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REVIEW ARTICLE

Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature☆

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Abstract

Current data indicate a change in the epidemiology of inflammatory bowel diseases. The disease has become more widespread and the rise in the incidence has been reported in all age groups including early childhood and according to recent data also the elderly population. Some earlier studies have suggested that the phenotype and natural history of the disease may be different according to age of onset. Recently the importance of age at onset was reported in two population-based studies from France and Hungary including both paediatric and adult onset inception cohorts. Early onset disease was associated with more frequent disease extension in both Crohn's disease and ulcerative colitis and in most but not all studies with higher frequency of complicated disease behaviour. This is also accompanied by striking differences in the medical management with earlier and more prevalent (2–3-fold) use of immunosuppressives and

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IM, immunomodulators; UGI, upper gastrointestinal; AZA, azathioprine; MTX, methotrexate; CI, confidence interval; 5-ASA, 5-aminosalicylic acid; Anti-TNF, anti tumoral necrosis factor; OR, odds-ratio; HR, hazard-ratio; CCR, colorectal cancer; SBC, small bowel cancer; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

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to some extent biologicals in patients with early compared to elderly-onset disease, especially in Crohn's disease. However, the results of population-based studies on impact of age on surgery rates in Crohn´s disease as well as ulcerative colitis are conflicting. Furthermore, published data indicate that relative but not absolute risk of developing cancer and mortality is higher in patients with an early onset disease. Critical reviews that focus on the importance of age at onset in inflammatory bowel disease are rare. Therefore, the aim of this review is to describe the differences in epidemiology, clinical characteristics, and natural history of paediatric and elderly-onset inflammatory bowel disease based on studies performed in general population.
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1. Introduction

Inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders that result from a combination of genetic predisposition, environmental factors, and abnormal immune responses to the gastrointestinal microbiota.[1,2] IBD occurs mostly in young adulthood even though paediatric and elderly patients are increasingly affected.[3–6] The causes determining the age of IBD onset remain unexplained. IBDs represent a heterogeneous group of diseases with similar final phenotypes, but different causes. In paediatric-onset disease genetic factors seem to play a greater role, particularly in some specific cases,[7–9] while in elderly-onset IBD environmental factors show a more prominent role. Recent reports from Europe have shown an increasing incidence of paediatric CD in the last 20 to 30 years, whereas the incidence of UC has remained stable or slightly decreased.[4,5,10] But the prevalence of IBD is increasing worldwide and the ageing of the population makes elderly-onset IBD a rising concern.[11–13] In the French study the incidence of UC is higher than that of CD only in the elderly patients, suggesting a change in the pattern of disease according to age.[14]

There is an ongoing debate whether childhood onset disease represents a different entity compared to older patients. Indeed clinical experience suggests that paediatric patients have a more aggressive disease needing early treatment with immunomodulators (IMs) or biological therapy.[4,15] But there are still uncertainties regarding clinical presentation, disease course and impact of treatments according to age at IBD diagnosis. The difference in impact of IBD on mortality and cancer risk according to age at diagnosis is also unknown. Recently the importance of age at onset was reported in two population-based cohort studies from France and Hungary including both paediatric and adult onset inception cohorts.[4,6,14] This is of utmost importance since local reimbursement and ethnical factors may largely influence the patient care and an unbiased evaluation of patient management strategy and outcomes is only available in the same cohort with harmonized practice plans.

The aim of the present narrative review is to summarise an update of the current data on incidence, phenotypes at diagnosis, natural course, therapeutic managements including surgery and risk of cancer and mortality according to age at IBD diagnosis through population-based studies from the literature.

2. Incidence of IBD according to age

In the vast majority of populations, patients with CD and UC are usually diagnosed in their 20s and 30s[12,13]; however, the diagnosis can be made at any age from 0 to >90 years.[16–20] Mean and median ages at the time of diagnosis for patients with CD are, in general, 5–10 years earlier than those of patients

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diagnosed with UC.[16,18,21,22] Some studies have reported a smaller, second peak in incidence, typically in the sixth or seventh decade, and especially among UC patients,[17,19,23] however others have not[18,21,24] and it remains uncertain whether these differences in age distribution are real or whether they are caused by, for instance, differences in the diagnostic tools available, fewer cases of ischemic colitis and microscopic colitis previously misinterpreted as IBD, and/or an overweight of a young-age-debut phenotype of the diseases.

