.5. Sensitivity analysis

We performed two sensitivity analyses. First, sensitivity analyses were conducted by excluding studies only published as a

conference abstract or assessed as high risk of bias [Table 1]. Furthermore, studies with fewer than ten patients were also excluded from sensitivity analysis [Supplementary Figures S21–S26], and the results were comparable with the original analyses.

3.6. Reporting bias

Statistical assessment of funnel plots showed potential small study publication bias in the case of two outcomes: new skin manifestations and new EN [Supplementary Figures S31 and S38].

3.7. Certainty of evidence

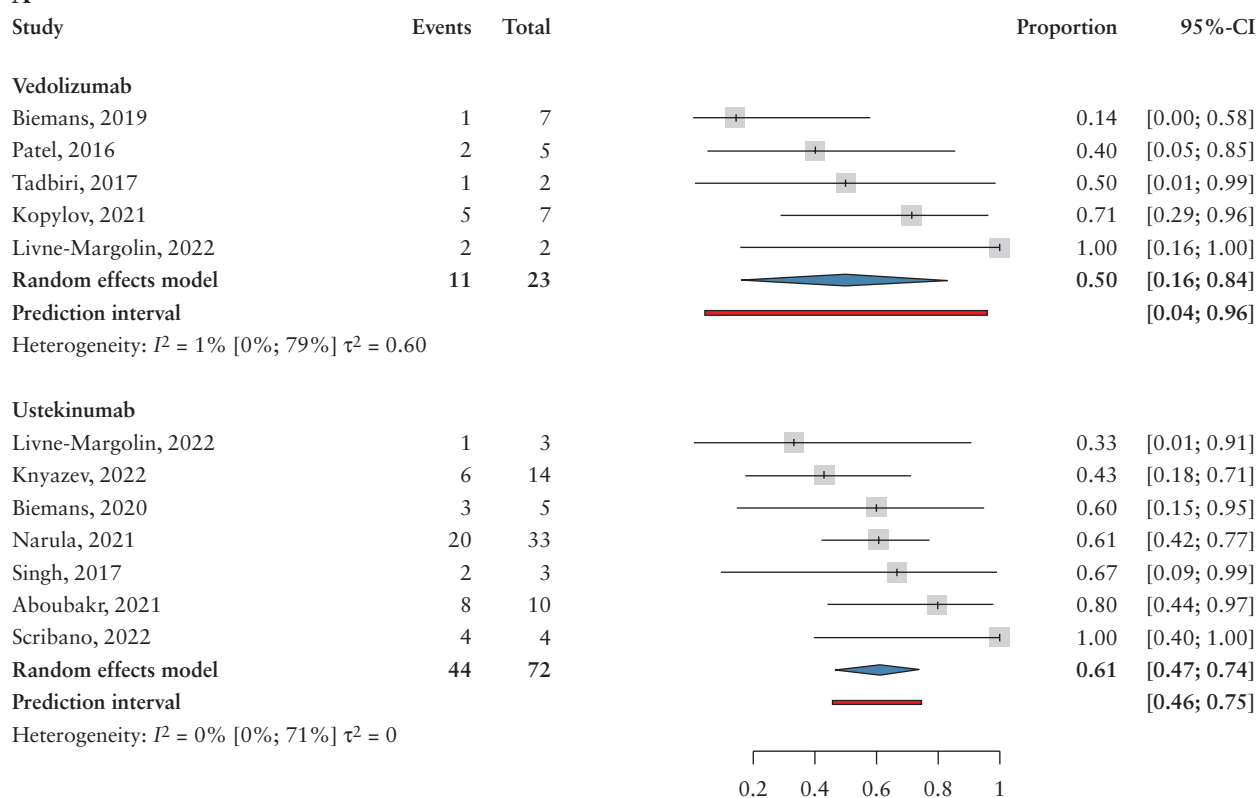
Quality was further evaluated based on GRADE [Supplementary Tables S4–S7]. The certainty of evidence was very low in all outcomes. The low level of evidence can be attributed first to the fact that the examined studies were mostly labelled as ‘moderate’ or ‘high’ during the risk of bias assessment, second, to the serious imprecision because of the small sample sizes, and third, to the serious inconsistency based on wide confidence intervals. Furthermore, indirectness was also present in some of the studies, since EIMs were not assessed as a primary outcome.

4. Discussion

In this study, we have summarized the information on the prevalence and clinical course of EIMs during advanced therapy. We found that the overall proportion of new EIMs and the frequency of new EIMs by organs were low. Based on subgroup analysis the overall proportion of new EIMs was also low in all advanced therapy groups. Interestingly, the frequency of new EIMs was comparable between VDZ and UST. The occurrence of new EIMs was lowest in patients treated with TOFA, although the number of included studies was small. Improvement or deterioration did not differ statistically between patients treated with VDZ or UST in any type of pre-existing EIM, except for joint manifestations. However, due to the absence of direct comparison studies, and the considerably high heterogeneity, no definitive conclusions can be drawn. Data on TOFA were limited and showed beneficial effects in reported EIMs.

