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SPECIAL ARTICLE

Predicting Outcomes in Pediatric Ulcerative Colitis for Management Optimization: Systematic Review and Consensus Statements From the Pediatric Inflammatory Bowel Disease–Ahead Program

Esther Orlanski-Meyer,[1,*] **Martine Aardoom**,[2,*] **Amanda Ricciuto**,[3,*] Dan Navon,[1] Nicholas Carman,[4] Marina Aloi,[5] Jiri Bronsky,[6] Jan Däbritz,[7,8] Marla Dubinsky,[9] Séamus Hussey,[10] Peter Lewindon,[11] Javier Martin De Carpi,[12] Víctor Manuel Navas-López,[13] Marina Orsi,[14] Frank M. Ruemmele,[15] Richard K. Russell,[16] Gabor Veres,[17] Thomas D. Walters,[3] David C. Wilson,[18] Thomas Kaiser,[19] Lissy de Ridder,[2] **Anne Griffiths**,[3,*] and Dan Turner[1]

[1]Institute of Pediatric Gastroenterology, Shaare Zedek Medical Center, the Hebrew University of Jerusalem, Israel; [2]Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, the Netherlands; [3]Division of Gastroenterology, Hepatology and Nutrition, the Hospital for Sick Children, Toronto, Canada; [4]Children's Hospital of Eastern Ontario, IBD Centre, University of Ottawa, Ottawa, Canada; [5]Pediatric Gastroenterology Unit, Sapienza University of Rome, Umberto I Hospital, Rome, Italy; [6]Department of Pediatrics, University Hospital Motol, Prague, Czech Republic; [7]University Medical Center Rostock, Department of Pediatrics, Rostock, Germany; [8]Queen Mary University of London, The Barts and the London School of Medicine and Dentistry, Blizard Institute, Center for Immunobiology, London, United Kingdom; [9]Pediatric Gastroenterology and Nutrition, Mount Sinai Kravis Children's Hospital; Susan and Leonard Feinstein IBD Clinical Center, Icahn School of Medicine, Mount Sinai, New York; [10]National Children's Research Centre, Royal College of Surgeons of Ireland and University College Dublin, Dublin, Ireland; [11]University of Queensland, Brisbane, Australia; [12]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Hospital Sant Joan de Déu, Barcelona, Spain; [13]Pediatric Gastroenterology and Nutrition Unit, Hospital Regional Universitario de Málaga, Spain; [14]Pediatric Gastroenterology, Hepatology and Transplant Unit, Hospital Italiano de Buenos Aires, Argentina; [15]Université Paris Descartes, Sorbonne Paris Cité; Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades, Service de Gastroentérologie Pédiatrique; Institute IMAGINE Inserm U1163, Paris, France; [16]Department of Paediatric Gastroenterology, Royal Hospital for Sick Children, Edinburgh, Scotland, United Kingdom; [17]Pediatric Institute-Clinic, University of Debrecen, Hungary; [18]Child Life and Health, University of Edinburgh, Paediatric Gastroenterology and Nutrition, Royal Hospital for Sick Children, Edinburgh, Scotland, United Kingdom; and [19]Department of General Pediatrics, University Hospital Münster, Germany

BACKGROUND & AIMS: A better understanding of prognostic factors in ulcerative colitis (UC) could improve patient management and reduce complications. We aimed to identify evidence-based predictors for outcomes in pediatric UC, which may be used to optimize treatment algorithms. **METHODS:** Potential outcomes worthy of prediction in UC were determined by surveying 202 experts in pediatric UC. A systematic review of the literature, with selected meta-analysis, was performed to identify studies that investigated predictors for these outcomes. Multiple national and international meetings were held to reach consensus on evidence-based statements. **RESULTS:** Consensus was reached on 31 statements regarding predictors of colectomy, acute severe colitis (ASC), chronically active pediatric UC, cancer and mortality. At diagnosis, disease extent (6 studies, N = 627; $P = .035$), Pediatric Ulcerative Colitis Activity Index score (4 studies, n = 318; $P < .001$), hemoglobin, hematocrit, and albumin may predict colectomy. In addition, family history of UC (2 studies, n = 557; $P = .0004$), extraintestinal manifestations (4 studies, n = 526; $P = .048$), and disease extension over time may predict colectomy, whereas primary sclerosing cholangitis (PSC) may be protective. Acute severe colitis may be predicted by disease severity at onset and hypoalbuminemia. Higher Pediatric Ulcerative Colitis Activity Index score and C-reactive protein on days 3 and 5 of hospital admission predict failure of intravenous steroids. Risk factors for malignancy included concomitant diagnosis of primary sclerosing cholangitis, longstanding colitis (>10 years), male sex, and younger age at diagnosis. **CONCLUSIONS:** These evidence-based consensus statements offer predictions to be considered for a personalized medicine approach in treating pediatric UC.

Keywords: Prognostic Factors; Pediatric Ulcerative Colitis; Prediction; Acute Severe Colitis; Colectomy; Cancer; Mortality.

Pediatric-onset ulcerative colitis (UC) has a somewhat more severe phenotype than in adults.[1,2] Disease is twice as often extensive[3] and more often requires hospitalization[4,5] as well as colectomy for medically refractory

***Authors share co-first authorship.**

Abbreviations used in this paper: **ANCA, antineutrophil cytoplasmic antibodies; ASC, acute severe colitis; ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IBD, inflammatory bowel disease; OR, odds ratio; OSCI, Outcome of Steroid Therapy in Colitis Individuals; PIBD, pediatric inflammatory bowel disease; PSC, primary sclerosing cholangitis; PUCAI, Pediatric Ulcerative Colitis Activity Index; SIR, standardized incidence ratio; TNF, tumor necrosis factor; UC, ulcerative colitis; WBC, white blood cells.**

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disease.[3,6] Indeed, high cumulative rates of colectomy have been reported in children: 8% at 1 year, 26% at 5 years, and 20%–41% at 10 years.[3,6]

Children also have unique age-related considerations, including pubertal development, nutrition, and bone mineral density accretion, as well as unique psychosocial needs. Because of such differences, prognostic factors associated with pediatric UC should be examined separately from those of adults.

The international Pediatric Inflammatory Bowel Disease (PIBD) Ahead Program (PIBD-Ahead) was aimed at identifying evidence-based predictors for outcomes in PIBD. Here, we present the predictors of UC to guide evidence-based individualization of management in childhood-onset UC.

Methods

PIBD-Ahead encompassed several stages, aiming to systematically reach international consensus on the predictors of poor outcomes in PIBD. The methods of this project have been described in the companion Crohn's disease (CD) article by Ricciuto et al.[7] Briefly, a survey among international experts in pediatric gastroenterology and inflammatory bowel disease (IBD) was first performed to determine undesirable outcomes of interest to be predicted in pediatric UC. The survey aimed to identify outcomes that may justify treatment escalation to biologics to prevent the said outcomes. Chronically active colitis was defined as reported in the studies, including any of the following repeatedly assessed over time: physician global assessment, Pediatric Ulcerative Colitis Activity Index (PUCAI), endoscopic grading, and intractability index (duration of active disease as a proportion of length of follow-up). The same variables may have served as both predictors and outcomes because they were analyzed independently. For instance, the occurrence of an episode of acute severe colitis (ASC) may predict poor disease outcome but also is a poor outcome by itself. Thereafter, a systematic literature review was performed to identify studies examining predictors of these outcomes. We included articles enrolling children of all ages, namely, 0–18 years of age. Meta-analyses were conducted to pool the effects of predictors of colectomy, the key selected outcome. Selection of studies for meta-analyses was determined by data sufficiency and clinical relevance. To reflect the degree of heterogeneity across studies, the I^2 method was used, describing the percentage of variability stemming from heterogeneity rather than chance.[8] To compensate for the heterogeneity, a random effects model was used. Pooling of study results used either odds ratio (OR) or hazard ratio (HR) based on the study methodology; some studies allowed the calculation of both measures. A series of national and international meetings were convened to formulate and validate consensus statements based on the identified evidence. At the final February 2018 consensus meeting in Vienna, Austria, the steering committee with national representatives (53 participants) voted on the statements. A consensus was reached if $\geq$80% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1–5. Statements not achieving agreement were further revised and revoted upon until consensus was reached for all statements. In general, soft wording such as "may predict" has been used when only 1 positive study was available or when more than 1 positive study was found but also with negative studies.

Results

The international survey, which informed outcome selection, was completed by 202 pediatric gastroenterologists from 33 countries. It was concluded that the most important undesirable outcomes to prevent in children with UC are colectomy, ASC, chronically active disease, cancer and mortality. Because of the expected limited number of studies for the latter, these were evaluated for both CD and UC and are reported in this article.

The results of the search are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram (Supplementary Figure 1). Fifty-nine studies were included, of which 17 were included in the quantitative meta-analysis. Study characteristics and risk of bias for studies examining predictor-outcome combinations included in the meta-analysis are shown in Tables 1 and 2, respectively. The equivalent data for studies examining predictor-outcome combinations not included in the meta-analysis are shown in Supplementary Tables 1 and 2. All of the included studies were observational; 19 studies were high quality, 38 were moderate quality, and 2 were low quality.

Figure 1 tabulates the final consensus, and Table 3 presents the extracted numeric data for predictor-outcome pairs included in meta-analyses. Table 4 presents an intuitive summary of each outcome. A brief summary of the most pertinent literature is provided below each statement. (For a full review of each predictor, see the Supplementary Materials).

Prognostic Factors for Colectomy

Statement 1.1. At diagnosis, disease extent, PUCAI score (≥65 points), hemoglobin, hematocrit, and white blood cells (WBCs) may predict colectomy; PUCAI score ≥65 during the subsequent 3 months, family history of UC, and extraintestinal manifestations may predict colectomy (96% agreement).

The association between disease extent and colectomy was assessed in 11 studies.[6,9–18] Seven studies individually reported no association,[6,9–14] but the other 4 were positive[10,14,15,18] (OR of 6 studies, 1.71; 95% confidence interval [CI], 0.87–3.34; n = 630; I^2 = 53%[6,9–13]; HR of 3 studies, 1.81; 95% CI, 0.73–4.52; n = 436; I^2 = 61%[6,12,14]) (Figure 2*A*).

Colectomy was predicted by disease severity at diagnosis (as measured by the PUCAI) in 4 meta-analyzable studies out of 6 studies that explored this association[9–11,13,14,19] (OR, 4.50; 95% CI, 1.83–11.06; n = 318, I^2 = 49%) (Figure 2*B*).[9–11,19] The 2 other studies found that PUCAI score also predicted colectomy at 3 months.[13,14] Similarly, in the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study published after the completion of our systematic review, time to colectomy was associated with week 4 clinical remission (defined as PUCAI of <10).[20,21] Additionally, colectomy rate at 52

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Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Study design	Population by IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Aloi et al (2013)[10]	Retrospective, single center	110 pediatric patients with UC Median: 10.2 y (range 1.2–18.3 y) 39/110 (39%) early onset (0–7 y); 71/110 (61%) 8–18 y 38% M	Age (EO $\leq$7 y vs later) Disease extension (involvement during follow-up of at least 1 additional segment) Disease extent Disease severity at diagnosis EIM (skin, joint, and ocular manifestations, and PSC) Family history of IBD (first-degree relative UC/CD) Sex	Colectomy	Mean: 48 mo (range, 28–94 mo)
Aloi et al (2015)[9]	Retrospective, single center	31 pediatric patients with UC Mean: 10.6 y (SD 4.9) 48% M	Age (mean age) CRP Disease extension (according to Paris classification) Disease extent (E4 vs E1, E2, E3) Disease severity at diagnosis ESR (>25 mm/h) Hypoalbuminemia Sex	Colectomy	2 y
Assa (2018)[11]	Retrospective, single center	126 pediatric patients with UC Median: 13.7 y (IQR, 11.1–15.8) 46% M	Disease extent Disease severity at diagnosis (ASC)	Colectomy	8.5 y (IQR, 5.1–12)
Chhaya et al (2015)[25]	Retrospective (registry), multicenter	1175 pediatric patients with UC (0–25 y) 0–9 y: 61/1175 10–13 y: 111/1175 14–16 y: 143/1175 17–24 y: 860/1175 48% M	Age (10–13 y vs 17–24 y as reference) Sex (female vs male)	Colectomy	Mean: 4.3 y/person

Table 1. Continued

Study	Study design	Population by IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Falcone et al (2000)[15]	Retrospective, single center	73 pediatric patients with UC (1–18 y) Mean: 11.3 y (SD, 0.5) at first symptom 48% M	Family history of IBD Sex	Colectomy	Mean: 5.4 y (SD, 0.6; range, 0.4–13.8 y)
Gower-Rousseau et al (2009)[6]	Retrospective (EPIMAD registry), multicenter	113 pediatric patients with UC (<17 y at diagnosis) Median: 14 y (IQR, 11–16) 39% M	Age (<10 y vs ≥10 y) CRP (<10 mg/L vs ≥10 mg/L) Disease extension (involvement with time of at least 1 additional segment) Disease extent (E3 vs E1) EIM (joint, skin, and ocular manifestations, and PSC) Family history of IBD (first-degree relative with UC/CD) Family history of UC Sex	Colectomy	Median: 77 mo (range, 46–125 mo)
Kelley-Quon et al (2012)[23]	Retrospective (PedIIBDC registry), multicenter	407 pediatric patients with UC Mean: 10.6 y (SD, 4.4) 49% M	Age CRP (>5 mg/dL) ESR (>20 mm/h) Family history of IBD Family history of UC (first-degree relative with UC) Hemoglobin level (<10 g/dL) Hypoalbuminemia (<3.5 g/dL) Sex (male vs female)	Colectomy (predictors reported for overall colectomy rate and not colectomy at 2 years)	Mean: 6.8 y (SD, 4)
Lascurain et al (2016)[31]	Retrospective, multicenter, case control (PSC-IBD vs non–PSC-IBD)	37 patients with PSC-IBD/148 non–PSC matched IBD control individuals (155 patients UC) Median: 14.2 y (IQR, 9.9–16.7)/median: 14.2 y (IQR 11.7–16.8) 64.9% M/56.1% M	Sex	Colectomy	Median: 4.75 y (IQR, 3.7–7.2)/median 5.19 y (IQR, 3.1–7.8)

Table 1. Continued

Study	Study design	Population by IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Ledder et al (2014)[26]	Retrospective, case control, multicenter	30 patients with early-onset IBD (<6 y) (20 UC, 8 CD, 2 indeterminate)/60 patients with later-onset disease (6–17 y) (19 UC, 39 CD, 2 indeterminate) Median: 3 y (IQR, 2.0–4.4)/ median 12.4 y (IQR, 10.2–14.4) 63% M/66% M	Age (<6 y vs 7–16 y)	Colectomy (results for UC alone were presented)	Mean: 4.9 y (SD, 2.5)/ mean: 4.5 y (SD, 2.5)
Malaty (2013)[16]	Retrospective, single center	115 pediatric patients with UC Mean: 10.6 y (SD, 5.1) 45% M	EIM (arthritis, aphthous stomatitis, arthralgia, erythema nodosum, skin lesions, and/or PSC) Sex	Colectomy	Median: 4.4 y (±2.1)
McAteer et al (2013)[22]	Retrospective (Pediatric Health Information System database), multicenter	8688 pediatric patients with UC and indeterminate colitis (8066 patients with UC) Mean: NA, divided into categories 0–4, 5–10, 11–14, 15–17 y 48% M	Age (0–4 y, 5–10 y, 11–14 y, with 15–17 y reference) Hemoglobin level (anemia by ICD-9 category) Sex	Colectomy	Study period between 2004 and 2011
Moore et al (2011)[12]	Retrospective, single center	135 pediatric patients with UC Mean: 12.5 y (SD, 4.1) 55% M	Age (mean) Disease extent (extensive if proximal to splenic flexure) ESR (mean)	Colectomy	NA
Nambu et al (2016)[27]	Retrospective, single center	63 pediatric patients with UC 10 patients with early-onset UC (0–7 y), 53 patients with late-onset UC (8–15 y) 47% M	Age (0–7 y vs 8–15 y)	Colectomy	Early-onset mean: 42 mo (SD, 40) Late-onset mean: 36.1 mo (SD, 26.5)

Table 1. Continued

Study	Study design	Population by IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Newby et al (2008)[28]	Retrospective, multicenter	210 pediatric patients with IBD (74 UC, 116 CD, 20 indeterminate) UC median: 11.96 y (range 2.08–15.3 y) UC: 60% M	Sex	Colectomy	UC mean: 3.3 y (range, 1–6.83 y)
Piekkala et al (2013)[19]	Retrospective, case control, single center	51 pediatric patients with UC Surgery group median, 13.1 y (range, 3.1–16 y) Disease control, 12.1 y (range, 2.8–16.6 y) Non–IBD control: 13.5 y (range, 2.7–16.8 y) NA	Disease severity at diagnosis (PUCAI of >65)	Colectomy	Median: 6 y (range, 3–11 y)
Rinawi et al (2017)[14]	Retrospective, single center	188 pediatric patients with UC Median: 13.1 y (IQR, 10.2–15.2) 55% M	Age (median) CRP (median) Disease extent (E4 and E3 each vs proctitis) EIM (undefined) Family history of IBD Hemoglobin level (median) Hypoalbuminemia (mean) Sex (female vs male)	Colectomy	Median: 6.9 y (range, 1–30 y)
Schechter et al (2015)[13]	Retrospective, multicenter	115 pediatric patients with UC (2–18 y) Mean: 11 y (SD, 4.1) 50% M	Disease extent (extensive/pancolitis vs left sided/proctitis)	Colectomy	Median: 23.1 mo (IQR, 15.3–43.4)

EIM, extraintestinal manifestations; EPIMAD, epidemiology of inflammatory bowel disease; ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; M, male; NA, not available; PediIBDC, Pediatric Inflammatory Bowel Disease Consortium; SD, standard deviation.

Table 2. Risk of Bias of Included Studies in the Meta-Analysis

Study	Representativeness of exposed cohort	Representativeness of nonexposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Aloi et al (2013)[10]	1	1	1	1	0	1	1	1	7
Aloi et al (2015)[9]	1	1	1	1	0	1	1	1	7
Assa (2018)[11]	1	1	1	1	2	1	1	1	9
Chhaya et al (2015)[25]	1	1	1	1	2	1	1	1	9
Falcone et al (2000)[15]	1	1	1	1	0	1	1	1	7
Gower-Rousseau et al (2009)[6]	1	1	1	1	2	1	1	1	9
Kelley-Quon et al (2012)[23]	1	1	1	1	2	1	1	1	9
Lascurain et al (2016)[31]	1	1	1	1	1	1	1	0	8
Ledder et al (2014)[26]	1	1	1	1	0	1	1	1	7
Malaty (2013)[16]	1	1	1	1	0	1	1	1	7
McAteer et al (2013)[22]	1	1	1	1	2	1	0	0	7
Moore et al (2011)[12]	1	1	1	1	2	1	1	0	8
Nambu et al (2016)[27]	1	1	1	1	0	1	1	0	6
Newby et al (2008)[28]	1	1	1	1	0	1	1	1	7
Piekkala et al (2013)[19]	1	1	1	1	0	1	1	0	6
Rinawi et al (2017)[14]	1	1	1	1	2	1	1	1	9
Schechter et al (2015)[13]	1	1	1	1	1	1	1	0	7

NOTE. Based on the Newcastle-Ottawa Scale. All columns, 0 or 1 stars except comparability (0–2 stars); the last column indicates the total number of stars.

