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Development of Extraintestinal Manifestations in Pediatric Patients with Inflammatory Bowel Disease

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Abstract

Background—Extraintestinal manifestations (EIMs) in pediatric patients with inflammatory bowel disease (IBD) are poorly characterized. We examined the prevalence of EIMs at diagnosis, subsequent incidence, and risk factors for EIMs.

Methods—Data for 1649 patients from the PediIBD Consortium Registry, diagnosed with IBD before 18 years of age [1007(61%) with Crohn's disease, 471(29%) with ulcerative colitis, and 171(10%) with indeterminate colitis], were analyzed using logistic regression, Kaplan-Meier, log rank tests and Cox models.

Results—EIMs were reported prior to IBD diagnosis in 97 of 1649 patients (6%). Older children at diagnosis had higher rates compared with younger children, and arthritis (26%) and aphthous stomatitis (21%) were most common. Among the 1552 patients without EIM at diagnosis, 290 developed at least one EIM. Kaplan-Meier estimates of cumulative incidence were 9% at 1 year, 19% at 5 years, and 29% at 15 years after diagnosis. Incidence did not differ by IBD type (p=0.20), age at diagnosis (p=0.22), or race/ethnicity (p=0.24). Arthritis (17%) and osteopenia/ osteoporosis (15%) were the most common EIMs after IBD diagnosis.

Conclusions—In our large cohort of pediatric IBD patients, 6% had at least one EIM before diagnosis of IBD. At least one EIM will develop in 29% within 15 years of diagnosis. Incidence of EIMs both before and after diagnosis of IBD differs by type of EIM and may be slightly higher in girls, but is independent of the type of IBD, age at diagnosis, and race/ethnicity.

Keywords

children; adolescents; ulcerative colitis; Crohn's disease; arthritis; sclerosing cholangitis

Background

Approximately 25% of all new patients with inflammatory bowel disease (IBD) are diagnosed before 20 years of age 1. Patients with IBD may present with extraintestinal manifestations (EIMs) of disease before or after diagnosis of IBD. Up to 50% of adults with IBD are reported to have at least one EIM 2–5. A higher prevalence is reported in a few studies done in children 6, 7. We explored the relationship of EIMs to age at diagnosis of IBD, type of IBD, sex, and race/ethnicity in a large cohort of children and adolescents in the Pediatric IBD Consortium Registry.

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Materials and Methods

Patient population

Data were collected from January 2000 to November 2003 by the Pediatric IBD Consortium, comprised of the following centers: (1) UCSF Children's Hospital, San Francisco, and Kaiser Permanente of Northern California; (2) University of Chicago Comer Children's Hospital; (3) Emory University School of Medicine, Egleston Children's Hospital, and Scottish Rite Children's Hospital of Children's Healthcare of Atlanta; (4) Texas Children's Hospital, Baylor College of Medicine; (5) Children's Hospital of Philadelphia; and (6) Mass General Hospital for Children, Boston. Each center obtained institutional review board approval for the registry protocol and complied with the Health Insurance Portability and Accountability Act. Patients and parents provided assents and consents prior to entry into the registry. Details of the establishment of the registry, enrollment, and data collection were previously reported 8. Patients were entered in the Pediatric IBD Consortium Registry when IBD was suspected or confirmed, and then followed prospectively. Of 1736 patients in the registry, we identified 1649 patients with IBD diagnosed before 18 years of age, in many cases substantially before entry into the registry. EIMs were detected both retrospectively before entry into the registry and prospectively over cohort follow-up ending on October 31, 2003.