Previous studies reported new articular manifestations not only in patients treated with VDZ, but also in patients on UST, although the latter has a systemic mechanism of action in contrast to VDZ and has a proven clinical efficacy in psoriatic arthritis. In our meta-analysis we did not observe a significant difference in the frequency of new joint manifestations between VDZ and UST. Our results are consistent with the systematic review by Chateau *et al.*,⁹⁰ who concluded that VDZ could potentially reduce the occurrence of new EIMs. These new rheumatic manifestations can be caused by the steroid tapering during the induction phase of VDZ and UST rather than by true side effects, although we could not analyse this due to the lack of precise data on concomitant medication.⁹¹ SpA is a heterogeneous group of joint manifestations in IBD. The analysis of axial and peripheral joint involvement separately, and likewise arthralgia, was feasible, but the available limited data suggest that there is no difference in newly appearing joint manifestations among the treatment groups. This finding is similar to a recent study comparing new joint EIMs in patients receiving UST and VDZ.⁶³

A



B

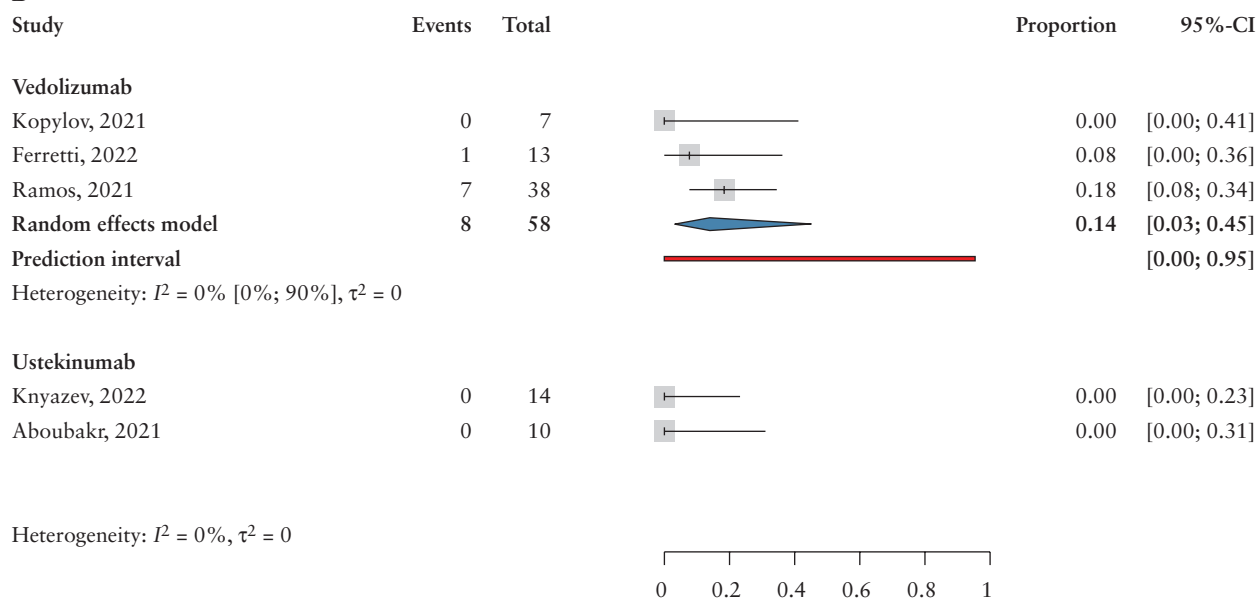


Figure 5. [A] Proportion of improving skin manifestations with subgroup analysis based on advanced therapy. [B] Proportion of deteriorating skin manifestations with subgroup analysis based on advanced therapy.

However, it is notable that the frequency of improvement in pre-existing joint manifestations was significantly lower in the VDZ subgroup compared to the UST subgroup; in addition, the proportion showing worsening was higher in patients treated with VDZ. Studies comparing VDZ and UST directly also observed that patients on VDZ experienced a higher occurrence of deteriorating pre-existing rheumatic EIMs than patients receiving VDZ, although the difference did not reach statistical significance.⁶³

Previous studies have provided evidence that UST may be beneficial for peripheral arthritis in IBD, but not for axial SpA,¹⁸ although the IL23/Th17 pathway is also involved in the pathogenesis of axial SpA.⁶³ Furthermore, TOFA Phase 3 trials are under way to establish its safety and efficacy in axial SpA. In addition to signalling pathways, improvement in some joint manifestations can be achieved by controlling intestinal inflammation, which is why VDZ may be also considered in peripheral arthritis that follows the intestinal inflammation.⁹² Based on analysis of

the evolution of pre-existing joint involvement in different locations [peripheral, axial] or based on the documented inflammation [SpA, arthralgia], VDZ did not seem to be inferior to other treatment options. However, the highest rate of worsening and the lowest rate of improvement were found in patients treated with VDZ for almost all types of joint manifestations.