Question 1: What are the prognostic risk factors of colectomy?
Colectomy
Statement 1.1. At diagnosis, disease extent, PUCAI score (≥65 points), hemoglobin, hematocrit, and white blood cells (WBC) may predict colectomy; PUCAI score ≥65 during the subsequent 3 months, family history of UC, and extraintestinal manifestations may predict colectomy
Statement 1.2. At diagnosis, age, sex, endoscopic severity, erythrocyte sedimentation rate (ESR), hypoalbuminemia, C-reactive protein (CRP), ferritin, ethnicity, anthropometric measures (ie, growth, weight, and body mass index [BMI] z-scores), duration of symptoms prior to diagnosis, genetic polymorphisms, and antineutrophil cytoplasmic antibodies (ANCA) status do not predict colectomy
Statement 1.3. Primary sclerosing cholangitis (PSC) may be protective for colectomy (82% agreement).
Statement 1.4. Disease extension over time may predict the need for colectomy; neutrophilic infiltration of the stomach and duodenum (but not the esophagus) at diagnosis may predict the need for colectomy
Statement 1.5. Clostridium difficile infection may be associated with increased risk of colectomy
Question 2: What are the prognostic risk factors of acute severe colitis (ASC)?
Episodes of ASC
Statement 2.1. Disease severity at onset, evaluated by PUCAI or endoscopic assessment, may predict future ASC
Statement 2.2. Hypoalbuminemia at diagnosis may predict future ASC; no other blood tests (ie, hemoglobin, ESR, and CRP) during the first 3 months after diagnosis are predictors of ASC
Statement 2.3. Age and disease extent at diagnosis do not predict development of ASC
Short-term outcomes of children hospitalized with ASC
Statement 2.4. PUCAI scores on days 3 and 5 of hospital admission predict the need for treatment escalation in the short- and long-term period following intravenous corticosteroid treatment
Statement 2.5. Higher CRP at both days 3 and 5 of treatment predicts response to intravenous steroids; ESR and hemoglobin do not predict outcomes at any time
Statement 2.6. Shorter time from disease onset to ASC may predict nonresponse to intravenous steroids
Statement 2.7. Genetic polymorphisms and cytokine status may predict the outcome in ASC
Statement 2.8. Fecal inflammatory markers are weak predictors of steroid response and have limited value in addition to the PUCAI in ASC
Statement 2.9. Age, sex, disease extent, ANCA positivity, and family history of IBD do not predict outcomes of ASC
Question 3: What are the prognostic risk factors of chronically active UC?
Disease activity
Statement 3.1. Age at diagnosis and sex do not predict disease activity
Statement 3.2. Rectal sparing at diagnosis does not predict disease activity; no studies have evaluated the association between disease extent and disease activity in pediatrics
Statement 3.3. ANCA positivity may not predict disease activity or endoscopic inflammatory grading
Disease extension over time
Statement 3.4. Family history of IBD may predict disease extension over time
Statement 3.5. At diagnosis, age, sex, weight, height, ethnicity, PUCAI, ANCA positivity, disease extent at diagnosis, and routine laboratory measures (CRP, ESR, hemoglobin/hematocrit, albumin, WBC, and ferritin level) do not predict disease extension
Disease severity over time (ie, medication use, response to treatment, hospitalization, and relapse)
Statement 3.6. PUCAI score (≤10) at 3 months predicts sustained steroid-free remission; disease severity at diagnosis (assessed clinically or endoscopically) does not predict subsequent use of immunomodulators or biologics
Statement 3.7. Genetic polymorphisms, particularly in genes associated with the treatment pathways, and ethnicity may predict response to medications
Statement 3.8. Serology (ANCA/anti-Saccharomyces cerevisiae antibodies [ASCA]) may predict anti-TNF use, but not immunomodulator use
Statement 3.9. At diagnosis, age, sex, weight, height, family history of IBD, clinical/endoscopic disease severity, and laboratory blood tests (CRP, ESR, albumin, hemoglobin, platelets) do not predict medication intensification
Statement 3.10. Disease extent at diagnosis may predict medication use and response to treatment; it does not, however, predict relapse
Statement 3.11. Duration of symptoms prior to diagnosis does not predict response to subsequent treatment
Question 4: What are the prognostic risk factors of cancer and/or mortality in patients with childhood-onset IBD?
Statement 4.1. Concomitant diagnosis of PSC, longstanding colitis (>10 years), male sex, and younger age at IBD diagnosis are risk factors for any cancer; having a first-degree relative with any cancer before 50 years of age may be a risk factor for cancer in UC
Statement 4.2. Malignancy and infection (sepsis and opportunistic infections) may be risk factors for mortality, but no population-based studies are currently available

Figure 1. Summary of consensus recommendations for the management of inflammatory disease.

weeks was lower in those with mild disease (2/163; 1.2%) compared with moderate to severe disease (23/237; 9.7%; $P = .0006$).

Findings were inconsistent across studies for the predictive utility of hemoglobin and hematocrit at diagnosis on colectomy rates,[12–14,22,23] of which 2 were positive[12,22] (OR of 2 studies, 1.26; 95% CI, 0.28–5.68; n = 8472; $I^2 = 83\%$[22,23]; HR of 2 studies, 1.03; 95% CI, 0.86–1.22; n = 594; $I^2 = 0\%$[14,23]) (Figure 2*B*). After the completion of this study, the prospective PROTECT cohort similarly found that higher hemoglobin levels at diagnosis were associated with a favorable outcome at 52 weeks.[20]

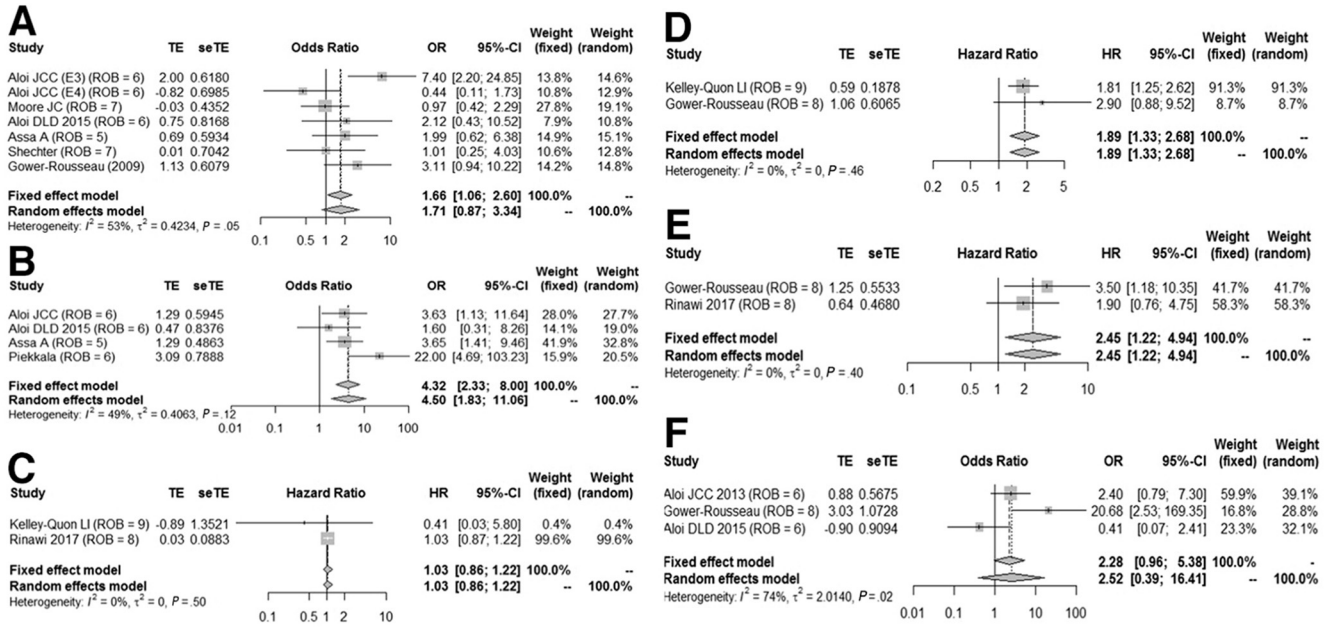

Figure 2. Forest plots for predictors that may be associated with colectomy in pediatric ulcerative colitis (UC): (*A*) disease extent; (*B*) disease severity; (*C*) hemoglobin; (*D*) family history of UC; (*E*) extraintestinal manifestations; and (*F*) disease extension. DLD, Digestive and Liver Disease; JCC, Journal of Crohn's and Colitis; ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

All 6 studies[6,9,10,14,15,23] assessing family history of IBD as a predictor for colectomy found no association; 5 were meta-analyzable (pooled OR of 4 studies, 1.27; 95% CI, 0.82–1.97; n = 777; I^2 = 0%[10,14,15,23]; pooled HR of 2 studies, 1.51; 95% CI, 0.80–2.82; n = 301; I^2 = 0%[6,14]) (Figure 3*A*). One other study included a mixed IBD population of 411 patients (244 UC, 129 CD, and 38 IBD unclassified) and showed no association between family history of IBD and need for surgery.[24] However, family history of only UC as opposed to any IBD was positive in 1[23] of 2 studies and in the meta-analysis (pooled HR of 2 studies, 1.89; 95% CI, 1.33–2.68; P = .0004; n = 557; I^2 = 0%) (Figure 2*D*).[6,23]

Association between extraintestinal manifestations and colectomy was explored in 5 studies; 1[6] found an association with colectomy, 1[14] found borderline significance on univariate

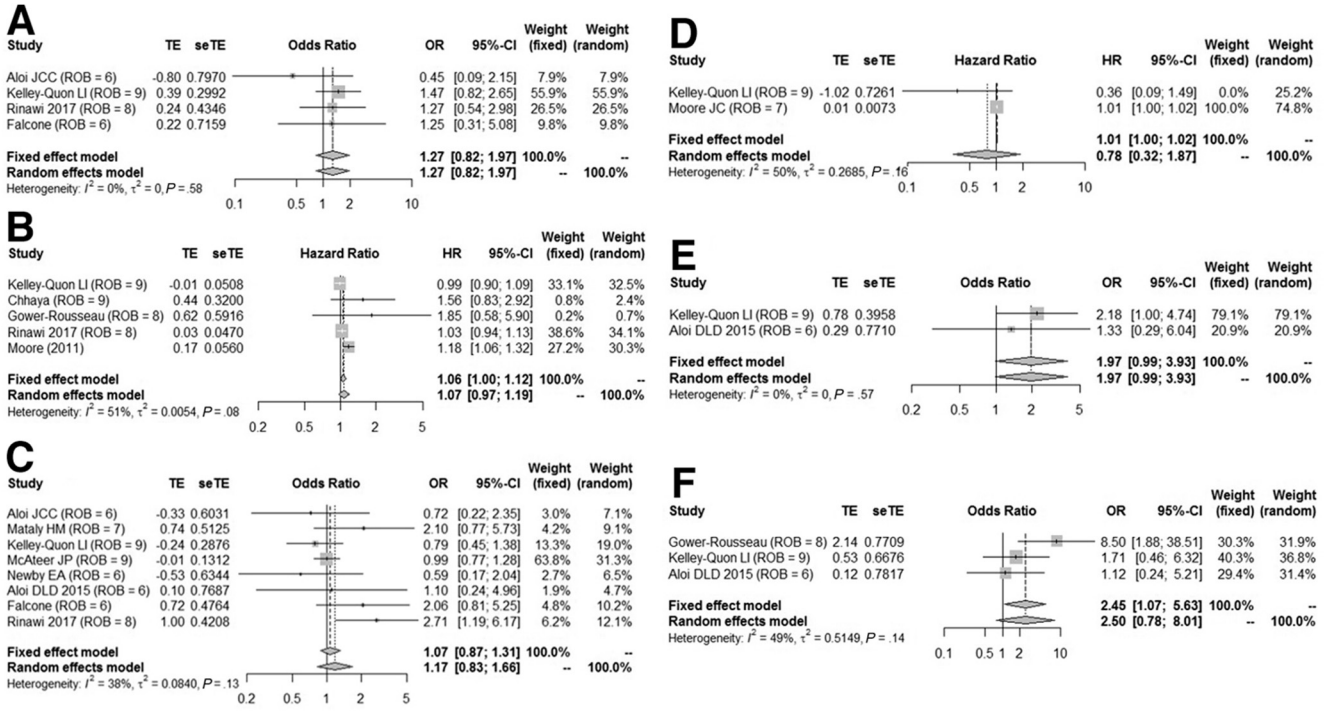

Figure 3. Forest plots for predictors that do not predict colectomy in pediatric UC: (*A*) family history of inflammatory bowel disease, (*B*) age, (*C*) sex, (*D*) erythrocyte sedimentation rate, (*E*) albumin, and (*F*) C-reactive protein.

Table 3. Individual Findings of Studies Included in the Meta-Analysis

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
Colectomy vs age											
Aloi et al (2013)[10]	Colectomy	Age (≤7 y vs ≥8 y)	15/110	5/34	10/76						
*Aloi et al (2014)[29]	Intestinal resection	Age	10/31					NS			
Aloi et al (2015)[9]	Colectomy	Age (mean)	10/31			0.2 (0.12–5.9)		NS			
Chhaya et al (2015)[25]	Colectomy	Age (10–13 y vs 17–24 y as reference)	73/1175				1.89 (1.02–3.5)	.04		1.56 (0.83–2.91)	.17
*Falcone et al (2000)[15]	Colectomy	Age (<18 y vs ≥18 y)	37/73					NS			
Gower-Rousseau et al (2009)[6]	Colectomy	Age (<10 y vs ≥10 y)	27/113				1.85 (0.6–6.1)	.32			
Kelley-Quon et al (2012)[23]	Colectomy	Age	57/406				0.99 (99% CI 0.87–1.13)	.837			
*Ledder et al (2014)[26]	Colectomy	Age (<6 y vs 6–17 y)	3	3/20	0/19						
*Malaty (2013)[16]	Colectomy (partial/total)	Age	/115					NS			
McAteer et al (2013)[22]	Colectomy	Age (0–4 y, 5–10 y, 11–14 y, with 15–17 y reference) (all NS, results presented for 0–4 y vs 15–17y)	227/8066						1.06 (0.61–1.85)		.827
Moore et al (2011)[12]	Colectomy	Age (mean)	37/135				1.16 (1.05–1.29)	.01		1.18 (1.06–1.32)	0.00 (imputed model)
Nambu et al (2016)[27]	Colectomy	Age (0–7 y vs 8–15 y)	11/63	1/10	10/53						
*Newby et al (2008)[28]	Major surgery	Age	/210					.14			
Rinawi et al (2017)[14]	Colectomy	Age (median)	34/188				1.03 (0.94–1.13)	.524			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
*Schechter et al (2015)[13]	Colectomy	Age	4/115 at 12 months; 12/115 at last follow-up					NS			
*Størdal (2004)[30]	Surgery	Age (mean)	3/14					NS			
Colectomy vs sex											
Aloi et al (2013)[10]	Colectomy	Sex	15/110			0.72 (0.22–2.34)		0.82			
Aloi et al (2015)[9]	Colectomy	Sex (male vs female)	10/31	5/15	5/16	1.2 (0.2–6.0)		NS			
Chhaya et al (2015)[25]	Colectomy	Sex (female vs male)	73/1,175				1.25 (0.79–1.99)	.35			
Falcone et al (2000)[15]	Colectomy	Sex (male vs female)	37/73	21/35	16/38						
Gower-Rousseau et al (2009)[6]	Colectomy	Sex (male vs female)	27/113				0.8 (0.4–1.8)	.6			
Kelley-Quon et al (2012)[23]	Colectomy	Sex (male vs female)	57/406	25/199	32/207		0.91 (99% CI, 0.30–2.78)	.827			
Lascurain et al (2016)[31]	Colonic Surgery	Sex (male vs female)	PSC-IBD: 0.4 colonic surgeries/1 000 patient-years Non–PSC-IBD: 0.54 surgeries/ 1000 patient-years				1.9 (0.9–3.8)	.054		2.1 (1.1–4.2)	.034
Malaty (2013)[16]	Colectomy	Sex	20/115				2.1 (1.1–8.2)	.04			
McAteer et al (2013)[22]	Colectomy	Sex (male vs female)	227/8066						0.96 (0.74–1.26)		.789
*Moore et al (2011)[12]	Colectomy	Sex	/135					NS (female trend)			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
Newby et al (2008)[28]	Surgery	Sex (male vs female)	12/74	6/45	6/29						
Rinawi et al (2017)[14]	Colectomy	Sex (female vs male)	34/188	9/85 male	25/103		0.41 (0.19–0.87)	.021		0.24 (0.1–0.57)	.001
*Schechter et al (2015)[13]	Colectomy	Sex	4/115 at 12 months; 12/115 at last follow-up					NS			
*Zwintscher et al (2015)[18]	Surgical intervention	Sex	NA/511 (31 UC)						0.85 (0.77–0.94)		.001
Colectomy vs EIM											
Aloi et al (2013)[10]	Colectomy	EIM (skin, joint, and ocular manifestations, and PSC)	15/110			0.66 (0.17–2.54)		.77			
*Falcone et al (2000)[15]	Colectomy	EIM (mostly arthralgia)	37/73					NS			
Gower-Rousseau et al (2009)[6]	Colectomy	EIM (joint, skin, and ocular manifestations, and PSC)	27/113				3.4 (1.2–10.0)	.02		3.5 (1.2–10.5)	.03
Malaty (2013)[16]	Colectomy	EIM (arthritis, aphthous stomatitis, arthralgia, erythema nodosum, skin lesions, and/or PSC)	20/115				1.4 (0.3–4.0)	NS			
Rinawi et al (2017)[14]	Colectomy	EIM (undefined)	34/188	12/39	22/127		2.03 (1.01–4.1)	.05		1.9 (0.76–4.76)	.171
Colectomy vs family history of IBD											
Aloi et al (2013)[10]	Colectomy	Family history of IBD (first-degree relative UC/CD)	15/110			0.45 (0.095–2.16)		.49			
*Aloi et al (2015)[9]	Colectomy	Family history of IBD	10/31					NS			
Falcone et al (2000)[15]	Colectomy	Family history of IBD	37/73	5/9	32/64						
Gower-Rousseau et al (2009)[6]	Colectomy	Family history of IBD	27/113				2.4 (0.9–6.4)	.08		2.1 (0.7–5.7)	.15
Kelley-Quon et al (2012)[23]	Colectomy	Family history of UC (first degree)	57/406	21/120	36/286						