Measurements

Age at diagnosis of IBD was based on age at which the final type of IBD was made, and was categorized as 0-5, 6-12, and 13-17 years inclusive, based on modified IBD Consortium FDA categories 8. IBD was classified as Crohn's disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC). Race/ethnicity was assessed based on self report and classified as Caucasian, African American, Asian/Pacific Islander, Hispanic and Unknown/Other. EIMs were ascertained retrospectively by history at registry entry and prospectively by history, physical examination, and radiologic study. EIMs in the registry were based on clinical documentation in the medical history during the course of follow up, referral diagnoses confirmed by the gastroenterologist, or reports from diagnostic procedure confirmed by specialist. The data included any EIMs that might have occurred before, concurrent with, or after diagnosis of IBD.

EIMs were recorded based upon standards established by all study coordinators for each EIM at the inception of the data collection, although the study is limited by initial clinical impression of the gastroenterologist.

EIMs were subdivided into the following categories: colitis related, specifically skin, eye, joint, and mouth, where the activity of the EIM parallels the activity of the underlying intestinal disease; hepatobiliary; impaired growth; EIMs secondary to complications ofor as direct extensions of bowel disease, more frequently noted in patients with CD than with UC and including nephrolithiasis, obstructive uropathy, cholelithiasis, and pancreatitis; iatrogenic EIMs such as drug-induced bone marrow suppression, pancreatitis, and corticosteroid-associated myopathy, and EIMs that cannot be categorized clearly in one of the other groups, such as amyloidosis and cancer 9. In accordance to the above classification we defined EIMs as signs and symptoms extrinsic to the gastrointestinal system, including (1) dermatologic (erythema nodosum, psoriasis, and pyoderma gangrenosum), (2) ophthalmologic (iritis and uveitis), (3) musculoskeletal (arthritis; axial and peripheral, compression fractures and osteopenia/osteoporosis), (4) renal (renal calculi), (5) hepatobiliary (primary sclerosing cholangitis [PSC], autoimmune hepatitis), (6) oral (aphthous stomatitis), (7) pancreatitis, and (8) iatrogenic (anemia, papilledema, corneal

infiltrate, and glaucoma). This classification is controversial because anemia, glaucoma, and pancreatitis may also be considered complications of therapy and not as primary EIMs.

Follow-up for this study was censored on October 30, 2003.

Statistical Methods

Descriptive statistics were used to characterize the cohort for our data analyses. Kaplan-Meier methods were used to estimate cumulative incidence of EIMs after diagnosis of IBD. The curves were compared by age at diagnosis of IBD and type of EIM using the log rank test. Two regression models were used to identify risk factors for developing EIMs. First, we fit a logistic model for history of EIM at diagnosis of IBD. Second, we applied a Cox proportional hazards model for time from diagnosis of IBD to first EIM among patients without any history of EIM at diagnosis of IBD. Because of some controversy of inclusion of osteopenia/osteoporosis, glaucoma, papilledema and anemia as EIMs, a sensitivity analysis excluding these EIMs was also performed. Observations with missing dates of diagnosis of IBD or EIM were excluded from the analysis. Registry data were collected and stored in Microsoft Access 2000. Data were analyzed using STATA, Version 9.2 (Stata Corp, College Station, TX) and are expressed as Mean ± SD.

Results

The study population was 54% male and 81% Caucasian (Table 1). About 28% of the patients were 6 years old or younger at IBD diagnosis. Mean (median) age at diagnosis was 11.1±4.15 (11.8) years. The majority of patients (61%) had Crohn's disease.

Overall 387(24%) children developed at least one EIM by the end of follow up. Of these EIMS, 33% were musculoskeletal, 7.5% dermatologic, 7% ophthalmologic, 7.8% hepatobiliary, 13.7% oral, and 13.4% iatrogenic (Table 2). No overlap syndrome was identified.

At least one EIM was reported in 97(6%) patients at IBD diagnosis; these children accounted for 25% of the total of 387 developing at least one EIM by the end of the follow-up period. Prevalence was 3% among children diagnosed with IBD before age 6 years and 6-7% among those who were older at IBD diagnosis ($p<.05$ after adjustment for covariates using the logistic model; Table 3). No other risk factors for prevalent EIMs were identified in the logistic analysis. Arthritis (26%) and aphthous stomatitis (21%) were the most common EIMs before IBD diagnosis.