Concerning pre-existing cutaneous EIMs, we did not observe any relevant difference between the effects of VDZ and UST. Both Ramos *et al.* and the OBSERV-IBD study found that the worsening of pre-existing skin manifestations was not remarkable, and most cutaneous EIMs had a stable course after VDZ initiation.^{73,79} Livne-Margolin *et al.*,⁷⁰ in comparing UST and VDZ, did not demonstrate a difference in deterioration of cutaneous EIMs between the two groups. We expected VDZ to be sufficient to control EN via the control of intestinal inflammation. Accordingly, there was no difference in the course of EN during VDZ or UST treatment. Our findings do not support the statement of Romano *et al.*⁹² that VDZ appears to be less effective than UST in the treatment of EN; however, only limited data were available. In contrast, PG is known to be independent from intestinal disease activity, and UST has been proven beneficial in some cases. Our data indicate that there was no relevant difference in the course of PG in patients receiving VDZ or UST treatment, but given the scarcity of cases, personalized treatment should be considered, and decisions made on a case-by-case basis.

There is still no effective treatment to prevent the progression of PSC. The included studies investigating PSC during VDZ treatment showed only a slight improvement in laboratory results, which was not always sustained. Despite the lack of evidence supporting the impact of VDZ on PSC progression, it remains a valuable therapy in the treatment of IBD/PSC, particularly for post-liver transplant patients, as it provides a potential safety advantage by allowing control of IBD without intensifying systemic immunosuppression.⁹³ Interestingly, in one study, patients treated with TOFA also showed improvement in laboratory parameters, and this has been supported in another recently published study. Schregel *et al.*⁹⁴ showed that serum levels of alkaline phosphatase declined significantly in patients with IBD/PSC receiving TOFA.

4.1. Strengths and limitations

To date, this is the first meta-analysis comparing the effects of different non-TNFi drugs on EIMs. Another strength of our meta-analysis is that we were able to include a relatively high number of studies, conducted in more than 14 countries, all of which were published recently. Moreover, we investigated several types of EIMs, performed a detailed subgroup analysis, and applied a rigorous methodology.

Regarding the limitations of this study, most of the included studies were retrospective cohorts, often with a low number of EIM cases, and there was no direct comparison between different advanced therapies in most studies. Furthermore, the follow-up times were heterogeneous which could influence the occurrence of EIMs. The assessment and reporting system for EIMs has not been standardized in the studies. We were not able to identify which patients received concomitant medications, and whether advanced therapy was a first- or second-line treatment.

4.3. Implications for practice and research

The systematic effect of non-gut-selective drugs makes them a preferred choice for patients with EIMs based on expert

opinions.⁹⁵ However, our findings suggest that VDZ could be considered as a treatment option where EIMs are present, especially for vulnerable patients who would benefit from its favourable safety profile. Given the absence of robust evidence, comparative randomized clinical trials should be conducted to evaluate this question more precisely. Furthermore, additional prospective registries with detailed information about EIMs and advanced therapeutic regimens with longer follow-up times are needed to obtain more data on this clinical question.

5. Conclusion

The available data suggest that the proportion of new EIMs is low during advanced therapy. Furthermore, our data suggest that there may be no need to underprioritize VDZ in patients with pre-existing EIMs, except for joint manifestation.

Funding

This paper was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences [BO/00693/25/5].

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None.

Author Contributions

Study conceptualization and design [ÁT, KM, MH, KB, PH, MG, SzV, AP]; investigation and data extraction [ÁT, KB, EK]; analysis and interpretation of the data [RT, DV]; drafting of the manuscript [ÁT, KM, MH]; critical revision of the manuscript for important intellectual content [all authors]; methodology supervision [MH, SzV]; study supervision [KM].