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
Rinawi et al (2017)[14]	Colectomy	Family history of IBD	34/188	9/43	25/145		1.25 (0.56–2.69)	.562			
Colectomy vs family history of UC											
Gower-Rousseau et al (2009)[6]	Colectomy	Family history of UC	27/113				2.9 (0.9–9.7)	.08			
Kelley-Quon et al (2012)[23]	Colectomy	Family history of UC (first degree)	57/406				1.81 (1.25–2.61)	<.001			
Colectomy vs disease extent											
Aloi et al (2013)[10]	Colectomy	Disease extent (extensive disease E3)	15/110			7.4 (2.2–24.8)		.001			
Aloi et al (2015)[9]	Colectomy	Disease extent (E4 vs E1, E2, E3)	10/31	7/18	3/13	1.6 (0.3–8.0)		NS			
Assa (2018)[11]	Colectomy	Disease extent (E3/E4 at diagnosis)	22/126	18/88	4/35			.18			
*Falcone et al (2000)[15]	Colectomy	Disease extent (pancolitis)	37/73					S			
Gower-Rousseau et al (2009)[6]	Colectomy	Disease extent (E3 vs E1)	27/113	8/42	5/71		2.4 (0.8–6.6)	.11		2.4 (0.8–6.8)	.10
*Hochart et al (2017)[17]	Colectomy	Disease extent (E1 vs E2–E4)	NA/158					NS			
*Malaty (2013)[16]	Colectomy	Disease extent (proctitis)	20/115			1.4 (0.7–4.5)		NS			
Moore et al (2011)[12]	Colectomy	Extensive disease (proximal to splenic flexure) vs nonextensive disease	37/135	27/99	10/36		1.44 (0.56–3.74)				
Rinawi et al (2017)[14]	Colectomy	E4 and E3 each vs proctitis	34/188				0.33 (0.04–2.81) /3.44 (1.26–9.36)	.309/.016		0.4 (0.1–2.2)/5.3 (0.9–8.2)	
Schechter et al (2015)[13]	Colectomy	Disease extent (extensive/pancolitis vs left sided/proctitis)	4/115 at 12 months; 12/115 at last follow-up	9/86	3/29			NS			
*Zwintscher et al (2015)[18]	Surgical intervention	Perianal disease				2.01 (1.63–2.48)		<.001			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
Colectomy vs disease extension											
Aloi et al (2013)[10]	Colectomy	Disease extension (involvement during follow-up of at least 1 additional segment)	15/110			2.4 (0.8–7.4)		.12			
Aloi et al (2015)[9]	Colectomy	Disease extension (according to Paris classification)	10/31	2/10	8/21	0.4 (0.4–2.6)		NS			
Gower-Rousseau et al (2009)[6]	Colectomy	Disease extension (yes vs no)	27/113	13/35	1/36		13.3 (1.7–101.7)				
Colectomy vs disease severity											
Aloi et al (2013)[10]	Colectomy	Disease severity at diagnosis	15/110			3.63 (1.13–11.62)		.05			
Aloi et al (2015)[9]	Colectomy	Disease severity at diagnosis	10/31			1.4 (0.2–7.2)		NS			
Assa (2018)[11]	Colectomy	Disease severity at diagnosis (ASC)	22/126	12/37	10/86		3.5 (1.5–8.2)	.002			.008 (only *P* value provided)
Piekkala et al (2013)[19]	Colectomy	Disease severity at diagnosis (PUCAI >65)	24/51	11/15	4/36						
*Rinawi et al (2017)[14]	Colectomy	Disease severity at diagnosis (PUCAI)	34/188					S			
*Schechter et al (2015)[13]	Colectomy	Disease severity at diagnosis (PUCAI)	4/115 at 12 months; 12/115 at last follow-up					NS			
Colectomy vs ESR											
Aloi et al (2015)[9]	Colectomy	ESR (>25 mm/h)	10/31	5/16	5/15	0.9 (0.2–4.1)		NS			
Kelley-Quon et al (2012)[23]	Colectomy	ESR (>20 mm/h)	57/406	8/86	49/320		0.36 (99% CI 0.09–1.55)	.073			
Moore et al (2011)[12]	Colectomy	ESR (mean)	37/135				1.01 (1.001–1.03)	.06			
*Schechter et al (2015)[13]	Colectomy	ESR (median)	4/115 at 12 months; 12/115 at last follow-up					NS			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
Colectomy vs CRP											
Aloi et al (2015)[9]	Colectomy	CRP (>10 mg/L)	10/31	6/18	4/13	1.1 (0.2–5.2)		NS			
Gower-Rousseau et al (2009)[6]	Colectomy	CRP (<10 mg/L vs ≥10 mg/L)	27/113			8.5 (1.9–39)					
Kelley-Quon et al (2012)[23]	Colectomy	CRP (>5 mg/dL)	57/406	3/14	54/392		2.75 (99% CI 0.75–10.15)	.045			
Rinawi et al (2017)[14]	Colectomy	CRP (median)	34/188				1.04 (0.88–1.23)	.629			
*Schechter et al (2015)[13]	Colectomy	CRP	4/115 at 12 months; 12/115 at last follow-up					NS			
Colectomy vs albumin											
Aloi et al (2015)[9]	Colectomy	Albumin (<3.2 g/dL)	10/31	5/14	5/17	1.3 (0.2–6.0)		NS			
Kelley-Quon et al (2012)[23]	Colectomy	Albumin (<3.5 g/dL)	57/406	10/41	47/365		6.05 (99% CI 2.15–17.04)	<.001			
*Moore et al (2011)[12]	Colectomy	Albumin	37/135					NS			
Rinawi et al (2017)[14]	Colectomy	Albumin (mean)	34/188				0.74 (0.4–1.4)	.334			
*Schechter et al (2015)[13]	Colectomy	Albumin	4/115 at 12 months; 12/115 at last follow-up					NS			
Colectomy vs hemoglobin											
Kelley-Quon et al (2012)[23]	Colectomy	Hemoglobin (<10 g/dL)	57/406				0.41 (99% CI 0.03–6.01)	.389			
McAteer et al (2013)[22]	Colectomy	Anemia (ICD-9 category)	227/8066						2.17 (1.64–2.87)		<.001

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
*Moore et al (2011)[12]	Colectomy	Hematocrit	37/135					S			
Rinawi et al (2017)[14]	Colectomy	Hemoglobin (median)	34/188				1.03 (0.87–1.23)	.731			
*Schechter et al (2015)[13]	Colectomy	Hemoglobin	4/115 at 12 months; 12/115 at last follow-up					NS			

NOTE. An asterisk before the study denotes specific predictor-outcome pairs that could not be meta-analyzed because of heterogeneity or insufficient data, including lack of UC-specific data.
EIM, extraintestinal manifestations; ICD-9, International Classification of Diseases, Ninth Revision; NS, not significant; S, significant but no numerical data provided.

analysis but not on multivariate analysis, and 3 found no association.[10,15,16] Meta-analysis of 4 of the studies found a positive association (pooled OR of 3 studies, 1.50; 95% CI, 0.79–2.84; n = 413; $I^2 = 5\%$[10,14,16]; pooled HR of 2 studies, 2.45; 95% CI, 1.22–4.94; n = 301; $I^2 = 0\%$[6,14]) (Figure 2*E*).

Two studies[12,23] were conflicting regarding WBC count at diagnosis, with the larger study of 406 patients not finding a significant result,[23] whereas a smaller study of 135 patients reported an increased risk with either elevated WBC count (mean, 11.6 vs 9.5; $P = .008$) or elevated absolute neutrophil count, as well as an adjusted HR of 1.10 (95% CI, 1.02–1.19) for WBC count.[12]

Statement 1.2. At diagnosis, age, sex, endoscopic severity, erythrocyte sedimentation rate (ESR), hypoalbuminemia, C-reactive protein (CRP), ferritin, ethnicity, anthropometric measures (ie, growth, weight, and body mass index [BMI] *z*-scores), duration of symptoms before diagnosis, genetic polymorphisms, and antineutrophil cytoplasmic antibodies (ANCA) status do not predict colectomy (82% agreement).

Only 2[12,25] of 16 studies on the topic[6,9,10,13–16,22,23,26–30] found an association between age and colectomy. Four meta-analyzable studies[9,10,22,27] were pooled for OR (0.97; 95% CI, 0.43–2.21; n = 8270; $I^2 = 43\%$) and 5[6,12,14,23,25] for HR (1.07; 95% CI, 0.97–1.19; n = 2017; $I^2 = 51\%$) (Figure 3*B*).

Sex was not associated with colectomy in 9[6,9,12,13,15,22,23,25,26] of 13 relevant studies,[6,9,12–16,18,22,23,25,28,31] whereas the remaining 4 studies[14,16,18,31] indicated that boys may be more likely to undergo colectomy. Nonetheless, most studies were meta-analyzable, and the pooled association was negative (OR of 8 studies, 1.17; 95% CI, 0.83–1.66; n = 9063; $I^2 = 38\%$[9,10,14–16,22,23,28]; HR of 5 studies, 1.48; 95% CI, 0.89–2.47; n = 2094; $I^2 = 63\%$[6,14,23,25,31]) (Figure 3*C*).

Endoscopic severity at diagnosis did not predict colectomy in 2 retrospective studies (n = 115 and n = 185).[13,31] The prospective PROTECT pediatric study reached the same conclusion, in which baseline endoscopic severity was not associated with week 12 outcomes.[32]

Four studies[9,13,14,23] did not find an association between ESR at diagnosis and colectomy, consistent with the meta-analysis results of 3 of the studies (OR of 2 studies, 0.63; 95% CI, 0.31–1.26; n = 437; $I^2 = 0\%$[9,23]; HR of 2 studies 0.78; 95% CI, 0.32–1.87; n = 541; $I^2 = 50\%$[12,23]) (Figure 3*D*).

Hypoalbuminemia did not predict colectomy; only 1[23] of 5 studies[9,12–14,23] was positive. Three studies were meta-analyzable[9,12,23] (OR of 2 studies, 1.97; 95% CI, 0.99–3.93; n = 437; $I^2 = 0\%$[9,23]; HR of 2 studies, 2.09; 95% CI, 0.27–16.35; n = 594; $I^2 = 94\%$[14,23]) (Figure 3*E*).

Four[9,13,14,23] of 5[6,9,13,14,23] studies found that CRP at diagnosis did not predict colectomy, consistent with the meta-analysis of 4 of these (OR of 3 studies, 2.5; 95% CI, 0.78–8.01; n = 550; $I^2 = 49\%$[6,9,23]; HR of 2 studies 1.49; 95% CI, 0.59–3.73; n = 594; $I^2 = 72\%$[14,23]) (Figure 3*F*). Of note, in the only positive study, the rate of colectomy was higher among children whose CRP was greater than 10 mg/L at diagnosis.[6] A retrospective study found no association between ferritin at diagnosis and colectomy.[14]

Table 4. Summary of Outcomes and Respective Predictors in Pediatric UC

Outcomes	Predictors	Possible predictors	No association
Colectomy		• At diagnosis: o Disease extent o PUCAI $\geq$65 o Hemoglobin, hematocrit, albumin o Neutrophilic infiltration in the upper gastrointestinal tract • At 3 months: o Family history of UC o Extraintestinal manifestations • PSC • Disease extension over time • *Clostridium difficile* infection	• At diagnosis: o Age o Sex o Endoscopic severity o ESR, CRP, ferritin o Ethnicity o Anthropometric measures o Duration of symptoms before diagnosis o Genetic polymorphisms o ANCA status
ASC		• Disease severity (PUCAI or endoscopic) at onset • Hypoalbuminemia at diagnosis	• Hemoglobin, ESR, CRP • Age • Disease extent
Outcomes of ASC	• PUCAI scores on days 3 and 5 of admission • CRP at days 3 and 5 of treatment • Shorter time from disease onset to ASC	• Ulcerations on x-ray imaging and evidence of megacolon • Genetic polymorphisms • Cytokine status • Fecal inflammatory markers (but not in addition to PUCAI)	• ESR, hemoglobin • Radiologic features other than ulcerations and megacolon • Age • Sex • Disease extent • ANCA$^+$ • Family history of IBD
Disease activity			• Age at diagnosis • Sex • Rectal sparing • ANCA$^+$
Disease extension over time		• Family history of IBD	• Age • Sex • Weight, height • Ethnicity • PUCAI • ANCA$^+$ • Disease extent at diagnosis • CRP, ESR, hemoglobin, hematocrit, albumin, WBC, ferritin

Table 4. Continued

Outcomes	Predictors	Possible predictors	No association
Disease course	• Ethnicity • PUCAI (≤10) at 3 months (predicts steroid-free remission)	• Genetic polymorphisms • Serology may predict anti-TNF use • Disease extent at diagnosis may predict treatment response	• At diagnosis: o Disease severity o Age o Sex o Weight, height o Family history of IBD o Clinical/endoscopic disease o CRP, ESR, hemoglobin, albumin, platelets o Disease extent dose not predict relapse • Duration of symptoms before diagnosis
Cancer	• Concomitant diagnosis of PSC • Longstanding colitis • Male sex • Younger age at IBD diagnosis	• Having a first-degree relative with any cancer before 50 years of age	• Anti-TNF therapy alone

Ethnicity did not predict colectomy in 4 studies.[14,15,23,33] Six studies examined the association between anthropometric characteristics and colectomy.[12,14,18,22,23,34] Only 1 retrospective study of 406 children reported an association between weight loss at diagnosis and colectomy.[23] Two large studies suggested that obesity does not predict colectomy.[22,34]

Delay in diagnosis did not predict colectomy in 3 studies.[6,16,28] The predictive utility of genetic polymorphisms was examined in 6 studies.[35–40] However, reliable relationships are difficult to establish because different polymorphisms were assessed across studies. Specifically, *CARD15* polymorphisms,[35,39] DLG5 polymorphisms,[39] the presence of TC haplotype of OCTN1/2 variants,[39] anti–tumor necrosis factor (TNF) variants,[38] and MDR1 C3425T variants[38] were not associated with colectomy. A genome-wide association study including 1213 patients with UC (261 with childhood-onset UC) found an association between the minor allele of the NKX2-3 gene (s11190140) and the need for surgery ($P = .038$); however, this effect became trend-level among the childhood-onset patient subset.[37] Three studies found no association between ANCA status and colectomy.[9,41,42]

Statement 1.3. Primary sclerosing cholangitis (PSC) may be protective for colectomy (82% agreement).

Two studies found that PSC is protective against the need for colectomy for chronically active or medically refractory colitis, including a study of 8688 children using the Pediatric Health Information System database.[22,31]

Statement 1.4. Disease extension over time may predict the need for colectomy; neutrophilic infiltration of the stomach and duodenum (but not the esophagus) at diagnosis may predict the need for colectomy (86% agreement).

Statement 1.5. *Clostridium difficile* infection may be associated with increased risk of colectomy (85% agreement).

One[6] of 3[6,9,10] studies found an association between disease extension over time and colectomy (HR, 13.3; 95% CI, 1.72–102.87; n = 113), but meta-analysis was possible only on OR and did not reach significance (pooled OR of 3 studies, 2.52; 95% CI, 0.39–16.41; n = 292; $I^2 = 74\%$) (Figure 2*F*). One study identified a significant association between neutrophil infiltration of the stomach and duodenum (but not the esophagus) and greater likelihood of colectomy.[43]

C difficile infection was associated with colectomy in the Pediatric Health Information System database of 8688 children with UC (OR, 1.76; 95% CI, 1.5–3.25).[22]

Prognostic Risk Factors of Acute Severe Colitis and Related Outcomes

Statement 2.1. Disease severity at onset, evaluated by PUCAI or endoscopic assessment, may predict future ASC (96% agreement).

Statement 2.2. Hypoalbuminemia at diagnosis may predict future ASC; no other blood tests (ie, hemoglobin, ESR, and CRP) during the first 3 months after diagnosis are predictors of ASC (92% agreement).

Statement 2.3. Age and disease extent at diagnosis do not predict development of ASC (88% agreement).

Effect of disease severity on ASC was investigated in a chart review of 115 children with new-onset UC.[13] Upon correction with the Bonferroni threshold for multiple testing, only endoscopic severity ($P = .006$) and hypoalbuminemia ($P = .003$) at diagnosis, and PUCAI at diagnosis and at 3 months (both $P < .001$), predicted ASC. Age at diagnosis did not predict ASC in 2 retrospective studies of children with UC.[27,44] One of these studies also found no association between ASC and disease extent.[44]

Statement 2.4. PUCAI scores on days 3 and 5 of hospital admission predict the need for treatment escalation in the short- and long-term period following intravenous corticosteroid treatment (100% agreement).

Statement 2.5. Higher CRP at both days 3 and 5 of treatment predicts response to intravenous steroids; ESR and hemoglobin do not predict outcomes at any time (96% agreement).

Four studies examined PUCAI scores as predictors of steroid response in children hospitalized for ASC.[4,9,45,46] In a prospective study of 128 children and a retrospective study of 99 children hospitalized for ASC, PUCAI of >45 at day 3 and of >70 at day 5 predicted response to steroids and the need for second-line therapy.[4,45] Day 3 PUCAI score also predicted response up to 1 year after discharge ($P < .001$ for time to salvage therapy).[45] After the systematic review, this association was observed further in a small randomized controlled trial of children admitted for ASC[47] but not in another prospective study of 31 children.[9]

Two of 3 studies associated CRP determined at days 3 and 5 of admission for ASC with corticosteroid response.[4,9,45] ESR and hemoglobin did not predict response at any time during hospitalization.[9,45] In a retrospective study of 56 children with ASC, ulcerations and megacolon on abdominal x-ray imaging was associated with nonresponse to intravenous steroids.[48]

Statement 2.6. Shorter time from disease onset to ASC may predict nonresponse to intravenous steroids (94% agreement).

Three studies evaluated time-related parameters as predictors of response.[4,9,45] Two found no association between ASC at first presentation and corticosteroid response compared with those with a relapse.[4] On the other hand, in another prospective cohort, new-onset disease was associated with short-term corticosteroid failure on multivariate analysis, with an OR of 0.27 (95% CI, 0.1–0.7).[45]

Statement 2.7. Genetic polymorphisms and cytokine status may predict the outcome in Acute Severe Colitis (84% agreement).

In the prospective Outcome of Steroid Therapy in Colitis Individuals (OSCI) study of 128 children with ASC, 41 genes were expressed differentially among children who were steroid-resistant; a cluster of 10 genes classified responders from nonresponders with 80% sensitivity and 80% specificity.[40] However, in a case-control study of 588 children with IBD (318 with UC), the 41 polymorphisms identified in the previous study were not associated with colectomy.[36]

Statement 2.8. Fecal inflammatory markers are weak predictors of steroid response and have limited value in addition to the PUCAI in ASC (80% agreement).

In an analysis from the prospective OSCI study including 101 children with ASC, levels of M2-pyrovate kinase and calprotectin on day 3 of hospitalization were higher among steroid-refractory children.[46] However, stool markers did not improve ability to predict steroid nonresponse above and beyond PUCAI.