Among the 1552 patients with no history of EIM at the time of IBD diagnosis, 290(18%) subsequently developed a first EIM; of these, 52 developed a second EIM, and 13 developed a third. Osteopenia/osteoporosis, anemia and arthritis were the most common EIMs post IBD diagnosis. Kaplan-Meier estimates of the cumulative incidence were 9% (95% CI = 8%-11%) at 1 year, 19% (95% CI = 17%-22%) at 5 years and 29% (95% CI= 25%-33%) at 15 years from time of diagnosis of IBD (Figure 1). Follow-up ended at least 15 years after diagnosis of IBD for 68 of these patients. Cox analysis (Table 4) revealed weak evidence for greater risk of developing EIM among girls than boys (Hazard Ratio 1.22, 95% CI 0.97-1.54, $p = 0.09$), but did not differ by age of IBD diagnosis ($p = 0.22$; Figure 2), IBD type ($p=0.20$) or race ($p=0.24$).

In contrast, in analyses including second and third EIMs, EIM incidence did clearly differ by type of EIM (log rank $p= 0.0005$, Figure 3). Kaplan-Meier estimates of the cumulative incidence of the most common EIMs at 1, 5, and 10 years post IBD are shown in Table 5. Osteopenia/osteoporosis had the highest cumulative incidence at 5 and 10 years.

Kaplan-Meier estimates of the cumulative incidence of PSC 5 years after diagnosis of IBD were 0.5% (95% CI 0.2%-1.3%) for children with CD, 2.7% (95% CI 1.5%-4.8%) for those with UC, and 1.3% (95% CI 0.03%-5.0%) for those with IC. In a Cox model, children with UC were at increased risk compared to those with CD (Hazard Ratio 5.25, 95% CI 1.84-14.9, p=0.002). However, risk was similar among children with CD and IC (p = 0.31), and did not differ significantly by gender (p = 0.14).

The risk of developing other EIMs did not differ by IBD types except for anemia (log rank p = 0.003). In sensitivity analyses excluding 94 EIMs (osteopenia/osteoporosis, anemia, papilledema and glaucoma), history of at least one of the other EIMs was recorded among 85/1649 patients (5.2%) at diagnosis of IBD, compared with 97 (6%) when those EIMs are included. The number of patients with at least one post IBD EIM dropped from 290 to 208 and the Kaplan-Meier estimates of cumulative incidence were consequently lower: 6% at 1 year after IBD diagnosis, 14% at 5 years, and 21% at 15 years. Results of both risk factor analyses were similar.

Discussion

In this study from a large multicenter pediatric IBD registry, EIMs were reported in 6% before diagnosis of IBD, accounting for 25% of the total first EIMs reported by the end of the study follow-up period. EIMs before diagnosis of IBD were found more frequently in children who were older than 5 years at diagnosis. Subsequent EIM incidence after diagnosis of IBD differed by type of EIM, but not by age at IBD diagnosis, race/ethnicity or IBD type. Cumulative incidence was similar to the range reported in prior adult studies 2-5, 10. However our data show a much lower incidence among children compared with prior (and smaller) pediatric reports. Grossman et al, reported that 68% of 41 children and adolescents with IBD had EIMs. In a study of 184 children with IBD, Stawarski et al found that 50% of those with CD and 80% of those with UC had at least one EIM 6, 7. However while both investigators included osteopenia, they also added growth delay as an EIM.

A prevalence study of 873 adults revealed that age at presentation did not affect the likelihood of EIM occurrence, similar to our finding in the 1552 patients without EIMs at IBD diagnosis3. However, comparisons with prior studies are problematic because of differences in patient population size, demographics and methods. A report by Monsen et al. excluded stomatitis and episcleritis from the EIMs, while Bernstein et al excluded arthropathies from their study 11, 12. No large cohort cumulative incidence study has been reported to date.