Conference Presentation

Part of the work was presented at the 31st Meeting of the European Society of Paediatric Clinical Research, May 2023, Budapest, Hungary.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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

Ágnes Eszter Tímár,^{1,2} Márk Hernádfői,^{1,3} Brigitta Teutsch,^{1,4,5} Zsolt Abonyi-Tóth,^{1,6} Nelli Farkas,^{5,7} Zoltán Sipos,^{5,7} Péter Hegyi ,^{1,5,8} Anna Karoliny,² Andrea Párniczky,^{1,2} Áron Cseh,⁹ Antal Dezsőfi,⁹ Miklós Garami,^{1,9} Judit Czelecz,³ Ildikó Guthy,¹⁰ Márta Kovács,¹¹ Ágnes Horváth,¹² Márta Balogh,¹³ András Tárnok,¹⁴ Dániel Szűcs,¹⁵ Orsolya Kadenczki,¹⁶ Éva Kosaras,¹⁷ Natália Lásztity,¹⁸ Katalin Eszter Müller ^{2,19}

To cite: Tímár ÁE, Hernádfői M, Teutsch B, *et al.* Association of extraintestinal manifestations and disease severity in paediatric inflammatory bowel disease: a multicentre cohort study. *BMJ Open Gastroenterol* 2026;**13**:e002130. doi:10.1136/bmjgast-2025-002130

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bmjgast-2025-002130>).

Received 15 October 2025
Accepted 3 February 2026

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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For numbered affiliations see end of article.

Correspondence to

Dr Katalin Eszter Müller;
muller.katalin@semmelweis.hu

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.

Author affiliations

¹Centre for Translational Medicine, Semmelweis University, Budapest, Hungary

²Heim Pál National Pediatric Institute, Budapest, Hungary

³MRE Bethesda Children's Hospital, Budapest, Hungary

⁴Department of Radiology, Medical Imaging Centre, Semmelweis University, Budapest, Hungary

⁵Institute for Translational Medicine, University of Pécs Medical School, Pécs, Hungary

⁶University of Veterinary Medicine, Budapest, Hungary

⁷Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary

⁸Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary

⁹Pediatric Center, Semmelweis University, Budapest, Hungary

¹⁰Jósa András Hospital, Nyíregyháza, Hungary

¹¹Petz Aladár University Teaching Hospital of Győr-Moson-Sopron County, Győr, Hungary

¹²Csolnoky Ferenc Hospital, Veszprém, Hungary

¹³Markusovszky Hospital, Szombathely, Hungary

¹⁴Department of Pediatrics, Medical School, University of Pécs, Pécs, Hungary

¹⁵Department of Pediatrics, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary

¹⁶Department of Pediatrics, Clinical Center, University of Debrecen, Debrecen, Hungary

¹⁷Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital, Pediatric Healthcare Centre, Miskolc, Hungary

¹⁸Department of Pediatrics, North-Buda Saint John's Central Hospital, Budapest, Hungary

¹⁹Department of Family Care Methodology, Faculty of Health Sciences, Semmelweis University, Budapest, Hungary

Contributors ÁET: conceptualisation, project administration, data curation, visualisation, writing—original draft; MH: conceptualisation, methodology, project administration, visualisation, writing—review and editing; BT: methodology, writing—review and editing; NF: conceptualisation, formal analysis, software, writing—review and editing; ZS: conceptualisation, formal analysis, software, writing—review and editing; ZA-T: conceptualisation, formal analysis, software, writing—review and editing; AK: data curation, writing—review and editing; AP:

conceptualisation, writing—review and editing; ÁC: data curation, writing—review and editing; MG: conceptualisation, writing—review and editing; AD: data curation, writing—review and editing; JC: data curation, writing—review and editing; IG: data curation, writing—review and editing; MK: data curation, writing—review and editing; ÁH: data curation, writing—review and editing; MB: data curation, writing—review and editing; AT: data curation, writing—review and editing; DS: data curation, writing—review and editing; OK: data curation, writing—review and editing; ÉK: data curation, writing—review and editing; NL: data curation, writing—review and editing; PH: conceptualisation, methodology, writing—review and editing; KEM: conceptualisation, writing—original draft. KEM is the guarantor and accepts full responsibility for the work, had access to the data and controlled the decision to publish. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing or revision of the manuscript. During the preparation of this work, the authors used ChatGPT (OpenAI) in order to improve the quality and clarity of the language. After using this tool, the authors reviewed and edited the content as needed. The authors take full responsibility for the content of the published article.

Funding This work was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (BO/00693/25/5), by the ÚNKP-23-5-SE22 New National Excellence Programme of the Ministry of Culture and Innovation funded by the National Research, Development and Innovation Fund and by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the KDP-2023 funding scheme (2023-2.1.2-KDP-2023-00016).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Hungarian Scientific and Research Ethics Committee of the Medical Research Council (IV/2162/2020EKU). The study adhered to the principles of the Declaration of Helsinki, revised in 2013. Written informed consent was obtained from the legal guardians of all participating patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data underlying this article will be shared on reasonable request to the corresponding author.

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ORCID iDs

Péter Hegyi <https://orcid.org/0000-0003-0399-7259>

Katalin Eszter Müller <https://orcid.org/0000-0001-5355-4224>

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