Statement 2.9. Age, sex, disease extent, ANCA positivity, and family history of IBD do not predict outcomes of ASC (92% agreement).

Age at diagnosis did not predict response to corticosteroids in 2 pediatric studies of ASC.[4,9] On the other hand, in the aforementioned OSCI study, younger age was associated with corticosteroid failure.[45] IBD family history did not predict corticosteroid response in 2 studies.[9,45] Sex and disease extent did not predict response to intravenous steroids in these studies, as well as in an additional study.[4] Perinuclear antineutrophil cytoplasmic antibody positivity similarly did not predict response to corticosteroids.[9]

Prognostic Factors for Chronically Active Pediatric Ulcerative Colitis

Statement 3.1. Age at diagnosis and sex do not predict disease activity (96% agreement).

Studies suggested that age at diagnosis[27,49] and sex[50] do not predict longitudinal disease activity. In another retrospective study of 8120 patients with UC (210 of whom diagnosed younger than 16 years of age), younger age was associated with disease worsening.[51] However, childhood-onset disease was not analyzed separately.

Statement 3.2. Rectal sparing at diagnosis does not predict disease activity; no studies have evaluated the association between disease extent and disease activity in pediatrics (94% agreement).

In a single study published to date including 30 children with UC, rectal sparing was not associated with disease activity.[52] Of note, a higher proportion of children with proctitis achieved remission with initial medical treatment than those with rectal sparing.

Statement 3.3. ANCA positivity may not predict disease activity or endoscopic inflammatory grading (96% agreement).

One small retrospective study of 38 children with ulcerative proctitis found no association between ANCA and disease activity or endoscopic inflammatory grading.[41]

Statement 3.4. Family history of IBD may predict disease extension over time (91% agreement).

Three studies evaluated family history as a predictor of disease extension over time, of which only 1 found an

association.[6,10,53] In that longitudinal study of 113 children, family history also predicted disease extension after controlling for follow-up duration and disease extent at diagnosis.[6]

Statement 3.5. At diagnosis, age, sex, weight, height, ethnicity, PUCAI, ANCA positivity, disease extent at diagnosis, and routine laboratory measures (CRP, ESR, hemoglobin/hematocrit, albumin, WBC, and ferritin level) do not predict disease extension (86% agreement).

Age at diagnosis and sex did not predict disease extension in 5 studies.[6,10,16,54,55] Similarly, weight, height, and BMI were not predictors in 2 studies.[53,55] One retrospective study reported no association between ethnicity and disease extension in 723 patients with childhood-onset IBD.[53]

Disease activity at diagnosis (measured by the PUCAI) was evaluated as a predictor for disease extension in 4 pediatric studies,[10,53–55] 1 of which (n = 113) found an association, with an adjusted HR of 8.77 (95% CI, 1.75–43.9).[53] The 3 others did not find any significant association.

Neither of the 2 studies exploring disease extent at diagnosis as a predictor for disease extension over time reported a significant association.[6,10] Four of the 5 studies reporting on differing laboratory values at diagnosis (ie, CRP, ESR, hemoglobin, hematocrit, albumin, WBC, and ferritin level) did not report an association with disease extension over time.[6,10,54,55] One study, which included 134 patients with UC with at least 5 years' follow-up, found an association between lower zinc levels at diagnosis and disease extension on multivariate analysis (HR, 0.94; 95% CI, 0.88–0.99; higher levels were protective).[53]

Statement 3.6. PUCAI score (≤10) at 3 months predicts sustained steroid-free remission; disease severity at diagnosis (assessed clinically or endoscopically) does not predict subsequent use of immunomodulators or biologics (81% agreement).

Disease severity (clinical or endoscopic) at diagnosis was not associated with subsequent use of immunomodulators or biologics in 4 studies.[13,56–58] However, at 3 months, the probability of achieving 1-year sustained steroid-free remission was higher among children with PUCAI of ≤10, regardless of thiopurine or steroid use (probability of 48% in children with inactive disease vs 9%; $P < .0001$).[13] In the same study, PUCAI scores at diagnosis and at 3 months predicted the need for anti-TNF or calcineurin inhibitors during the first year. After completion of the systematic review, the PROTECT inception prospective cohort of pediatric UC was published, verifying that PUCAI at baseline and at 1 month after diagnosis independently predicted 1-year steroid-free remission.[20]

Statement 3.7. Genetic polymorphisms, particularly in genes associated with the treatment pathways, and ethnicity may predict response to medications (92% agreement).

Three of 5 studies found a positive association between genetic polymorphisms and response to medications in pediatrics.[37–39,59,60] The rs2395185 variant of the HLA gene was associated with response to steroids in a study of 1213 children with UC, but this effect was lost after controlling for age at diagnosis.[37] In a study of 154 children with IBD, BclI polymorphism was associated with steroid response, and the NALP1 Leu55His mutant variant was associated with steroid resistance.[59] Single-nucleotide polymorphisms of TNF-α and MDR1 genes were not associated with any clinical characteristics of UC, although a trend toward increased steroid resistance was noted in carriers of the TNF-α risk genotype.[38] In another study of patients with childhood-onset IBD, HLA-DRB101 was more common among patients who required anti-TNF treatment; no similar association was identified for other haplotypes.[60] No association was noted between the need for steroids and other genes, including CARD15, AA/AG genotypes of DLG5 variant, and presence of TC haplotype of OCTN1/2 variants.[39] In the prospective PROTECT cohort, 33 genes were differentially expressed in the rectum in patients with moderate/severe disease who achieved week 52 corticosteroid-free remission compared with those who did not.[20]

Ethnicity was found to predict treatment escalation in 2 studies. In 107 children with IBD (45 with UC), treatment with steroids, methotrexate, and adalimumab at 1 year was more common among South Asian children than White children.[61] In a 10-year review of 245 children with IBD (40 with UC: 33 White, 7 Blac]), a higher proportion of Black children were prescribed steroids and/or infliximab.[33] After the systematic review, the prospective PROTECT cohort did not find an association between race and sustained corticosteroid-free remission at 52 weeks.[20]

Statement 3.8. Serology (ANCA/anti-*Saccharomyces cerevisiae* antibodies [ASCA]) may predict anti-TNF use, but not immunomodulator use (91% agreement).

The utility of serology to predict the use of medications was inconsistent across 2 pediatric studies. Although 1 showed that perinuclear antineutrophil cytoplasmic antibody$^+$/ASCA$^-$ predicted use of biologics in UC,[42] the other showed no association between serologic markers and steroid or immunomodulator use.[41]

Statement 3.9. At diagnosis, age, sex, weight, height, family history of IBD, clinical/endoscopic disease severity, and laboratory blood tests (CRP, ESR, albumin, hemoglobin, platelets) do not predict medication intensification (90% agreement).

None of 6 relevant studies identified an association between age at diagnosis and response to medications, including steroids.[13,27,57,59,62,63]

Two[26,64] of 5 studies[26,27,49,58,64] reported a positive association between younger age and medication use. Data obtained from a prospective, multicenter observational study (n = 1928 children, 27% with UC) did not find a difference between age groups 1–5, 6–10, and 11–16 years and the use of antibiotics, mesalamine, corticosteroids, or immunomodulators at 1 year after diagnosis. At 5 years, however, those in the youngest group were more likely to receive mesalamine or thiopurine compared with the oldest age group. As for the anti-TNF agents, treatment with infliximab and adalimumab did not differ significantly among the age groups,[49,64] although in the study by Oliva-Hemker et al,[49] exposure to adalimumab was minimal in the younger age group, thus limiting the conclusions that

could be drawn. Additionally, a retrospective chart review of children with IBD (20 of whom with UC were <6 years of age and 19 of whom with UC were between 6 and 17 years) showed a trend for a higher proportion of patients younger than 6 years at diagnosis requiring immunomodulatory therapy; no significant association was found for steroid treatment.[24]

Five of 6 studies identified no association between sex and medication use, treatment response, and sustained steroid-free remission.[50,57,58,62,63] One exception was a study of 154 children with IBD (74 with UC), in which boys were more likely to achieve better outcomes.[59] In retrospective study of 156 children with IBD (47 with UC), BMI and height *z*-scores were not associated with use of immunomodulators.[58] The PROTECT study, including 400 pediatric patients with UC, also did not find an association between age or sex and corticosteroid-free remission at 52 weeks.[20]

No association between family history of IBD and medication intensification was found in 2 studies.[24,62] Disease severity at diagnosis, assessed clinically or endoscopically, did not predict medication use in 4 studies.[13,56–58]

Findings exploring the utility of laboratory tests (CRP, ESR, albumin, hemoglobin, and platelet level) for predicting medication use were inconsistent across 6 studies.[13,56–58,65,66] In 124 children with UC, initial elevated CRP and abnormal iron levels were associated with subsequent use of azathioprine.[56] In a chart review of 115 children with new-onset UC, the need for salvage therapy during the first year was associated with ESR at 3 months.[13] Two other studies found no such association.[58,65] In a retrospective study of 96 children with newly diagnosed UC, tissue and peripheral eosinophil counts correlated with short-term use of corticosteroids, immunomodulators, and biologics.[66] The aforementioned PROTECT study found an association between albumin, ESR, CRP, calprotectin, and bioavailable 25-hydroxyvitamin D and corticosteroid-free remission at 52 weeks, although only hemoglobin ≥10 g/dL at baseline was significant in 386 patients included in a multivariable model. Additionally, on microbiome analysis, decreased expression of Clostridiales was associated with escalation to anti-TNF therapy.[20]

Statement 3.10. Disease extent at diagnosis may predict medication use and response to treatment; it does not, however, predict relapse (87% agreement).

Statement 3.11. Duration of symptoms prior to diagnosis does not predict response to subsequent treatment (96% agreement).

Two of 6 studies identified an association between disease extent and medication use.[11,13,17,58,62,63] Three evaluated response to medication,[13,62,63] and 2 evaluated medication use.[11,58] In 1 of the positive studies, the cumulative probability of immunomodulator use was lower among children with isolated proctitis compared with all others, but anti-TNF therapy use was similar.[17] The other found that those with extensive disease (E3/E4) at diagnosis increased the risk of receiving a biologic compared with patients with limited disease (E1/E2) (HR, 2.7; 95% CI, 1.2–6; $P = .015$).[11]

Two studies evaluated disease extent as a predictor for relapse. In a 1-year prospective study of 37 children with newly diagnosed UC, histologic upper gastrointestinal tract involvement did not differ among those who relapsed compared with those who did not, but children with more extensive disease trended toward a higher likelihood of relapse.[67] Rajwal et al[52] assessed relapse index in 30 patients with newly diagnosed UC, 7 (23%) of whom had rectal sparing at endoscopy. The relapse index was slightly higher for children presenting with proctitis but did not reach statistical significance.[52] Similarly to prior adult data,[68] the PROTECT cohort found that patients with lower rectal eosinophil counts (<32 per high-power field) before treatment were more likely to escalate to anti-TNF therapy.[20]

None of the 3 studies exploring time to diagnosis as a predictor for treatment response reported a significant association.[58,62,63]

Prognostic Risk Factors for Cancer and/or Mortality in Children With Inflammatory Bowel Disease

Studies investigating cancer or mortality in PIBD are scarce and typically do not differentiate between UC and CD. Therefore, for these specific outcomes, prognostic factors were described for patients with PIBD in general.

Statement 4.1. Concomitant diagnosis of PSC, longstanding colitis (>10 years), male sex, and younger age at IBD diagnosis are risk factors for any cancer; having a first-degree relative with any cancer before 50 years of age may be a risk factor for cancer in UC (91% agreement).

In a study of 698 patients with childhood-onset IBD (median 15-year follow-up), 9 developed cancer (standardized incidence ratio [SIR] 3.0; 95% CI, 1.3–5.9; $P < .02$).[69] In a cohort study comparing 9405 pediatric patients with IBD with 92,870 age- and sex-matched control individuals, a higher risk for cancer was found in boys (HR, 4.6; 95% CI, 4.4–6.4) than in girls (HR, 1.5; 95% CI, 1.4–1.7) and in those with a younger age at first diagnosis ($P = .006$).[70] This study also found that longstanding colitis (≥10 years) was associated with increased risk of cancer. Having a first-degree relative with a cancer diagnosis before 50 years of age was associated with increased risk of cancer among patients with UC but not with CD.[70]

PSC predicted colorectal cancer and cholangiocarcinoma.[70,71] In the previously described study of 9405 patients with childhood-onset IBD, patients with PSC IBD were at greater risk of developing cancer than those in the general population.[71] In addition, in a prospective case series from 20 European countries and Israel studying 60 patients with childhood-onset IBD who developed a malignancy or died, 56% of patients with fatal gastrointestinal cancer (cholangiocarcinoma or colorectal cancer) were also diagnosed with PSC.[71]

A pediatric study reported 15 malignancies among 5766 patients with 24,543 years of follow-up, including 8 hematopoietic tumors.[32] The SIR for the development of a

malignancy in patients exposed to a thiopurine with or without a biologic was significantly higher (SIR, 2.88; 95% CI 1.44–5.14), whereas this was not the case in patients exposed to a biologic monotherapy. In a population-based study of 2114 children who were ever treated with thiopurines, 15 cases of cancer were identified, of which 2 patients also received an anti-TNF agent at some point. Confidence intervals were wide and overlapping, with no significant differences between groups of different drug exposures, which led the researchers to conclude that they cannot rule out thiopurines or anti-TNF agents as risk factors of cancer.[70]

In the aforementioned study, when compared with the Surveillance, Epidemiology, and End Results (SEER) reference population, no increased risk of malignancy was identified in a infliximab-treated cohort and biologics cohort.[32]

Statement 4.2. Malignancy and infection (sepsis and opportunistic infections) may be risk factors for mortality, but no population-based studies are currently available (83% agreement).

A survey of 21 pediatric gastroenterologists from 20 European countries and Israel identified 18 cases of cancer and 31 deaths in 44 children with IBD.[72] Infection was the most common cause of mortality, particularly among patients receiving 2 or more immunosuppressive agents. The second leading cause of mortality was cancer (5 cases, of which 3 were considered treatment related and 1 disease related [2 hepatosplenic T-cell lymphomas, 1 Epstein-Barr virus–positive lymphoma, and 1 colonic adenocarcinoma]).[72]

After the index date of systematic review, Olen et al[73] reported 294 deaths among 138,690 patient-years of follow-up (n = 9442 individuals with pediatric IBD; 50 years of follow-up). This translated into 2.1/1000 person-years compared with 0.7/1000 person-years in matched control individuals. HRs for death were increased for UC (4.0; 95% CI, 3.4–4.7), CD (2.3; 95% CI, 1.8–3.0), and IBD unclassified (2.0; 95% CI, 1.2–3.4). Patients with IBD diagnosis at <6 years of age had higher HRs for death than children with later IBD onset. Apart from patients with very-early-onset IBD, the highest relative risk was observed in patients with UC with concomitant PSC (HR, 12.2; 95% CI, 8.4–17.8). Patients with UC undergoing bowel surgery or having a first-degree relative with UC were also at higher risk of death.

In the same aforementioned study, underlying causes for death in childhood-onset IBD included cancer (HR, 6.6; 95% CI, 6.3–8.2), infections (HR, 6.3; 95%, CI 2.1–16.9), and respiratory diseases (HR, 4.7; 95% CI, 1.8–11.3).[73]

Implications for Practice

The PIBD-Ahead educational program reviewed clinical studies that sought to identify predictors of disease outcomes and treatment response in pediatric UC. Because treatments for IBD have advanced rapidly in recent years, it is important to explore predictors to guide management of the disease. Although this project is unprecedented in its systematic approach, with comprehensive involvement of many PIBD experts from dozens of countries and stringent consensus methodology, it is not without limitations. The evidence was often limited, based on small retrospective cohorts, and with a paucity of well-designed population-based studies. This has also led to heterogeneity in the methodology and results of the included studies. We have thus meta-analyzed only major outcomes and used soft language in statements when evidence was incomplete. The inability to separate CD and UC as exposures associated with future cancer or mortality is also a limitation. Nonetheless, the consensus statements presented here synthesize the current body of empirical evidence for predictors of pediatric UC outcome with the aim of supporting optimal, personalized treatments for children. This systematic review also serves to underscore the importance of continued multicenter efforts to further elucidate outcomes in pediatric UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi:10.1053/j.gastro.2020.07.066.

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Correspondence
Address correspondence to: Dan Turner, MD, PhD, The Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, The Hebrew University; POB 3235, Jerusalem 91031, Israel. e-mail: turnerd@szmc.org.il; fax: +972-2-6555756.

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Conflicts of interest
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Supplementary Methods

Search String for Cochrane

('crohn*' or 'ulcerative colitis' or 'inflammatory bowel diseas*' or 'IBD') and ((infant or pediatric or paediatric or adolescent or teenagers or teens) and (predict* or prognos* or surgery or colectomy or resection or 'steroid depend*' or hospitalization* or complication or stenosis or fistul* or 'penetrat*' or growth or height or osteopenia or osteoporosis or 'acute severe colitis' or cancer or malignancy or lymphoma or 'colorectal carcinoma' or 'colorectal cancer' or 'colon cancer' or adenocarcinoma or death or mortality or outcome or 'quality of life' or melanoma))

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'crohn*' OR 'ulcerative colitis' OR 'inflammatory bowel diseas*' OR 'ibd' AND (infant OR pediatric OR paediatric OR adolescent OR teenagers OR teens) AND (predict* OR prognos* OR surgery OR colectomy OR resection OR 'steroid depend*' OR hospitalization* OR complication OR stenosis OR fistul* OR 'penetrat*' OR growth OR height OR osteopenia OR osteoporosis OR 'acute severe colitis' OR cancer OR malignancy OR lymphoma OR 'colorectal carcinoma' OR 'colorectal cancer' OR 'colon cancer' OR adenocarcinoma OR death OR mortality OR outcome OR 'quality of life' OR melanoma) AND [english]/lim AND [1992-2017]/py

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("crohn$"[MeSH Terms] OR "crohn$"[all fields])

OR ("ulcerative colitis"[MeSH Terms] OR "ulcerative colitis"[all fields] OR UC[MeSH Terms] OR UC[all fields]) OR ("inflammatory bowel diseas$"[MeSH Terms] OR "inflammatory bowel diseas$"[all fields] OR "IBD"[MeSH Terms] OR "IBD"[all fields]))

AND ((infant[MeSH] OR pediatric[MeSH] OR paediatric [MeSH] OR adolescent[MeSH] OR teenagers[MeSH] OR teens[MeSH]) AND (predict$[all fields] OR prognos$[all fields] OR surgery[all fields] OR colectomy[all fields] OR resection[all fields] OR "steroid depend$"[all fields] OR hospitalization$[all fields] OR complication[all fields] OR stenosis[all fields] OR fistul$[all fields] OR penetrat$[all field] OR growth[all fields] OR height[all fields] OR osteopenia[all fields] OR osteoporosis[all fields] OR "acute severe colitis"[all fields] OR cancer[all fields] OR malignancy[all fields] OR lymphoma[all fields] OR "colorectal carcinoma"[all fields] OR "colorectal cancer"[all fields] OR "colon cancer"[all fields] OR adenocarcinoma[all fields] OR death [all fields] OR mortality[all fields] OR outcome[all fields] OR "quality of life"[all fields] OR melanoma[all fields])))) AND english[la] AND "1992/01/01"[pdat]:"2017/06/01"[pdat]

Supplementary Results

Prognostic Factors for Colectomy. Rates of extensive colitis are high in childhood-onset UC, and many children with proctitis or distal UC require colectomies after disease progression to extensive colitis. Cumulative rates of colectomy are 8% at 1 year, 26% at 5 years, and 20%–41% at 10 years.[1,2] Meta-analyses were performed for several predictors of colectomy owing to the comparatively high number of studies investigating these relationships.