Our data reveal a non-significant but clinically relevant trend for higher risk of EIMs among girls. This finding could possibly be explained by the hypothesis that autoimmune diseases are more common in girls and is consistent with our earlier report of gender differences among children with Crohn's disease 13. A report by Lakatos et al on 873 adult patients also found EIMs more prevalent in females than males 14. Bernstein et al, found gender variation related to types of EIMs 11.

Our finding of no difference in risk by race/ethnicity is consistent with Eidelwein et al, who found no differences in symptom presentation and EIMs between Caucasians and African American pediatric patients 15.

While our analysis did not reveal strong evidence of variation in the overall incidence of EIMs by type of IBD, specific EIMs were more prevalent in patients with CD 3, 6, 9, 11, 16. Previous reports of prevalence of EIMs have also documented increased risk in patients with CD compared with UC, with the exceptions of PSC and ocular manifestations 2, 4, 9, 14 17. The cumulative incidence of PSC was 2.1% in this study, within the range reported in prior

prevalence adult studies 3, 11, 18, 19. The cumulative incidence of PSC was higher in UC than CD, similar to other studies 9, 11, 14, 20. The incidence in children may be higher than described in this study because clinical presentation of PSC in childhood is frequently different from that of PSC in adults and a high index of suspicion is required to make diagnosis of PSC in children. Though, our study did not show any gender difference in the incidence of PSC, other studies have shown that males have increased risk compared to females 11, 20-24.

Arthritis and aphthous stomatitis were the most frequent EIMs before diagnosis of IBD, while osteopenia/osteoporosis was the most common EIM after diagnosis of IBD. Peripheral arthritis was more common than axial arthritis. The cumulative incidence of peripheral arthritis at 10 years was 4.2%, lower than in three previous studies 9, 25, 26. The difference in results may be explained by differences in methods, study population and the type of referral centers. The high incidence of osteopenia/osteoporosis may be due to malabsorption of calcium and/or vitamin D, low body mass index, corticosteroid exposure, disease activity and elevation of inflammatory cytokines 27, 28. The pathogenesis of osteopenia/ osteoporosis is poorly understood, and patients with CD may develop bone-mineralization disorders even without exposure to corticosteroids. 29

As a multicenter registry, our study had several innate limitations. Although our study population was drawn primarily from tertiary care referral centers, most pediatric IBD patients are followed in such centers, so our findings should be representative for pediatric patients with IBD. Information on EIMs at diagnosis of IBD was retrospective. No *a priori* standard criteria were developed for the definition of each EIM. Risk of EIMs in relation to disease severity could not be assessed with this dataset. The effects of therapy of the underlying IBD on EIMs were not evaluated in this study. Some clinical presentations related directly to therapy of IBD may have been included as EIMs. Impaired growth, unique to the pediatric age group, was also not evaluated in this study, as the influence of the primary disease including disease activity could not be clarified from our data.

In our large cohort of pediatric IBD patients, EIMs were relatively uncommon before diagnosis of IBD, but substantially increase after diagnosis. Race and type of IBD provided no information about risk, but risk may be slightly higher among girls. Because many EIMs may be treatment-related and can significantly complicate treatment, effects of IBD therapy on EIMs deserve further prospective investigation.