Statement 1.1. At diagnosis, disease extent, Pediatric Ulcerative Colitis Activity Index (PUCAI) score (≥65 points), hemoglobin, hematocrit, and WBC may predict colectomy; PUCAI score ≥65 during the subsequent 3 months, family history of UC, and extraintestinal manifestations may predict colectomy (96% agreement).

Association between disease extent and likelihood of colectomy was assessed in 11 studies,[1,3–12] 7 of which were appropriate for inclusion in the meta-analysis.[1,3–8] A study by Aloi et al in 2013 was included twice in the OR analysis, once for the E3 outcome and once for the E4 outcome, which was also true for Rinawi et al in the HR analysis.[4,8] Seven studies[1,3–8] reported no significant association, but a meta-analysis of 6 analyzable studies was positive (OR of 6 studies, 1.54; 95% CI, 0.72–3.29; n = 627; I^2 = 38%[1,3–7]; HR of 3 studies, 1.81; 95% CI, 0.73–4.52; n = 436; I^2 = 61%[1,6,8]). Because Aloi et al and Rinawi et al were weighted twice for each of the E3/E4 outcomes, it is 6 absolute studies (n = 590). Two of these studies looked at proctitis or E1 disease and were meta-analyzed together (OR, 0.93; 95% CI, 0.45–1.91; P = .8434; n = 273; I^2 = 45.8%).[4,11]

Of the 6 studies, only 1 study including 110 children with UC found an association between E3 disease at diagnosis and colectomy (OR, 7.4; 95% CI, 2.2–24.8; P = .001). Of note, E4 disease did not predict colectomy, which may be attributable to the small subsample of patients with E4 disease in this study.[4] Conversely, the sixth study of 188 patients diagnosed between 1981 and 2013 with childhood-onset UC determined that a significantly greater proportion of children with pancolitis (50%) underwent surgery than those without (27.3%; P = .016) but found a significant association with colectomy for E4 disease and no significant association for E3 disease, perhaps owing to a relatively small subset of patients with E3 disease in this study.[8] The remaining 4 studies included in this meta-analysis did not support disease extent as a predictor of colectomy.[3,5–7]

The seventh study, with 73 patients, for which there were insufficient data for analysis, suggested that a greater proportion of patients with pancolitis underwent colectomy.[9] The eighth and ninth studies regarding disease extent assessed proctitis or E1 disease as a risk factor for colectomy and found no association; a retrospective study of 115 children diagnosed between 1986 and 2003 reported no association between proctitis and colectomy,[10] and a longitudinal study of childhood-onset ulcerative proctitis in 159 patients with UC found that the risk for colectomy rates did not differ between children with E1 disease compared with those with E2/E3/E4 disease[11] (0/2 studies positive; OR, 0.93; 95% CI, 0.45–1.91; P = .8434; 2 studies, n = 273; I^2 = 46%; fixed effects).

Four meta-analyzable studies out of 6 suggested that disease severity at diagnosis (ie, PUCAI score of ≥65 at diagnosis and at 3 months) predicts colectomy (OR of 4 studies, 4.50; 95% CI, 1.83–11.06; P = .001; n = 318; I^2 =

49%; random effects[3–5,13]). An additional study that was not suitable for inclusion in meta-analysis, because PUCAI was expressed as a continuous variable, also supports the finding that the PUCAI score at diagnosis was significantly associated with a higher likelihood of colectomy (HR, 1.07; 95% CI, 1.04–1.1; $P < .001$). The PUCAI score at diagnosis did not predict colectomy in a prospective study of 31 children with UC or in a chart review of 115 children with new-onset UC.[3,7] However, this chart review observed a significant association between PUCAI score at 3 months and likelihood of colectomy ($P = .036$), such that the rate for colectomy was 24% among children with moderate to severe disease and 6.5% for children with mild disease or in remission.[7] In contrast, ASC (ie, PUCAI score of >65 at diagnosis) predicted colectomy in a retrospective study of 110 children diagnosed with UC (OR, 3.63; 95% CI, 1.13–11.62; $P = .05$).[4] Additionally, in a study of 51 children with UC (24 requiring surgical treatment), severe disease at diagnosis (PUCAI score of >65 and hospitalization) was associated with a significantly greater likelihood for colectomy (46% with severe disease vs 15% without severe disease; $P = .03$).[13] Consistent with these results (but with an outcome that could not be included on meta-analysis), a PUCAI score of >45 at day 3 of hospitalization was associated with time to colectomy from the first day of intravenous corticosteroid therapy ($P = .001$) in a retrospective study of 99 children hospitalized for severe UC.[14]

Two studies assessed severe disease (PUCAI ≥65) after diagnosis; the first during the first 3 months of follow-up was also associated with colectomy, although this effect was lost in a multivariate analysis (HR, 4; 95% CI, 0.95–8.2),[8] and the second at the 3-month time point in 115 patients, as noted earlier.[7]

Findings were inconsistent across studies for the predictive utility of hemoglobin, hematocrit, and albumin at diagnosis on colectomy rates. Three studies assessing albumin were included in the meta-analysis, with the largest study including 406 patients showing a significant association.[3,8,15] Two additional studies with data that could not be meta-analyzed were not significant.[6,7] Meta-analyses showed that low hemoglobin (1[16] of 4 studies[7,8,15,16] positive; OR of 2 studies, 1.26; 95% CI, 0.28–5.68; n = 8472; $I^2 = 83\%$; fixed effects[15,16]; HR of 2 studies, 1.03; 95% CI, 0.86–1.22; $P = .7711$; n = 594; $I^2 = 0\%$; fixed effects[8,15]) and albumin (1[15] of 5 studies[3,6–8,15] positive; OR of 2 studies, 1.97; 95% CI, 0.99–3.93; $P = .0543$; n = 437; $I^2 = 0\%$; fixed effects[3,15]; HR of 2 studies, 1.67; 95% CI, 1.02–2.73; $P = .0403$; n = 594; $I^2 = 94\%$; fixed effects[8,15]) may predict colectomy. In a chart review of 470 patients with childhood-onset IBD (135 with UC), hematocrit at diagnosis was associated with a greater likelihood for colectomy, whereas albumin at diagnosis was not.[6] Association between hematocrit and colectomy persisted in a multivariate analysis (HR, 0.93; 95% CI, 0.89–0.98).[6] Of note, in a medical review of 8688 children with a primary UC diagnosis from the Pediatric Health Information System database, anemia (hemoglobin level) was associated with increased likelihood of colectomy (OR, 2.19; 95% CI, 1.65–2.92; $P < .001$).[16]

Six studies[1,4,8,9,15,17] assessing family history of IBD as a predictor for colectomy found no association (pooled OR of 4 studies, 1.27; 95% CI, 0.82–1.97; $P = .2857$, n = 777, $I^2 = 0\%$, fixed effects[4,8,9,15]; pooled HR of 2 studies, 1.51; 95% CI, 0.80–2.82; $P = .2015$; n = 301; $I^2 = 0\%$; fixed effects[1,8]). One study also did not find any significant association but did not contain significant data for inclusion.[3] However, family history of UC was positive in 1[15] of 2 studies and in the meta-analysis (HR of 2 studies, 1.89; 95% CI, 1.33–2.68; $P = .0004$; n = 557; $I^2 = 0\%$; fixed effects).[1,15] One study, including 406 patients, found a significant association between a first-degree relative with UC and colectomy,[15] whereas the other study of 113 patients with UC did not find any significant association.[1]

Association between extraintestinal manifestations and colectomy was explored in 5 studies; 1[1] found an association with colectomy (adjusted HR, 3.5; 95% CI, 1.2–10.5; $P = .03$), whereas the second[8] found borderline significance on univariate analysis (but not on multivariate analysis) (HR, 2.03; 95% CI, 1.01–4.1; $P = .05$). Three remaining studies found no association.[4,9,10] On meta-analysis, the association with colectomy was positive (pooled OR of 3 studies, 1.50; 95% CI, 0.79–2.84; n = 413; $I^2 = 5\%$[4,8,10]; pooled HR of 2 studies, 2.45; 95% CI, 1.22–4.94; n = 301; $I^2 = 0\%$; fixed effects[1,8]). One single-center study found no significant association between extraintestinal manifestations and colectomy in 115 children with new-onset UC diagnosed between 1986 and 2003,[10] whereas the remaining 3 showed significance. In a longitudinal study of 113 children with UC from a geographically derived incidence cohort diagnosed between 1988 and 2002, extraintestinal manifestations at diagnosis predicted colectomy in a multivariate analysis (HR, 3.5; 95% CI, 1.2–10.5; $P = .03$).[1] Consistent with this result, a study of 188 patients, 39 of whom had extraintestinal manifestations, found that a significantly greater proportion of children with extraintestinal manifestations at diagnosis (35.3%) underwent colectomy than those without (17.5%, HR, 2.03; 95% CI, 1.01–4.1; $P = .050$); however, this effect was lost in a multivariate analysis.[8]

Two studies[6,15] were conflicting regarding white blood cell (WBC) count at diagnosis, with the larger study of 406 patients not finding a significant result,[15] whereas a smaller study of 135 patients reported an increased risk with either elevated WBC count (mean, 11.6 vs 9.5; $P = .008$) or elevated absolute neutrophil count, as well as an adjusted HR of 1.10 (95% CI, 1.02–1.19) for WBC count.[6]

Statement 1.2. At diagnosis, age, sex, endoscopic severity, erythrocyte sedimentation rate (ESR), hypoalbuminemia, C-reactive protein (CRP), ferritin, ethnicity, anthropometric measures (ie, growth, weight, and body mass index [BMI] *z*-scores), duration of symptoms prior to diagnosis, genetic polymorphisms, and antineutrophil cytoplasmic antibodies (ANCA) status do not predict colectomy (82% agreement).

Age at diagnosis as a predictor for subsequent colectomy was examined in multiple studies and overall was found to lack correlation with need for colectomy (2/16 studies positive)[6,18] (4 meta-analyzable studies[3,4,16,19]: OR,

0.97; 95% CI, 0.43–2.21; n = 8270; I^2 = 43%; HR of 5 studies, 1.07; 95% CI, 0.97–1.19; n = 2017; I^2 = 51%[1,6,8,15,18]). Although 2 studies found a significant association between age and colectomy, they were conflicted as to the direction of significance; in 1 study of 135 children with UC, children without colectomy were significantly younger at diagnosis (98 children; mean age at diagnosis, 12 ± 4.2 years) than those with colectomy (37 children; mean age at diagnosis, 13.9 ± 3.5 years; HR, 1.16; 95% CI, 1.05–1.29; $P = .01$).[6] In contrast, in a study of 2770 children with IBD (1175 with UC), children diagnosed between ages 10 and 13 years were significantly more likely to undergo surgery than those diagnosed between ages 17 and 24 years (HR, 1.89; 95% CI, 1.02–3.50; $P = .04$).[18] Ten studies were included in the meta-analysis,[1,3,4,6,8,15,16,18–20] whereas 6 could not be included owing to a lack of sufficient data for analysis.[7,9,10,21–23] Three additional studies containing study populations that were too dissimilar for comparison on meta-analysis also found no significant correlation between age and need for colectomy.[5,12,24]

Sex was not associated with colectomy in 9[1,3,6,7,9,15,16,18,21] of 13 relevant studies.[1,3,6–10,12,15,16,18,21,25] Eleven studies with sufficient data included in the meta-analysis also showed no association (OR of 8 studies, 1.17; 95% CI, 0.83–1.66; $P = .3685$; n = 9063; I^2 = 38%; random effects[3,4,8–10,15,16,21]; HR of 5 studies, 1.48; 95% CI, 0.89–2.47; $P = .1317$; n = 2094; I^2 = 63%; random effects[1,8,15,18,25]). Three positive studies indicated that boys are more likely to undergo colectomy than girls.[8,10,25] One (with insufficient data for inclusion in the meta-analysis) showed a trend to a greater proportion of female patients requiring colectomy.[6] In a retrospective study of 37 patients with PSC IBD and 148 matched, non–PSC IBD children whose medical information was collected between 2005 and 2011, boys (n = 102) had significantly higher rates of colonic surgery (colectomy or hemicolectomy for children with UC) than girls (n = 74; HR, 1.9; 95% CI, 0.9–3.8,; $P = .054$; adjusted hazard ratio [aHR], 2.1; 95% CI, 1.1–4.2; $P = .034$).[25] In a longitudinal study of 115 children with UC identified between 1986 and 2003, boys were twice as likely as girls to undergo colectomy (OR, 2.1; 95% CI, 1.1–8.2; $P = .04$).[10] In a chart review of 188 children with UC diagnosed between 1981 and 2013 in a single center, boys were significantly more likely to have undergone colectomy (aHR, 4.2; $P = .001$).[8] In an additional study not included in this count owing to a dissimilar patient population, among 511 inpatients with IBD (31 with UC) admitted with perianal IBD, girls were significantly less likely to receive surgical intervention (OR, 0.85; 95% CI, 0.77–0.94; $P = .001$).[12]

Endoscopic severity at diagnosis did not predict colectomy in 2 retrospective studies, in a chart review of 115 children with new-onset UC and a retrospective study of 37 patients with PSC IBD and 148 matched, non–PSC IBD children whose data were collected between 2005 and 2011.[7,25]

ESR at diagnosis was not a predictor of colectomy based on 4 studies[3,7,8,15] (OR of 2 studies, 0.63; 95% CI, 0.31–1.26; $P = .1916$; n = 437; I^2 = 0%; fixed effects[3,15]; HR of 2 studies, 0.78; 95% CI, 0.32–1.87; n = 541; I^2 = 50%; fixed effects[6,15]). In a medical records review of 406 children with UC extracted from the Pediatric Inflammatory Bowel Disease Consortium (PedilBDC) database, ESR of >20 mm/h at diagnosis was not associated with colectomy status.[15] In a chart review of 115 children with new-onset UC, risk for colectomy was not associated with ESR at diagnosis.[7] Similarly, ESR was not associated with colectomy in a prospective study of 31 children hospitalized for ASC.[3] Additionally, in a chart review of 188 patients with childhood-onset UC diagnosed between 1981 and 2013, ESR did not predict colectomy status.[8] In contrast, a chart review of 470 patients with childhood-onset IBD (155 with UC) at a single center over 10 years reported a trend toward a higher ESR among children with colectomy (38 mm/h) than among those without (28 mm/h; $P = .06$).[6]

Hypoalbuminemia did not predict colectomy; only 1[15] of 5 studies[3,6–8,15] was positive. Three studies were meta-analyzable[3,8,15] (OR of 2 studies, 1.97; 95% CI, 0.99–3.93; n = 437; I^2 = 0%[3,15]; HR of 2 studies, 2.09; 95% CI, 0.27–16.35; n = 594; I^2 = 94%[8,15]).

CRP level at diagnosis was examined as a predictor for colectomy in 5 studies[1,3,7,8,15] and was found not to be a significant predictor (1/5 studies positive[1]); 4 studies included sufficient data for meta-analysis[1,3,8,15] (OR, 2.5; 95% CI, 0.78–8.01; 3 studies,[1,3,15] n = 550; I^2 = 49%; HR, 1.49; 95% CI, 0.59–3.73; 2 studies,[8,15] n = 594; I^2 = 72%). In the 1 positive longitudinal study of 113 children with UC in a geographically derived incidence cohort diagnosed between 1988 and 2002, the rate of colectomy was higher among children whose CRP was greater than 10 mg/L at diagnosis (HR, 8.5; 95% CI, 1.9–39). However, CRP level records were available for only 42 children; thus, the conclusions that can be drawn from this finding are limited.[1] All other studies found no relationship between CRP at diagnosis and colectomy among children with UC, for example, in a medical record review, where CRP >5 mg/dL at diagnosis did not predict colectomy,[15] and in a chart review study of 115 children with new-onset UC, a prospective study of 31 children with UC, and the retrospective chart review study of 188 patients with childhood-onset UC diagnosed between 1981 and 2013.[3,7,8] A retrospective study found no association between hemoglobin or ferritin at diagnosis and colectomy.[8]

Ethnicity did not predict colectomy in 4 studies (0/4 studies positive). These studies included an analysis of medical records data of 406 children with UC extracted from the PedilBDC database, a 10-year retrospective review of medical record review of 245 children with IBD (73 with UC), and a retrospective chart review study of 188 patients diagnosed between 1981 and 2013 with childhood-onset UC.[8,9,15,26]

Six studies examined the association between anthropometric characteristics and colectomy, including, obesity, weight loss, growth failure, weight, height, and BMI *z*-scores at diagnosis.[6,8,12,15,16,27] Only 1 retrospective study of 406 children with UC extracted from the PedilBDC database reported a significant association between weight loss at diagnosis and colectomy at 2 years (HR, 4.01; 99% CI, 1.82–8.83; $P < .001$) and overall risk for colectomy (HR, 2.55;

95% CI, 1.21–5.35; $P = .001$).[15] A chart review of 470 patients with childhood-onset IBD (155 with UC) at a single center over 10 years and a retrospective chart review of 188 patients diagnosed between 1981 and 2013 with childhood-onset UC found no relationship between height at diagnosis and colectomy.[6,8] A retrospective chart review also failed to identify the predictive utility of both weight and BMI on colectomy.[6] Studies also suggest that obesity does not predict colectomy. A chart review of 12,465 children with IBD admitted to the 2009 Kids' Inpatient Database (164 labeled as obese) found no association between obesity and surgery (OR, 0.80; 95% CI, 0.48–1.31; $P = .37$).[27] Similarly, a medical review of 8688 children with a primary UC diagnosis derived from the Pediatric Health Information System database reported a 2.8% incidence of colectomy (n = 240) and identified no relationship between obesity and colectomy.[16]

Duration of symptoms before diagnosis (0/3 studies positive) also did not predict colectomy in 3 studies: a retrospective study of 115 children diagnosed between 1986 and 2003, a longitudinal study of pediatric inflammatory bowel disease of 190 children with IBD (74 with UC), and a longitudinal study of UC in a geographically derived incidence cohort of 113 children with UC diagnosed between 1988 and 2002.[1,10,21]

Genetic polymorphisms as predictors for colectomy were examined in 6 studies[28–33]; however, because different genetic variables were assessed across studies, reliable relationships between genetic polymorphisms and colectomy are difficult to establish and could not be meta-analyzed (1/6 studies positive). In a prospective study of 128 children with severe UC who were hospitalized for intravenous corticosteroid treatment, 41 genes were expressed differentially among children who were steroid-resistant (ie, required second-line therapy or colectomy or PUCAI of >5 at day 5) compared with treatment-responsive children. Of these 41 genes, expression pattern of a cluster of 10 genes classified responders from nonresponders.[32] In a case-controlled study of 588 children with IBD (318 with UC) from the Danish National Patient Registry, the 41 polymorphisms identified in the previous study were not associated with colectomy.[31] *CARD15* polymorphisms were not predictive of colectomy in a study of 227 Italian children with IBD (134 with CD, 93 with UC) and a study of 186 children with UC.[29,30] A study of 186 children with UC also failed to identify any relationships between colectomy and DLG5 polymorphisms or the presence of TC haplotype of OCTN1/2 variants.[29] A genome-wide association study that included 1213 patients with UC (261 with childhood-onset UC) found a significant negative association between the minor allele of the NKX2–3 gene (s11190140) and the need for surgery ($P = .038$); however, this effect became trend-level among the childhood-onset patient subset when age at diagnosis was controlled.[33] In a study of children with IBD (186 with UC), none of the 308 anti-TNF variants or MDR1 C3425T variants were associated with colectomy.[28]

Three studies found no association between ANCA status and colectomy (0/3 studies positive), including a prospective study of 31 children with UC, a study of 102 children with IBD (33 with UC), and a retrospective study of 188 children with UC (unadjusted HR, 1.67; 95% CI, 0.705–3.97; $P = .243$).[3,8,34] Three studies examined found no association between ANCA status as a predictor for colectomy, and none found a significant association.[3,34,35] An additional multicenter, retrospective longitudinal study of 406 patients with IBD, 143 with UC, did find an association between perinuclear ANCA $(pANCA)^+$/anti-$ASCA^-$ patients and a composite outcome of requirement of calcineurin inhibitors, biologics, or colectomy.[35]

Statement 1.3. PSC may be protective for colectomy (82% agreement).

Two studies found that PSC may protect against the need for colectomy for chronically active or medically refractory colitis (1 study positive, 1 insignificant trend). In a retrospective, multicenter study of 37 children with PSC IBD and 148 matched, non–PSC IBD children whose medical information was collected between 2005 and 2011, children with PSC IBD had significantly lower surgery rates (0.4 colonic surgeries per 1000 patient-years; $P = .44$) than children with non-PSC IBD (0.54 colonic surgeries per 1000 patient-years).[25] In a study of 8688 children with a primary UC diagnosis from the Pediatric Health Information System database, 2.8% (240 children, 227 with pure UC) underwent colectomy, and PSC was significantly inversely associated with colectomy (OR, 0.21; 95% CI, 0.05–0.86; $P = .031$).[16]

Statement 1.4. Disease extension over time may predict the need for colectomy; neutrophilic infiltration of the stomach and duodenum (but not the esophagus) at diagnosis may predict the need for colectomy (86% agreement).

One[1] of 3 studies found a positive association between disease extension over time and colectomy (HR, 13.3; 95% CI, 1.72–102.87; n = 113).[1,3,4] The meta-analysis of the 3 studies had not reached significance (pooled OR, 2.52; 95% CI, 0.39–16.41; $P = .3324$; n = 292; $I^2 = 74\%$; random effects).[1,3,4] A positive longitudinal study included a meta-analysis of 113 children with UC from a geographically derived incidence cohort diagnosed from 1988 to 2002 and noted a significant association between disease extension and colectomy among children with limited disease at diagnosis (32 patients with E1 disease or 39 patients with E2 disease), and the likelihood of colectomy was higher among patients who experienced disease extension than among those without disease extension (37% vs 3%; HR, 13.3; 95% CI, 1.7–101.7).[1] The remaining 2 studies did not show any significant association, including a prospective study of 31 children hospitalized with ASC and a medical records review of 110 children with UC that did not find disease extension to predict colectomy.[3,4]

Association between neutrophil infiltration and treatment refractory status requiring colectomy was examined in a retrospective longitudinal study of 406 children with IBD (143 with UC). Neutrophil infiltration of the upper gastrointestinal tract, including all locations except the esophagus, was associated with greater likelihood of colectomy. In particular, neutrophil infiltration of the duodenal bulb showed the highest specificity (100%; 95%

CI, 59–100) and positive predictive value (0.46–1.0), whereas infiltration of the antrum showed the highest sensitivity (67%; 95 CI%, 45–84).[36]

Statement 1.5. *Clostridium difficile* infection may be associated with increased risk of colectomy (85% agreement).

C difficile infection was associated with colectomy in a retrospective study using the Pediatric Health Information System database of 8688 children with UC (OR, 1.76; 95% CI, 1.5–3.25; $P < .001$); however, a significant limitation to this finding is that *C difficile* was identified by International Classification of Diseases, Ninth Revision, and the timing of infection is unknown.[16]

Prognostic Risk Factors of Acute Severe Colitis and Related Outcomes. Statement 2.1. Disease severity at onset, evaluated by PUCAI or endoscopic assessment, may predict future ASC (96% agreement).

Effect of disease severity on ASC was investigated in a chart review of 115 children with new-onset UC.[7] Clinical severity (ie, PUCAI score) at diagnosis and 3 months ($P <$ .001 for both) and endoscopic severity at diagnosis ($P =$ .006) predicted ASC.[7]

Statement 2.2. Hypoalbuminemia at diagnosis may predict future ASC; no other blood tests (ie, hemoglobin, ESR, and CRP) during the first 3 months after diagnosis are predictors of ASC (92% agreement).

Albumin, hemoglobin, ESR, and CRP at diagnosis and at 3 months were examined as risk factors for ASC; only hypoalbuminemia at diagnosis predicted subsequent ASC ($P = .003$).[7]

Statement 2.3. Age and disease extent at diagnosis do not predict development of ASC (88% agreement).

Age at diagnosis did not predict ASC in 2 retrospective studies of children with UC ($n = 63$ and $n = 37$; both $P <$ .001).[19,37] One of these studies also found no association between ASC and disease extent at diagnosis.[37]

Statement 2.4. PUCAI scores on days 3 and 5 of hospital admission predict the need for treatment escalation in the short- and long-term period following intravenous corticosteroid treatment (100% agreement).

Four studies examined PUCAI scores as predictors of steroid response in children hospitalized for ASC.[3,14,38,39] In a prospective study of 128 children hospitalized for ASC, intravenous corticosteroid therapy failed for 29%; those with a PUCAI score of >45 were more likely to experience failure of intravenous corticosteroids ($P < .001$), whereas a PUCAI score of >70 on day 5 predicted response to salvage therapy. Day 3 PUCAI score also predicted response up to 1 year after discharge ($P < .001$ for time to salvage therapy).[38] In a retrospective study of 99 children hospitalized for severe UC with long-term follow-up, PUCAI scores predicted treatment nonresponse.[14] After the systematic review, this association was observed further in a small, randomized, controlled trial of children admitted for ASC[40] but not in another prospective study of 31 children.[3]

Statement 2.5. Higher CRP at both days 3 and 5 of treatment predicts response to intravenous steroids; ESR and hemoglobin do not predict outcomes at any time (96% agreement).

Four studies assessed associations between CRP levels and intravenous steroid response. A retrospective study of 99 children hospitalized for severe UC reported that short-term steroid failure was associated with CRP levels at day 3 (OR, 2.4; 95% CI, 1.01–5.8) and day 5 (OR, 3.5; 95% CI, 1.4–8.4).[14] In a prospective study of 128 children, short-term corticosteroid failure was also associated with CRP at day 3 (OR, 1.3; 95% CI, 1.1–1.6) and day 5 (OR, 1.07; 95% CI, 1.02–1.1).[38] In contrast, in a prospective study of 31 children, CRP levels at admission, day 3, and day 5 were not associated with response to corticosteroid.[3] This association was observed further in a small randomized controlled trial of children admitted for ASC.[40]

ESR and hemoglobin did not predict response to intravenous steroid treatment at any time during hospitalization in a prospective study of 31 children hospitalized for ASC and a prospective study of 128 children hospitalized for severe UC.[3,38]

In a retrospective study of 56 children with ASC, intravenous corticosteroids nonresponse was associated with ulcerations ($P = .006$) and megacolon ($P = .064$) on abdominal x-ray imaging among patients without toxic megacolon.[41]

Statement 2.6. Shorter time from disease onset to ASC may predict nonresponse to intravenous steroids (94% agreement).

Three studies evaluated time-related parameters as predictors of response.[3,14,38] An Italian study found no association between ASC at first presentation and corticosteroid response, although the interval from diagnosis to ASC was shorter in nonresponders (7.4 ± 9.6 vs 23.1 ± 21.6 months, respectively; OR, 7.3; 95% CI, 1.2–42.8; $P = .01$). Another study found no significant difference in response rates in patients with new-onset disease vs those with relapse.[14] However, in a prospective cohort, new-onset disease was associated with short-term corticosteroid failure on multivariate analysis, with an OR of 0.27 (95% CI, 0.1–0.7).[38] It was also significant in a Cox proportional hazard model using day 3 variables to predict time to second-line therapy from admission to the 1-year follow-up evaluation (HR, 0.46; 95% CI, 0.23–0.91) together with PUCAI, whereas none of the laboratory values reached statistical significance.

Statement 2.7. Genetic polymorphisms and cytokine status may predict the outcome in ASC (84% agreement).

In the prospective OSCI study of 128 children with ASC, 41 genes were expressed differentially among children who were steroid-resistant; a cluster of 10 genes classified responders from nonresponders with 80% sensitivity and 80% specificity.[32] However, in a case-control study of 588 children with IBD (318 with UC), the 41 polymorphisms identified in the previous study were not associated with colectomy.[31]

Statement 2.8. Fecal inflammatory markers are weak predictors of steroid response and have limited value in addition to the PUCAI in acute severe colitis (80% agreement).

In an analysis from the prospective OSCI study including 101 children with severe ASC, levels of 2 stool markers, M2-

pyrovate kinase and calprotectin, on day 3 of hospitalization were higher among steroid-refractory children. However, stool markers did not improve ability to predict steroid nonresponse above and beyond PUCAI score.[39]

Statement 2.9. Age, sex, disease extent, ANCA positivity, and family history of IBD do not predict outcomes of ASC (92% agreement).

Age at diagnosis did not predict response to corticosteroids in 2 pediatric studies of ASC.[3,14] On the other hand, in the OSCI study, younger age was associated with corticosteroid failure.[38] IBD family history did not predict corticosteroid response in 2 studies.[3,38] Sex and disease extent did not predict response to intravenous steroids in these studies as well as in an additional study.[14] pANCA positivity similarly did not predict response to corticosteroids.[3]

Prognostic Factors for Chronically Active Pediatric Ulcerative Colitis. Statement 3.1. Age at diagnosis and sex do not predict disease activity (96% agreement).

Two studies suggest that age at diagnosis[19,42] does not predict longitudinal disease activity. In a study of 1928 North American children with IBD stratified by age at diagnosis (1–5, 6–10, and 11–16 years), disease activity at baseline and follow-up did not differ among groups.[42] In a retrospective study of children with UC, 1-year remission rates did not differ between children diagnosed at 0 and 7 years (n = 10) and those diagnosed at 8 and 15 years (n = 53).[19] Of note, in a retrospective study of 8120 patients with UC (210 diagnosed between 0 and 16 years), age at first submission to the registry (analogous to age at diagnosis) was significantly associated with disease exacerbation (ie, change from mild/moderate disease to severe disease). However, childhood-onset disease was not analyzed separately; thus, this study is insufficient to support age as a predictor for UC disease activity.[43]

Current evidence also does not support a relationship between sex and disease activity. In a study of 993 children with CD and 416 with UC participating in the ImproveCareNow network between 2007 and 2010, neither disease severity nor likelihood of remission was associated with sex.[44]

Statement 3.2. Rectal sparing at diagnosis does not predict disease activity; no studies have evaluated the association between disease extent and disease activity in pediatrics (94% agreement).

One study examined rectal sparing as a predictor for disease activity. In a retrospective, single-center study of 30 children with UC, rectal sparing (vs proctitis) was not significantly associated with duration of active disease ($P = .16$) or the intractability index (duration of active disease as a proportion of length of follow-up, $P = .22$). Of note, a significantly higher proportion of children with proctitis achieved remission with initial medical treatment than those with rectal sparing (87% [20/23] vs 43% [3/7], respectively; $P < .05$).[45]

The systematic literature search yielded no studies examining the association between disease extent and disease activity in pediatric UC.

Statement 3.3. ANCA positivity may not predict disease activity or endoscopic inflammatory grading (96% agreement).

One small retrospective study of 38 children with ulcerative proctitis examined ANCA as a predictor for disease activity or endoscopic inflammatory grading and found no such association. In this retrospective chart review of 38 children with ulcerative proctitis, $ANCA^+$ did not predict disease course or endoscopic grade.[34]

Statement 3.4. Family history of IBD may predict disease extension over time (91% agreement).

Three studies[1,4,46] evaluated family history of IBD as a predictor of disease extension over time, 2 of which found no association between family history of IBD and disease extension.[4,46] In a longitudinal study of 113 children with UC (mean follow-up, 77 months; range, 46–125 months), family history of IBD significantly predicted disease extension (OR, 11.8; 95% CI, 1.3–111.3) and remained a significant predictor after controlling for length of follow-up and disease localization at diagnosis (OR, 10.3; 95% CI, 1.2–92.4).[1] Two other studies found no significant association between family history of IBD and disease extension: the first, a medical record review of 110 children with UC, which identified a rate of disease extension rate of 29%, and the second, a longitudinal IBD study of 723 patients, which found a disease extension rate of 35%.[4,46]

Statement 3.5. At diagnosis, age, sex, weight, height, ethnicity, PUCAI, ANCA positivity, disease extent at diagnosis, and routine laboratory measures (CRP, ESR, hemoglobin/hematocrit, albumin, WBC, and ferritin level) do not predict disease extension (86% agreement).

Age at diagnosis and sex did not predict disease extension in 5 studies identified for this review. These studies were a retrospective cohort analysis of medical records of 98 children with IBD (54 with UC), a retrospective chart review of 38 children with UC, a longitudinal study of UC in 113 children with UC with at least 2 years of follow-up, another a longitudinal study of UC in 115 children with UC, and an analysis of medical records of 110 children with UC from a single center.[1,4,10,47,48]

Weight, height, and BMI were not predictors of disease extension in 2 studies. In the retrospective single-center study of 723 patients with childhood-onset IBD (134 with UC; median follow-up, 13.1 years; range, 5–28 years), *z*-scores for weight, height, and BMI were not significantly associated with disease extension over time.[46] Similarly, in a retrospective analysis of children with IBD (54 with UC, 44 with CD), histopathologic disease progression was not associated with weight and height *z*-scores at diagnosis.[48] Disease extension (E1/E2 disease to E3/E4) was not associated with ethnicity (ie, Ashkenazi vs Sephardic Jews, and Jewish sample vs others).[46]

Disease activity at diagnosis (measured by the PUCAI) was evaluated as a predictor for disease extension in 4 pediatric studies.[4,46–48] A longitudinal study of 113 patients with childhood-onset UC reported a significant association between disease extension and disease severity at diagnosis (aHR, 8.77; 95% CI, 1.75–43.9). Severe disease (PUCAI of $\geq$65) at 1 year was associated with disease extension on

univariate analysis, although this effect was lost during multivariate analysis.[46] ASC at diagnosis and PUCAI at diagnosis did not predict disease extension over time in a retrospective medical record review of 110 children with UC.[4] In a retrospective study of 98 children with UC, PUCAI score and presenting symptoms at diagnosis were not associated with disease extension over time.[48] A medical record review of 110 children with UC also identified no relationship between initial symptom severity and disease extension over time.[47]

Neither of the 2 studies exploring disease extent at diagnosis as a predictor for disease extension over time reported a significant association. These studies include the medical record review of 110 children with UC and the longitudinal study of 113 children with UC.[1,4]

Similarly, 4 of the 5 studies did not report associations between laboratory values at diagnosis (ie, CRP, ESR, hemoglobin, hematocrit, albumin, WBC, and ferritin level) and disease extension over time.[1,4,5,47] CRP was assessed in 3 studies, including the longitudinal study of IBD in 723 patients, the retrospective chart review study of 38 children with UC, and the longitudinal study of 113 children with UC.[1,8,47] ESR was examined in 2 studies, including the retrospective medical record review of 98 children with UC and the retrospective chart review study of 171 children with UC. Hematocrit was examined in the retrospective chart review study of 38 children with UC, and hemoglobin was examined in the longitudinal study of IBD in 723 patients.[8,47] Albumin was examined in 3 studies, including the retrospective chart review study of 38 children with UC, the retrospective medical review study of a cohort of 98 children with UC, and the longitudinal study of IBD in 723 patients.[8,47,48] Both WBC count and ferritin level were examined in the longitudinal study of IBD in 723 patients.[8] On the contrary, 1 study, which included 134 patients with UC with at least 5 years of follow-up, found a significant association between lower zinc levels at diagnosis and disease extension on multivariate analysis (HR, 0.94; 95% CI, 0.88–0.99; higher levels were protective).[8]

Statement 3.6. PUCAI score (≤10) at 3 months predicts sustained steroid-free remission; disease severity at diagnosis (assessed clinically or endoscopically) does not predict subsequent use of immunomodulators or biologics (81% agreement).

Disease severity (clinical or endoscopic) at diagnosis was not associated with subsequent immunomodulators or biologics use. In a medical review of 420 children with new-onset IBD (103 with UC, all recruited as part of the Hungarian nationwide inception cohort with data collected from January 2007 to December 2009), initial PUCAI score was not associated with need for immunomodulator at 1 year among children with UC.[49] Similarly, another study found that sustained steroid-free remission was not associated with endoscopic severity or PUCAI at diagnosis. However, the probability of achieving sustained steroid-free remission was 48% among patients with a PUCAI score of $\leq$10 and 9% with a PUCAI score of >10 at 3 months ($P < .0001$) regardless of thiopurine or steroid use at 3 months. Of note, PUCAI scores at diagnosis and at 3 months predicted the need for salvage therapy (TNF or calcineurin inhibitor) during the first year ($P = .001$ and $P < .001$, respectively; significance threshold after Bonferroni correction for multiple tests, $P < .007$).[7] In a prospective study of 213 children with UC, initial physician global assessment was not associated with corticosteroid-free inactive UC at 1 year after initiation of 5-aminosalicylate (5-ASA) within 30 days of diagnosis (± concomitant steroid use) and no rescue therapy.[50] In a retrospective study of 156 children (93 with CD, 47 with UC, 16 with indeterminate colitis), baseline endoscopic severity did not predict the need for azathioprine in UC.[51] The PROTECT inception prospective study with a cohort of 467 children with UC was recently published, verifying that PUCAI at baseline and at 1 month after diagnosis independently predicted 1-year steroid-free remission.[52]

Statement 3.7. Genetic polymorphisms, particularly in genes associated with the treatment pathways, and ethnicity may predict response to medications (92% agreement).