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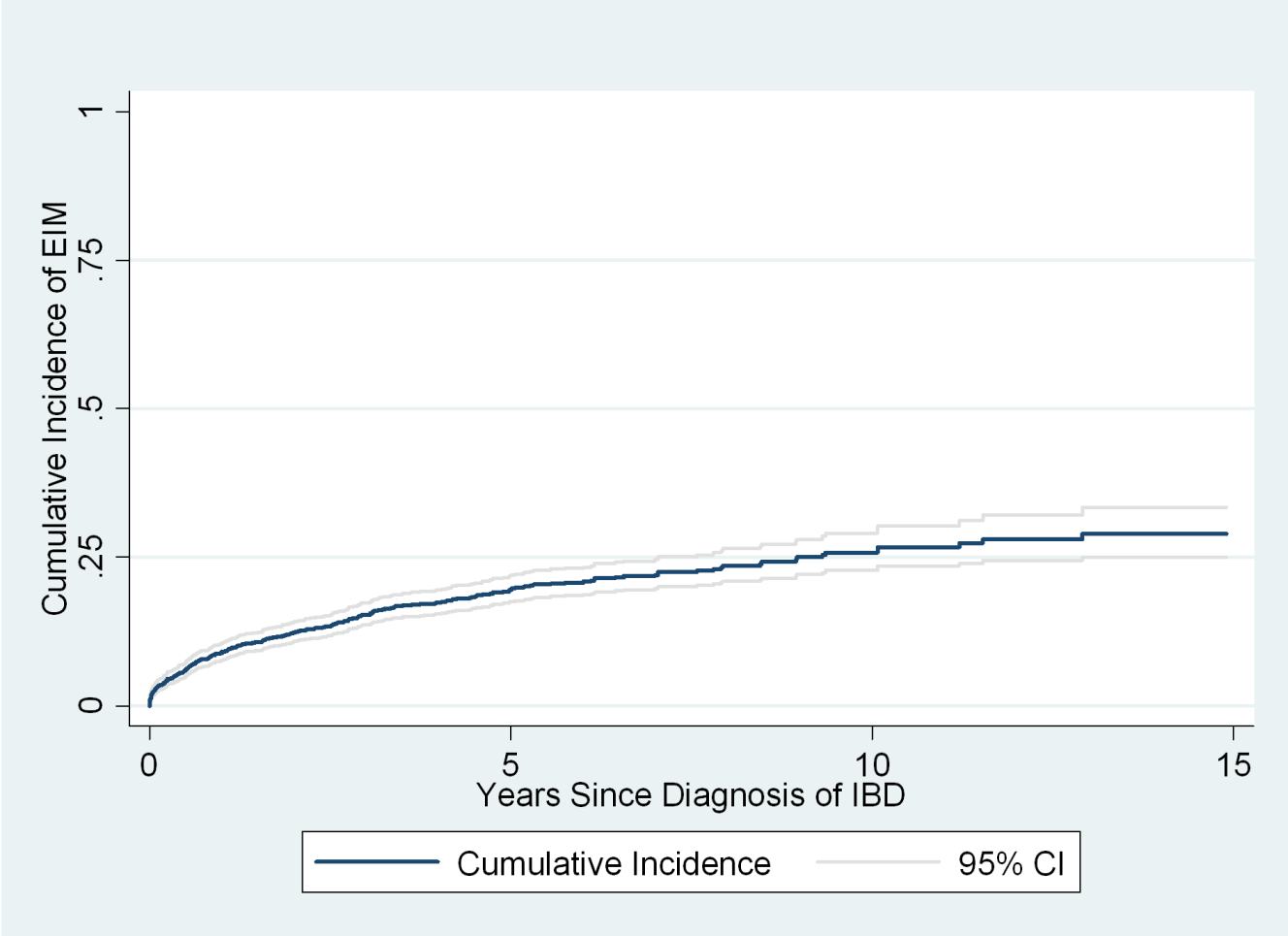

Figure1.
Kaplan Meier estimates of the cumulative incidence of EIM after diagnosis of IBD among patients with no history of EIM.

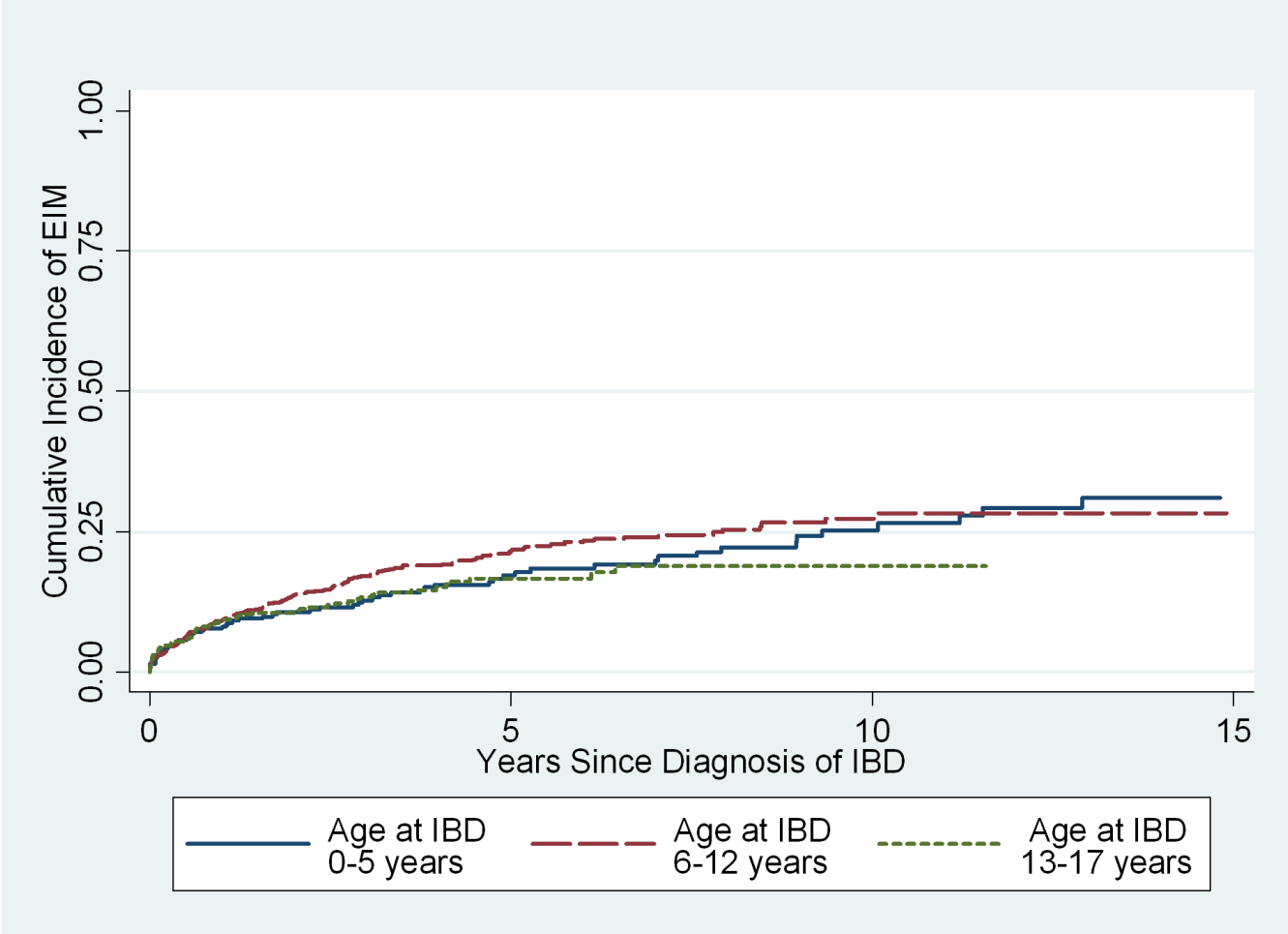

Figure 2.
Kaplan Meier estimates of the cumulative incidence of EIM after diagnosis of IBD among patients with no history of EIM, stratified by age at IBD diagnosis.