Five studies examined associations between genetic polymorphisms and medication response in pediatric patients. Eight single-nucleotide polymorphisms were explored in a study of children with IBD (1213 with UC). Findings suggest an association between the rs2395185 variant of the HLA gene and was associated with response to steroids (OR, 2.07; 95% CI, 1.1–3.89), but this effect was lost after controlling for age at diagnosis.[33] In a study of 154 children with IBD with $\geq$1 year follow-up, the BclI polymorphism was associated with steroid response (OR, 0.29; 95% CI, 0.09–0.89; $P = .03$), and the NALP1 Leu55His mutant variant was associated with steroid nonresponse (OR, 3.12; 95% CI, 1.10–8.90; $P = .033$) and steroid resistance (OR, 8.25; 95% CI 1.18–57.96, $P = .034$).[53] Single-nucleotide polymorphisms of TNF-α and MDR1 genes were investigated in 200 patients with childhood-onset CD and 186 with UC and compared with parents and unrelated healthy control individuals. These genetic polymorphisms were not associated with any clinical characteristics of UC, although a trend toward increased steroid resistance was noted in carriers of the TNF-α risk genotype.[28] In another study of patients with childhood-onset IBD, HLA-DRB101 was more common among patients who required anti-TNF treatment (19 of 71 patients [26.8%] vs 18 of 32 patients [56.2%]; OR, 0.28; 95% CI, 0.12–0.68); no similar association was identified for other haplotypes.[54] No association was noted between the need for steroids and other genes, including CARD15, AA/AG genotypes of DLG5 variant, and presence of TC haplotype of OCTN1/2 variants.[29]

Ethnicity as a predictor for treatment escalation was evaluated in 2 studies. In 1 study of 107 children with IBD (57 with CD [46 White, 11 South Asian]; 45 with UC [43 White, 2 South Asian]), treatment with steroids ($P = .02$), methotrexate ($P = .002$), and adalimumab ($P = .02$) at 1 year was significantly more common among South Asian children than among White children.[55] In a 10-year review of medical records of 245 children with IBD (137 with CD [103 White, 34 Black] and 40 with UC [33 White, 7 Black]), a significantly higher proportion of Black children were

prescribed steroids or infliximab than White children (89.7% vs 77%; $P = .035$ and 24.1% vs 12.8%; $P = .037$, respectively). Although White children were twice as likely as Black children to receive immunomodulator therapy within the first 3 months after diagnosis (OR, 2.2; 95% CI, 0.65–9.37), there was no significant difference in immunomodulator use between groups.[26]

Statement 3.8. Serology (ANCA/ASCA) may predict anti-TNF use, but not immunomodulator use (91% agreement).

The utility of serology to predict the use of medications was inconsistent across 2 pediatric studies. Among children with newly diagnosed IBD within the Hungarian nationwide inception cohort, $pANCA^+/ASCA^-$ predicted use of biologics in UC (20 of 57 children [35%] vs four of 31 children [13%]; $P = .026$).[35] In a separate study, no association between serologic markers and steroid or immunomodulator use was noted.[34]

Statement 3.9. At diagnosis, age, sex, weight, height, family history of IBD, clinical/endoscopic disease severity, and laboratory blood tests (CRP, ESR, albumin, hemoglobin, platelets) do not predict medication intensification (90% agreement).

Many studies assessed use of corticosteroids (response to treatment, dependency, need for, etc), immunomodulators, anti-TNFs, cyclosporine, and tacrolimus use as a proxy for disease severity. It is important to note that in some of the studies, anti-TNF agents were not yet available for treatment of UC (infliximab was approved for use in the United States in 1998 for CD and in 2005 for UC and received approval in the European Union in 2006[56]; adalimumab was approved for use in IBD in the United States and European Union in 2007[57]). In total, 26 studies examined outcomes of medication use.

None of 6 relevant studies identified an association between age at diagnosis and response to medications (ie, short- and long-term steroid response, steroid dependence and refractoriness/resistance, and corticosteroid-free remission). These studies included a retrospective study of 63 Japanese children with UC, a cohort study of 205 children with IBD (100 with UC) with a median follow-up of 5.1 years, a study of an inception cohort of children with IBD (34 with UC) that examined 1-year outcomes after an initial course of systemic corticosteroids, a study of an inception cohort of 213 children with UC treated with 5-ASA, a chart review of 115 children with new-onset UC, and an analysis of 154 children with IBD.[7,19,50,53,58,59]

Two[20,24] of 5 studies reported a positive association between younger age and medication use.[19,20,24,42,51] One of these studies (an analysis of 49 patients with UC and 28 patients with UC-like, but unclassified, IBD) reported that thiopurine use within the first 3 months after diagnosis was more likely among children diagnosed between 5 and 10 years (58 of 80 children) than among those diagnosed between 11 and 16 years (45 of 80 children; OR, 1.86; 95% CI, 1.02–4.33). However, no age-related difference in need for corticosteroids or anti-TNF therapy was noted.[24] Data obtained from a prospective, multicenter observational study (n = 1928 children, 27% with UC) did not find a difference among age groups 1–5, 6–10, and 11–16 years and the use of antibiotics, mesalamine, corticosteroids, or immunomodulators at 1 year after diagnosis. At 5 years, however, those in the youngest group were more likely to receive mesalamine or thiopurine compared with the oldest age group. As for the anti-TNF agents, treatment with infliximab and adalimumab did not differ significantly among the age groups,[24,42] although in the study by Oliva-Hemker et al, exposure to adalimumab was minimal in the younger age group, thus limiting the conclusions that could be drawn.[42] Additionally, a retrospective chart review of children with IBD (20 of whom had UC and were <6 years of age and 19 with UC between 6 and 17 years old) showed a trend for a higher proportion of patients younger than 6 years at diagnosis requiring immunomodulatory therapy; no significant association was found for steroid treatment.[20]

Five of 6 studies identified no association between sex and medication use, response, and sustained steroid-free remission.[44,50,51,58,59] However, in the study of 154 children with IBD (74 with UC), boys were more likely to achieve better outcomes (OR, 0.46; 95% CI, 0.22–0.94).[53]

In 1 retrospective study of 156 children with IBD (93 with CD, 47 with UC16 with indeterminate colitis), BMI and height *z*-scores were not associated with use of immunomodulators.[51]

No association between family history of IBD and medication intensification was found in 2 studies. In a retrospective study of 411 children with IBD (244 with UC, 129 with CD, 38 with unclassified IBD), steroid use and the need for early aggressive treatment (immunomodulators, cyclosporine, or biologics) were not associated with IBD family history.[17] In a study of 205 children with IBD (100 with UC), no association between steroid response and either short-term (30 days after initial treatment) or long-term (30 days after termination of treatment) steroid use was noted.[58]

Disease severity at diagnosis, assessed clinically or endoscopically, did not predict medication use in 4 studies.[7,49–51] A prospective cohort of 213 patients with UC examined initial physician global assessment as a predictor of corticosteroid-free inactive UC at 1 year after initiation of 5-ASA within 30 days of diagnosis (with or without concomitant steroid use) and need for rescue therapy and found no significant association on logistic regression.[50] Mossop et al did not find endoscopically severe UC to be a predictor of azathioprine use in 47 UC patients.[51] Muller et al assessed initial PUCAI score and need for immunomodulatory therapy at 1 year and found no significant association in 103 patients with UC.[49] A multicenter retrospective cohort of 115 patients with new-onset UC assessed sustained steroid-free remission and found no association with endoscopic severity at diagnosis or PUCAI at diagnosis.[7]

Findings exploring the utility of laboratory tests (CRP, ESR, albumin, hemoglobin, and platelet level) for predicting medication use were inconsistent across 6 studies.[7,49–51,60,61] In a prospective analysis of 124 children newly diagnosed with UC in the Hungarian nationwide inception cohort study, initial elevated CRP (OR, 6.2; 95% CI, 2.3–

16.4) and abnormal iron levels ($P = .018$) were associated with subsequent azathioprine use.[49] A study of 465 children with IBD found no association between CRP level at diagnosis and azathioprine use in children with UC ($P = .795$, although a significant association was noted for the overall sample).[60] Hemoglobin, platelet, ESR, CRP, and albumin levels were not predictive of azathioprine use in a retrospective cohort study of 156 children with IBD (47 with UC).[51] However, in a chart review of 115 children with new-onset UC, need for salvage therapy during the first year after diagnosis was associated with ESR at 3 months ($P = .006$). In contrast, hemoglobin level, CRP at 3 months, and albumin level at diagnosis were not associated with a need for salvage therapy.[7] In a retrospective study comparing 96 children with newly diagnosed UC to 50 age- and sex-matched control individuals, tissue and peripheral eosinophil counts correlated with corticosteroid, immunomodulator, and biologic therapy use ($P < .05$). However, only the correlation between tissue eosinophil at diagnosis and corticosteroid therapy remained significant after multivariate analysis ($P = .04$). Additionally, neither parameter correlated with biologic therapy during follow-up, suggesting that eosinophil counts best predict short-term outcomes.[61]

Statement 3.10. Disease extent at diagnosis may predict medication use and response to treatment; it does not, however, predict relapse (87% agreement).

Only 2 of 6 studies[3,5,7,11,58,59] identified an association between disease extent and medication use. Three evaluated response to medication,[7,58,59] and 2 evaluated medication use.[5,51] None reported a significant association. One positive study reported a lower likelihood of immunomodulator treatment among children with isolated proctitis compared with all others. In this longitudinal study of ulcerative proctitis in 158 children with UC, the cumulative probability of immunomodulators use was lower among children with proctitis than among children with E2/E3/E4 disease (5% vs 14% at 1 year, 8% vs 33% at 5 years, and 10% vs 39% at 10 years; $P = .0049$). However, cumulative risk for anti-TNF therapy did not differ between groups.[11] The other found that those with extensive disease (E3/E4) at diagnosis had increased risk of receiving a biologic compared with patients with E1/E2 disease (HR, 2.7; 95% CI, 1.2–6; $P = .015$).[5]

Predictors for relapse were examined in 4 studies.[24,45,47,62] However, relapse was defined differently across studies, thus complicating identification of reliable predictors for relapse.

Two studies evaluated disease extent at diagnosis as a predictor for relapse. In a 1-year prospective study of 37 children with newly diagnosed UC, histologic upper gastrointestinal involvement did not differ among those who relapsed compared with those who did not relapse. Children with more extensive disease trended toward a higher likelihood of relapse ($P = .145$).[62] Rajwal et al assessed relapse index (number of relapses per year) in 30 patients with newly diagnosed UC, 7 (23%) of whom had rectal sparing at endoscopy. The relapse index was slightly higher for children presenting with proctitis but did not reach statistical significance ($P = .22$).[45]

Statement 3.11. Duration of symptoms prior to diagnosis does not predict response to subsequent treatment (96% agreement).

None of the 3 studies exploring time to diagnosis as a predictor for treatment response reported a significant association. In a study of 205 children with IBD (100 with UC; median follow-up of 5.1 years), time to diagnosis and time to initiation of treatment were not associated with short- or long-term responses to steroids.[58] Similarly, in a study of children with IBD (34 with UC) that examined 1-year outcomes after a first course of systemic corticosteroids, disease duration was not associated with nonresponse at 1 year.[59] Mossop et al found no association in 47 children with UC between time to diagnosis and azathioprine use.[51]

Prognostic Risk Factors for Cancer and/or Mortality in Children With Inflammatory Bowel Disease. Studies investigating cancer or mortality in PIBD are scarce and typically do not differentiate between UC and CD. Therefore, for these specific outcomes, prognostic factors were described for PIBD patients in general.

Statement 4.1. Concomitant diagnosis of PSC, longstanding colitis (>10 years), male sex, and younger age at IBD diagnosis are risk factors for any cancer; having a first-degree relative with any cancer before 50 years of age may be a risk factor for cancer in UC (91% agreement).

Few studies have investigated genetic risk factors for malignancy and mortality in patients with pediatric-onset IBD; however, multiple studies associate childhood-onset IBD with a higher risk for cancer. In a study of tumor development among 698 patients with childhood-onset IBD (median 15-year follow-up), 9 developed cancer (standardized incidence ratio [SIR], 3.0; 95% CI, 1.3–5.9; $P < .02$).[64] Similarly, in a cohort study comparing 9405 pediatric patients with IBD with 92,870 age- and sex-matched control individuals, cancer incidence rates were 3.3 per 1000 person years versus 1.5 per 1000 person years, respectively (HR, 2.2; 95% CI, 2.0–2.5). A significantly higher risk was found in boys (HR, 4.6; 95% CI, 4.4–6.4) than in girls (HR, 1.5; 95% CI, 1.4–1.7; $P < .001$). HR was also higher in patients with a younger age at first diagnosis ($P = .006$).[63] This study also found that longstanding colitis ($\geq$10 years; HR, 3.9; 95% CI, 2.9–5.0) and having a first-degree relative with a cancer diagnosis before age 50 years (HR, 4.4; 95% CI, 3.2–5.8, for patients with UC) were also associated with increased risk of cancer among patients with childhood-onset IBD.

PSC predicted colorectal cancer and cholangiocarcinoma. In a study of 9405 patients with childhood-onset IBD, patients with PSC IBD were at greater risk of developing cancer than those in the general population (HR, 6.6; 95% CI, 4.9–8.7).[63] In a survey study of physicians, 60 patients with childhood-onset IBD developed malignancies or died, and 56% of patients with fatal cancer (cholangiocarcinoma or colorectal cancer) were also diagnosed with PSC.[65]

A pediatric study reported 15 malignancies among 5766 patients with 24,543 years of follow-up, including 8 hematopoietic tumors.[66] The SIR for the development of a malignancy in patients exposed to a thiopurine with or without a biologic was significantly higher (SIR, 2.88; 95% CI, 1.44–5.14), whereas this was not the case in patients exposed to a biologic monotherapy. In a population-based study, of the 2114 children who were ever treated with thiopurines, 15 cases of cancer were identified, of which 2 patients also received an anti-TNF agent at some point. Confidence intervals were wide and overlapping, with no significant differences among groups of different drug exposures, which led the authors to conclude they cannot rule out thiopurines or anti-TNF agents as risk factor of cancer.[63]

The risk ratio for malignancy and mortality in pediatric patients with IBD was examined in a study of 698 patients with childhood-onset IBD (538 CD and 160 UC). Over a median follow-up period of 15 years, 9 patients with cancer were identified (SIR, 3.0; 95% CI, 1.3–5.9; $P < .02$). Four of the 9 patients with cancer had received immunosuppressants or anti–TNF-α therapy.[64]

Statement 4.2. Malignancy and infection (sepsis and opportunistic infections) may be risk factors for mortality, but no population-based studies are currently available (83% agreement).

A study of 21 pediatric gastroenterologists from 20 European countries and Israel investigated predictors for mortality in patients with childhood-onset IBD.[67] The study identified 18 cases of cancer and 31 deaths in 44 children with IBD. Infection was the most common cause of mortality (14 deaths), particularly among patients receiving 2 or more immunosuppressive agents. The second leading cause of mortality was cancer (5 deaths, of which 3 were considered treatment related and 1 was considered disease related [2 hepatosplenic T-cell lymphomas, 1 Epstein-Barr virus–positive lymphoma, and 1 colonic adenocarcinoma]).[67]

After the index date of systematic review, Olen et al reported 294 deaths among 138,690 patient-years of follow-up (n = 9442 individuals with pediatric IBD; 50 years of follow-up).[68] This translated into 2.1/1000 person-years compared with 0.7/1000 person-years in matched control individuals. HRs for death were increased for UC (4.0; 95% CI, 3.4–4.7), CD (2.3; 95% CI, 1.8–3.0) and IBD unclassified (2.0; 95% CI, 1.2–3.4). Patients with IBD diagnosis at <6 years of age had higher HRs for death than children with later IBD onset. Apart from patients with very-early-onset IBD, the highest relative risk was observed in patients with UC with concomitant PSC (HR, 12.2; 95% CI, 8.4–17.8). Patients with UC undergoing bowel surgery or having a first-degree relative with UC were also at higher risk of death.

Cause-Specific Mortality

In the same aforementioned study, underlying causes for death in childhood-onset IBD included cancer (HR, 6.6; 95% CI, 6.3–8.2), infections (HR, 6.3; 95% CI, 2.1–16.9), and respiratory diseases (HR, 4.7; 95% CI, 1.8–11.3).[68]

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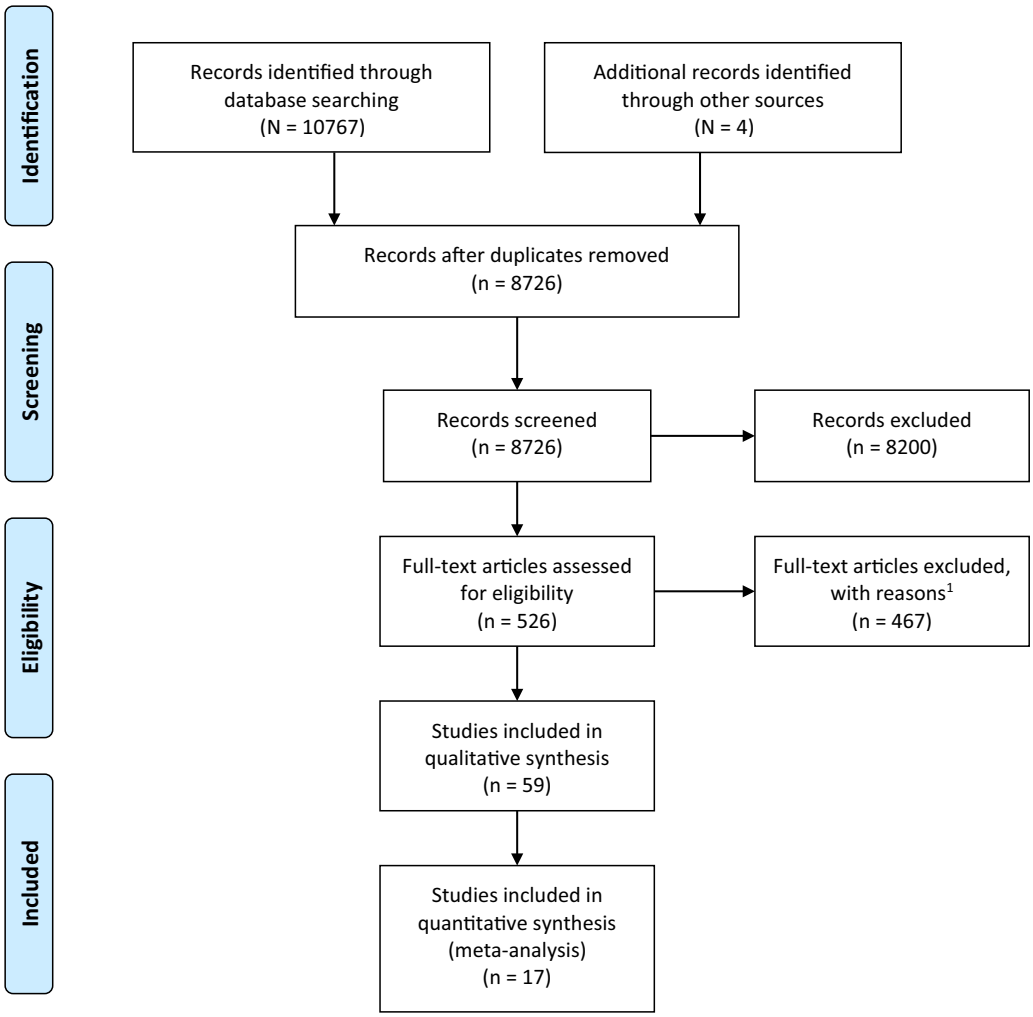

Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Supplementary Table 1. Characteristics of Studies Included in Systematic Review

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Aloi et al (2013)[4]	Retrospective, single center	110 pediatric patients with UC	Age Disease extent Family history of IBD Laboratory values (CRP) Sex	Disease extension	Mean: 48 mo (range, 28–94 mo)
Aloi et al (2014)[23]	Prospective, multicenter	506 pediatric patients with IBD (245 UC)	Age	Colectomy (data insufficient for MA)	Mean: 40 mo (range: 6–50 mo)
Aloi et al (2015)[3]	Retrospective, single center	31 pediatric patients with UC	Family history of IBD Serology (ANCA status)	Colectomy	2 y
			Age Disease extent Family history of IBD Serology (ANCA status) Sex	Med response	
Assa (2018)[5]	Retrospective, single center	126 pediatric patients with UC	Disease extent	Colectomy Med use	8.5 y (IQR, 5.1–12)
Barabino et al (2002)[37]	Retrospective, single center	37 pediatric patients with UC	Age at diagnosis Disease extent	Development of ASC	Remission: 40.7 mo (range, 21–66 mo) Urgent surgery mean: 6.7 mo (range, 1–18 mo) Elective surgery: 25 mo Lost to follow-up: 1 mo
Birimberg-Schwartz et al (2016)[35]	Retrospective, multicenter	406 pediatric patients with IBD (143 UC)	Serology (ANCA/ASCA status)	Colectomy Med use (biologics)	Median: 2.8 y (IQR, 1.6–4.2)
Cucchiara et al (2007)[28]	Retrospective, multicenter	386 pediatric patients with IBD (217 patients + parents, 109 UC) 347 control individuals	Genetic polymorphism	Colectomy Med response	Mean: 8–9 y
Cucchiara et al (2007)[29]	Retrospective, multicenter	386 pediatric patients with IBD (217 patients + parents, 109 UC) 347 control individuals	Genetic polymorphism	Colectomy Med response Med use (CS)	Mean: 8–9 y

Supplementary Table 1. Continued

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
De Iudicibus et al (2011)[53]	Retrospective, multicenter	154 pediatric patients with IBD (72 UC)	Genetic polymorphism Age at diagnosis Sex	Med response	Minimum: 1 y
Eidelwein et al (2007)[26]	Retrospective, single center	245 pediatric patients with IBD (40 UC, 68 IC)	Ethnicity (Black)	Med use	Mean: 5.3 y (SD, 3) for Black patients and 4.8 (SD, 3.3) for White patients
Falcone et al (2000)[9]	Retrospective, single center	73 pediatric patients with UC (1–18 y)	Age Disease extent EIM Ethnicity	Colectomy	Mean: 5.4 y (SD, 0.6; range, 0.4–13.8 y)
Ferraris et al (2006)[30]	Retrospective, multicenter	227 pediatric patients with IBD (93 UC) 166 control individuals	Genetic polymorphism	Colectomy	NA
Gasparetto et al (2016)[24]	Retrospective, multicenter	160 pediatric patients with IBD (49 UC)	Age at diagnosis	Med use	Median: 1.2–4.2 y Minimum: 12 mo
Gower-Rousseau et al (2009)[1]	Retrospective (EPIMAD registry), multicenter	113 pediatric patients with UC (<17 y at diagnosis)	Delay in diagnosis	Colectomy	Median: 77 mo (range, 46–125 mo)
			Age Disease extent Family history of IBD Laboratory values (CRP) Sex	Disease extension	
Henderson et al (2015)[60]	Retrospective, multicenter	465 pediatric patients with IBD (111 UC) 181 pediatric patients with IBD (with 2 y of follow-up)	Laboratory values (CRP)	Med use	Median: 5.2 y
Hochart et al (2017)[11]	Retrospective (EPIMAD registry), multicenter	158 pediatric patients with UC	Disease extent	Colectomy (data insufficient for MA) Med use	Median: 11.4 y (range, 8.2–15.8 y)
Hyams et al (1997)[47]	Retrospective, multicenter	38 pediatric patients with UC	Age Disease severity at diagnosis (PUCAI) Laboratory values (Hct, ESR, Alb)	Disease extension	Mean: 4.3 y (SD, 3.4)

Supplementary Table 1. Continued

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Hyams et al (2019)[52]	Prospective (PROTECT), multicenter	400 pediatric patients with UC at week 52 (age, 4–17 y) (386 included in prediction model) Mean: 12.7 y (SD, 3.3) 50% M	Age Disease activity (diagnosis/week 4) Ethnicity Laboratory values (Alb, Hb, calpro, CRP, ESR, 25[OH]D level, rectal gene expression, rectal eosinophil concentration [histology], microbiome) Sex	Med response Med intensification	Outcome at 1 y
			Disease activity (diagnosis/week 4)	Colectomy	
Jakobsen et al (2011)[58]	Retrospective (prospective Danish registry), multicenter	205 pediatric patients with IBD (100 UC)	Age Disease extent Family history of IBD Sex Time to diagnosis	Med response Medication intensification	Median: 5.1 y (IQR, 3.6–7.3)
Jakobsen et al (2014)[31]	Retrospective (prospective Danish registry), multicenter	588 pediatric patients with IBD (318 UC) 543 control individuals	Genetic polymorphism	Colectomy	Median: 4.7 y (IQR, 3.0–7.0)
Kabakchiev et al (2010)[32]	Prospective (subgroup of OSCI cohort), multicenter	40 pediatric patients with UC	Genetic polymorphism	Colectomy Outcome of ASC	NA
Kelley-Quon et al (2012)[15]	Retrospective (PediIBDC registry), multicenter	407 pediatric patients with UC	Anthropometric measures (weight loss) Ethnicity	Colectomy (predictors reported for overall colectomy rate and not colectomy at 2 years)	Mean: 6.8 y (SD, 4)
Kolho et al (2016)[54]	Retrospective, single center	103 pediatric patients with IBD (UC/IBDU 42) 149 control individuals	Genetic polymorphism	Med response Med use	Median: 4.9 y (range, 0.9–17.8 y)
Kuwahara et al (2017)[43]	Retrospective (CONNECT study), multicenter	705 pediatric patients with UC	Age (younger vs older)	Disease activity	Median: 2 y (IQR, 2 y)

Supplementary Table 1. Continued

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Lascurain et al (2016)[25]	Retrospective, multicenter, case-control (PSC-IBD vs non–PSC-IBD)	37 patients with PSC-IBD /148 non–PSC-matched IBD control individuals (155 patients with UC)	PSC	Colectomy	Median: 4.75 y (IQR, 3.7–7.2)/ median: 5.19 y (IQR, 3.1–7.8)
Latiano et al (2011)[33]	Retrospective, multicenter	1213 patients with UC (261 <16 y) 789 control individuals	Genetic polymorphism	Colectomy Med response Need for surgery	Mean: 9 y (SD, 7 y)
Lee et al (2012)[44]	Prospective (ImproveCareNow network), multicenter	416 pediatric patients with UC	Sex	Disease activity Med response Med use	Median: 12.8 mo (range, 6.2–21.1) M/15.7 mo (range, 8.6–26.6) F
Li et al (2013)[55]	Retrospective, single center	107 pediatric patients with IBD	Ethnicity (South Asian vs White)	Med use	Mean, 4.0 (SD, 2.9 y)
Livshits et al (2016)[41]	Retrospective, multicenter	56 pediatric patients with UC	X-ray imaging findings	Med use	Outcome at 1 y
Malaty (2013)[16]	Retrospective, single center	115 pediatric patients with UC	Delay in diagnosis Disease extent	Colectomy	Median, 4.4 y (±2.1)
			Age Sex	Disease extension	
McAteer et al (2013)[16]	Retrospective (Pediatric Health Information System database), multicenter	8688 pediatric patients with UC and indeterminate colitis (8066 patients with UC)	*Clostridium difficile* infection PSC	Colectomy	Study period between 2004 and 2011
Miele et al (2007)[62]	Prospective, single center	33 pediatric patients with UC	Disease extent (UGI histology)	Relapse	Median: 29 mo (range, 17–40 mo)
Moore et al (2011)[6]	Retrospective, single center	135 pediatric patients with UC	Laboratory values (Alb)	Colectomy	NA
Morgenstern et al (2017)[61]	Retrospective, single center	96 pediatric patients with UC 50 control individuals	Laboratory values (tissue/blood eosinophil count)	Colectomy Med use (short term/long term)	Median: 12.8 y (IQR, 7.2–17.1)

Supplementary Table 1. Continued

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Mossop et al (2008)[51]	Retrospective, single center	156 pediatric patients with IBD (47 UC)	Age (younger vs older) Anthropometric measures Disease extent Disease severity Laboratory values (Hb, Plt, ESR, CRP, Alb) Sex Time to diagnosis	Med response (only sex) Med use (all predictors)	Median: 3.9 y (range, 0.5–10.6)
Muller et al (2016)[49]	Prospective (HUPIR), multicenter	420 pediatric patients with IBD (124 UC)	Disease severity Laboratory values (CRP, Plt, iron levels)	Med use	Outcome at 1 y
Nambu et al (2016)[19]	Retrospective, single center	63 pediatric patients with UC	Age	Development of ASC Disease activity Med response	Early-onset mean: 42 mo (SD, 40) Late-onset mean: 36.1 mo (SD, 26.5)
Newby et al (2008)[21]	Retrospective, multicenter	210 pediatric patients with IBD (74 UC, 116 CD, 20 indeterminate)	Age Delay in diagnosis	Colectomy	UC mean: 3.3 y (range, 1–6.83)
Oliva-Hemker et al (2015)[42]	Prospective, multicenter	1928 pediatric patients with IBD (513 UC)	Age	Disease activity Med use	Median: 3.25 y
Olives et al (1997)[34]	Retrospective, multicenter	102 pediatric patients with IBD (UC 33/ unclassified 5)	Serology (ANCA status)	Colectomy Disease activity Med use	Median: 4.6 y (range, 3 mo to 16 y)
Rajwal et al (2004)[45]	Retrospective, single center	30 pediatric patients with UC	Disease extent Rectal sparing	Relapse (disease extent) Disease activity (rectal sparing)	Median: 2 y
Rinawi et al (2018)[46]	Retrospective, multicenter	134 pediatric patients with UC	Anthropometric measures Disease severity (PUCAI) Ethnicity EIM Family history of IBD Laboratory values (zinc) Serology (pANCA)	Disease extension	Median: 13.1 y (range, 5–28)
Rinawi et al (2017)[8]	Retrospective, single center	188 pediatric patients with UC	Ethnicity Laboratory values (Hb)	Colectomy	Median: 6.9 y (range, 1–30 y)
Roma et al (2010)[17]	Retrospective, single center	411 pediatric patients with IBD (UC 244)	Family history of IBD	Med intensification Surgery	Median 5 y (range, 1–16 y)

Supplementary Table 1. Continued

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Schechter et al (2015)[7]	Retrospective, multicenter	115 pediatric patients with UC (2–18 y)	Disease severity (PUCAI 3 months) Laboratory values (Alb, Hb)	Colectomy	Median: 23.1 mo (IQR, 15.3–43.4)
			Disease severity (PUCAI, endoscopy) Laboratory values (Alb)	Development of ASC	
			Disease extent Disease severity Laboratory values	Med use	
			Age	Med response	
Størdal (2004)[22]	Prospective, multicenter	33 pediatric patients with IBD (14 UC)	Age	Colectomy	Outcome at 5 y
Sullivan et al (2017)[36]	Retrospective, single center	52 pediatric patients with UC	Disease extent (UGI histology)	Colectomy	Mean: 3.5 y (SD, 2.0) patients with refractory disease/2.9 y (SD, 1.3) patients with nonrefractory disease
Tsang et al (2012)[48]	Retrospective, single center	98 pediatric patients with IBD (54 UC)	Age Anthropometric measures Laboratory values (Alb, ESR) Sex	Disease extension	Mean: 62.9 mo (SD, 8.54)
Tung et al (2006)[59]	Retrospective, multicenter	40 pediatric IBD patients (<19 y) (14 UC)	Age Disease extent Time to diagnosis Sex	Med response Med use	Outcome at 1 y
Turner et al (2008)[14]	Retrospective, single center	99 pediatric patients with UC	Age	Med response	Outcome at 1 y
Turner et al (2010)[38]	Prospective (OSCI study), multicenter	128 pediatric patients with UC	Age Disease extent Disease severity (PUCAI) Family history of IBD Laboratory values (CRP, ESR, Hb) New-onset disease (severe) Sex	Med response Med intensification	Outcome at 1 y
Turner et al (2010)[39]	Prospective, multicenter	101 pediatric patients with UC	Laboratory values (calpro, M2-pyruvate kinase)	Med response	NA

Supplementary Table 1. Continued

Study	Study design	Population by IBD type	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Zeisler et al (2013)[50]	Prospective, multicenter	213 pediatric patients with UC	Age Sex Disease severity (PGA) Laboratory values (Alb, ESR, Hb)	Med response Med use	5-ASA only median: 3 y (range, 1.0–8.25 y)/5–ASA + CS median: 3.25 y (range, 1.0–7.75 y)
Zwintscher et al (2014)[27]	Retrospective (KID database), multicenter	12465 pediatric patients with IBD (UC 4620)	Anthropometric measures (obesity)	Colectomy	NA
Zwintscher et al (2015)[12]	Retrospective (KID database), multicenter	511 pediatric patients with IBD	Anthropometric measures (growth) Sex	Colectomy	NA

25[OH]D, 25-hydroxy vitamin D; Alb, albumin; Calpro, calprotectin; CONNECT, Post-marketing observational cohort study of patients with inflammatory bowel disease treated with CT-P13 in usual clinical practice; CS, corticosteroids; EIM, extraintestinal manifestations; EPIMAD, Epidemiology of inflammatory bowel disease (French population-based registry); F, female; Hb, hemoglobin; Hct, hematocrit; HUPIR, Hungarian paediatric IBD registry; IBDU, inflammatory bowel disease unclassified; IC, indeterminate colitis; IQR, interquartile range; KID, Kids' Inpatient Database; M, male; MA, meta-analysis; Med, medication; NA, not available; PGA, physician global assessment; Plt, platelet count; PROTECT, predicting response to standardised paediatric colitis therapy; SD, standard deviation; UGI, upper gastrointestinal.

Supplementary Table 2. Risk of Bias of Studies in the Systematic Review

Study	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Aloi et al (2014)[23]	1	1	1	1	0	0	1	1	6
Barabino et al (2002)[37]	1	1	1	1	0	0	1	1	6
Birimberg-Schwartz et al (2016)[35]	1	1	1	1	1	1	1	0	7
Cucchiara et al (2007)[28]	1	1	0	0	0	0	1	1	4
Cucchiara et al (2007)[29]	1	1	0	0	1	0	1	1	5
De Iudicibus et al (2011)[53]	1	1	1	1	2	0	1	1	8
Eidelwein et al (2007)[26]	1	1	1	1	0	1	1	1	7
Ferraris et al (2006)[30]	1	1	1	0	0	0	0	1	4
Gasparetto et al (2016)[24]	1	1	1	1	2	0	1	1	8
Henderson et al (2015)[60]	1	1	1	1	2	0	1	1	8
Hochart et al (2017)[11]	1	1	1	1	0	1	1	1	7
Hyams et al (1997)[47]	1	1	1	1	0	1	1	1	7
Hyams et al (2019)[52]	1	1	1	1	2	1	1	1	9
Jakobsen et al (2011)[58]	1	1	1	0	0	1	1	1	6
Jakobsen et al (2014)[31]	1	1	1	1	0	1	1	1	7
Kabakchiev et al (2010)[32]	1	1	1	1	0	1	1	1	7
Kolho et al (2016)[54]	1	1	1	0	0	1	1	1	6
Kuwahara et al (2017)[43]	1	1	1	1	1	1	1	1	8
Latiano et al (2011)[33]	1	1	1	1	2	1	1	0	8
Lee et al (2012)[44]	1	1	1	1	1	1	0	1	7
Li et al (2013)[55]	1	0	1	1	0	1	0	1	5
Livshits et al (2016)[41]	1	1	1	0	0	1	1	1	6
Miele et al (2007)[62]	1	1	1	1	0	1	1	0	6
Morgenstern et al (2017)[61]	1	1	1	1	1	1	1	1	8
Mossop et al (2008)[51]	1	1	1	1	1	1	1	0	7
Muller (2013)[69]	1	1	1	1	0	1	1	0	6

Supplementary Table 2. Continued

Study	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Muller et al (2016)[49]	1	1	1	1	0	1	1	0	6
Oliva-Hemker et al (2015)[42]	1	1	1	1	0	1	1	1	7
Olives et al (1997)[34]	1	1	1	1	0	1	0	1	6
Piekkala et al (2013)[13]	1	1	1	1	0	1	1	0	6
Rajwal et al (2004)[45]	1	1	1	1	0	1	1	0	6
Rinawi et al (2018)[46]	1	1	1	1	2	1	1	1	9
Roma et al (2010)[17]	1	1	1	1	0	1	1	0	6
Størdal (2004)[22]	1	1	1	1	0	1	1	0	6
Sullivan et al (2017)[36]									
Tsang et al (2012)[48]	1	1	1	1	0	1	1	0	6
Tung et al (2006)[59]	0	1	1	1	0	1	1	0	5
Turner et al (2008)[14]	1	1	1	1	2	1	1	1	9
Turner et al (2010)[38]	1	1	1	1	2	1	1	0	8
Turner et al (2010)[39]	1	1	1	1	2	1	1	0	8
Zeisler et al (2013)[50]	1	1	1	1	2	1	1	0	8
Zwintscher et al (2014)[27]	1	1	1	1	2	1	0	0	7
Zwintscher et al (2015)[12]	1	1	1	1	1	1	0	0	6

NOTE. Based on the Newcastle-Ottawa Scale. All columns, 0 or 1 stars except comparability (0–2 stars); the last column indicates the total number of stars.