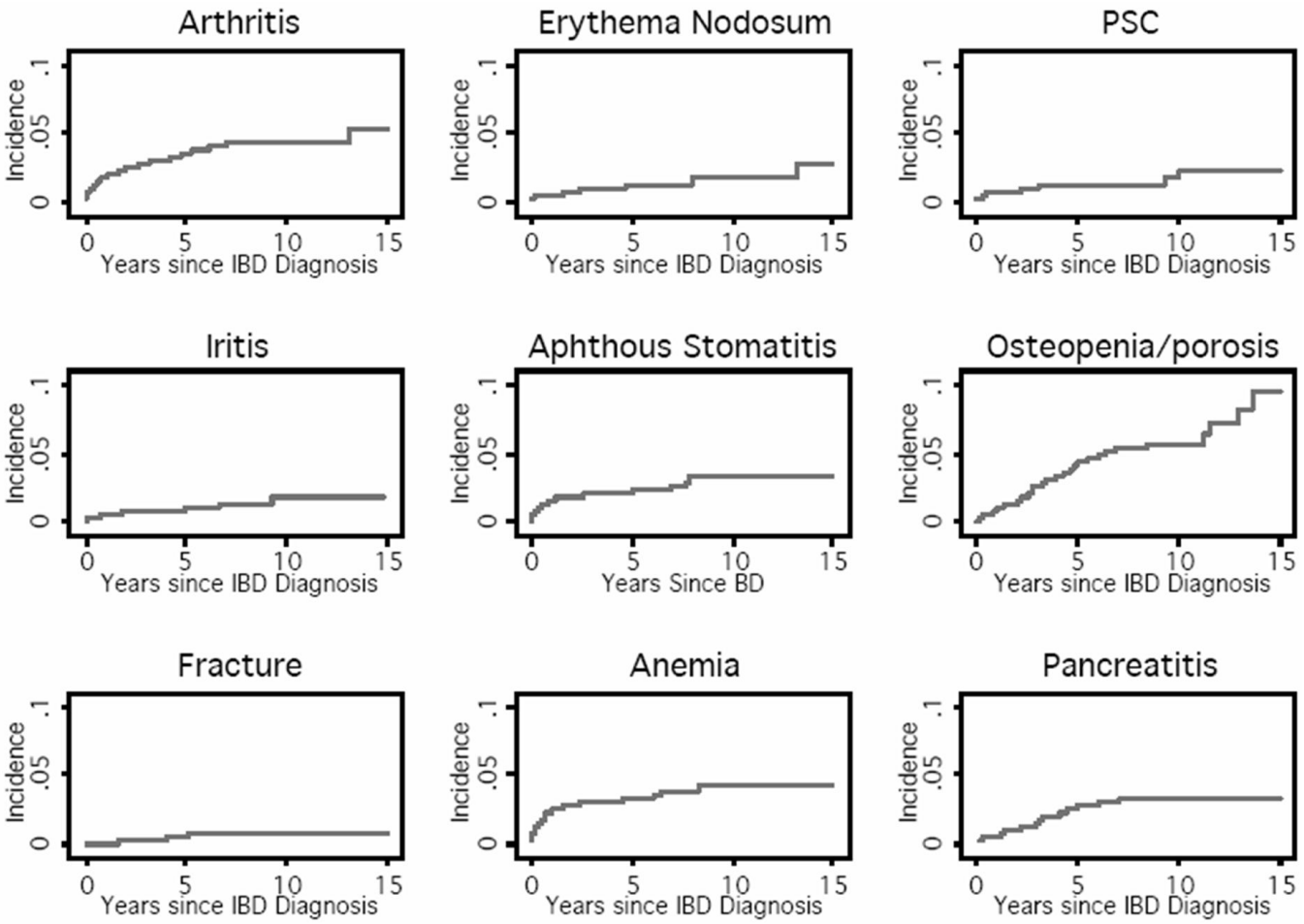

Figure 3.
Kaplan Meier estimates of the cumulative incidence of the most common EIMs after diagnosis of IBD.

Table 1

Characteristics of the study sample

	N	%
Gender		
Male	893	54
Female	756	46
Race/Ethnicity		
Caucasian	1337	81
African American	153	9
Hispanic	45	3
Asian/Pacific Islander	36	2
Other/unknown	78	5
Age at IBD diagnosis (years)		
0-5	292	18
6-12	900	54
13-17	457	28
IBD type		
Crohn’s disease	1007	61
Ulcerative colitis	471	29
Indeterminate colitis	171	10

Table 2

Classification of First EIMs before and after IBD diagnosis

First EIMs	N	%
Dermatologic	**29**	**7.5**
Erythema nodosum	21	5.4
Pyoderma gangrenosum	6	1.6
Psoriasis	2	0.5
Ophthamologic	**27**	**7.0**
Iritis	16	4.1
Uveitis	1	0.3
Papilledema/corneal infiltrate	7	1.8
Musculoskeletal	**129**	**33.3**
Axial arthritis	12	3.1
Peripheral arthritis	45	11.6
Axial and peripheral arthritis	14	3.6
Compression fracture	7	1.8
Osteopenia/osteoporosis	51	13.2
Renal calculi	21	5.4
Gallstones	9	2.3
Pancreatitis	37	9.6
Hepatobiliary	**30**	**7.8**
Primary sclerosing cholangitis	24	6.2
Gallstones	9	2.3
Autoimmune hepatitis	6	1.6
Oral	53	
Aphthous stomatitis	53	13.7
Iatrogenic		
Anemia	**52**	**13.4**
	387	100

Table 3

Logistic Model for History of EIM before IBD Diagnosis (N= 1649)

	Odds-Ratio	95% CI	p-value	p-value (heterogeneity)
Gender				0.38
Female	1.00	-	-	
Male	1.21	0.80-1.83	0.38	
Race/Ethnicity				0.33
Caucasian	1.00	-	-	
African American	1.28	0.68-2.43	0.45	
Hispanic	2.22	0.84-5.83	0.11	
Asian/Pacific Islander	1.07	0.25-4.58	0.93	
Other/unknown	0.43	0.10-1.79	0.24	
Age at IBD diagnosis				0.07
0-5	1.00	-	-	
6-12	2.33	1.09-5.01	**0.030**	
13-17	2.55	1.14-5.69	**0.022**	
IBD type				0.29
Crohn’s disease	1.00	-	-	
Ulcerative colitis	1.12	0.57-2.19	0.75	
Indeterminate colitis	0.68	0.41-1.15	0.15	

Table 4

Cox Model for Time from Diagnosis of IBD to Subsequent EIM (N = 1552)

	Hazard-Ratio	95% CI	p-value	p-value (heterogeneity)
Gender				0.09
Male	1.00	-	-	
Female	1.22	0.97-1.54	0.09	
Race/Ethnicity				0.24
Caucasian	1.00	-	-	
African American	1.18	0.80-1.74	0.41	
Hispanic	0.56	0.21-1.50	0.25	
Asian/Pacific Islander	0.45	0.14-1.41	0.17	
Other/unknown	0.68	0.36-1.29	0.24	
Ages (y)				0.22
0-5	1.00	-	-	
6-12	1.13	0.83-1.54	0.44	
13-17	0.87	0.60-1.27	0.47	
IBD type				0.20
Crohn’s disease	1.00	-	-	
Ulcerative colitis	0.70	0.44-1.10	0.12	
Indeterminate colitis	1.08	0.83-1.40	0.56	

Table 5

Cumulative incidence of the most common EIMs after diagnosis of IBD

EIMs	Cumulative Incidence (%)		
	1 yr	5 yrs	10 yrs
Osteopenia/osteoporosis	1.0	4.4	5.8
Peripheral Arthritis	1.7	3.6	4.2
Aphthous stomatitis	1.6	2.1	3.4
Pancreatitis	0.5	2.6	3.2
Iritis	0.5	1	1.8
Erythema Nodosum	0.4	1.1	1.6
PSC	0.7	1.2	1.6
Compression Fracture	0	0.5	0.7