Age definitions of early and elderly onset IBD within the literature vary and often depend on local clinical practice[5,12,13] (e.g. age of referral from paediatric to adult IBD care), making comparisons between populations difficult. Furthermore, heterogeneity in data collection methods and case ascertainment (e.g. diagnostic criteria, access to diagnostic procedures) – and hence differences in the ability to capture all cases of IBD within the population – might introduce bias in any such comparisons. Population-based, unselected cohort studies are therefore preferable when investigating epidemiological aspects of diseases, but the number of such cohorts is limited and even fewer address early and elderly onset IBD specifically. Incidence rates for early and elderly onset IBD in unselected, population-based cohorts who cover the whole age spectrum are shown in Table 1. In general, patients diagnosed before adulthood (early onset) account for approximately 5%–10% of all IBD cases.[5,25–27] Elderly onset IBD – most often defined as when diagnosis occurs at age >60 years – made up 9% of the total IBD population in a Hungarian (unselected) and a large French (selected) population-based cohort.[6,14,28]

Regardless of age of onset, the occurrence of IBD seems to be increasing worldwide[5,12,13,29] and the rise in early onset IBD mirrors this trend. Within the paediatric population the incidence of CD has risen significantly, while most studies have reported stable incidence of UC. For the elderly population only very few studies have addressed incidence over time,[6] but with an ageing population and rising incidence of IBD worldwide, the rate of elderly onset IBD is expected to increase accordingly.

Table 1 Incidence rates for Crohn's disease and ulcerative colitis in selected populations.

Country	Region	Study period	Early onset			Elderly onset		
			Age range	CD	UC	Age range	CD	UC
Denmark[19,20]	Copenhagen county	1962–1987	0–14	0.2	2.0	60–70	1.8	8.6
						>70	2.0	11.0
Denmark [17]	Copenhagen county	2003–2005	0–15	3.0	4.5	66–75	4.5	14.0
						76–85	8.0	16.0
						86–95	0.0	15.0
Denmark[78]	North Jutland	1978–2002	0–14	1.5	2.7	60–74	6.2	13.4
						≥75	5.7	10.5
Croatia[79]	Primorsko-Goranska County	2000–2004	0–14	8.7	0.9	≥65	4.8	6.5
Hungary[6]	Veszprem Province	2002–2007	0–18	7.5	5.5	>60	3.0	10.8
Hungary[30]	Veszprem Province	1977–2011	0–6	0.3	0.7			
			7–10	0.8	0.5			
			11–13	4.5	2.8			
			14–18	9.0	9.2			
Sweden[80]	Uppsala	1965–1983	0–4	0.0	0.3	60–64	3.5	7.5
			5–9	0.8	1.8	65–69	3.8	7.3
			10–14	4.0	9.5	70–74	3.0	9.0
						75–79	3.0	9.0
Iceland[22]	Nationwide	1990–1994	0–9	0.0	0.0	69–69	6.0	18.0
			10–19	9.0	10.0	70–79	7.5	7.5
						≥80	0.0	15.0
Norway[23,81]	South-Eastern Norway	1990–1993	0–14	1.0	1.0	65–74	3.8	13.0
						≥75	2.9	12.5
USA[24]	Olmsted County	1940–2000	0–19	3.4	2.4	60–69	5.6	7.6
						≥70	4.9	5.6
Spain[82]	Oviedo	2000–2002	0–14	5.5	1.5	65–74	1.5	8.0
						≥75	0.0	4.5
The Netherlands[83]	South Limburg	1991–2002	0–9	0.3	0.0	60–69	4.5	9.5
			10–19	9.8	3.5	70–79	3.3	7.0
						≥80	0.0	3.5
Italy[84]	8 Italian cities	1989–1992	0–10	0.5	1.0	61–70	1.3	5.8
			11–20	1.5	2.5	71–80	1.0	1.8
Germany[85]	Oberpfalz	2004–2006	0–15	2.3	1.0	66–75	1.8	4.0
						>75	1.0	2.0
France[3,4,14,37]	Northern France	1988–2006	0–17	2.6	0.8	>60	2.6	3.1

CD, Crohn's disease; UC, ulcerative colitis

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3. Clinical presentation and natural history

The occurrence of IBD seems to be increasing worldwide.
Within the paediatric population the incidence of CD has risen significantly, while most studies have reported stable incidence of UC.
With an ageing population and rising incidence of IBD worldwide, the rate of elderly onset IBD is expected to increase accordingly.

3.1. Crohn's disease

Upon diagnosis, the clinical presentation and phenotype of CD differ according to age. Indeed, elderly-onset CD is characterized by the predominance of pure colonic disease (L2) and inflammatory behaviour (B1) in sharp contrast with the youngest age-group (Fig. 1). Also, the disease course of CD is strikingly different between the early- and elderly-onset groups. First, disease extension occurs more frequently in paediatric-onset CD as compared with adult and elderly age groups. In a French population-based paediatric study, disease extension occurred in 31% of patients, whereas location remained stable in more than 92% of elderly patients (Fig. 2).[4,14]

In paediatric-onset CD, the most frequent location at maximal follow-up remained the ileocolonic distribution, and the changing pattern of location was also characterized by an increase in the number of patients with upper gastrointestinal tract involvement[15]; indeed in an Italian study, at least half of paediatric-onset CD patients had an upper gastrointestinal (UGI) localisation and UGI + patients presented an earlier onset and a more severe disease,[15] but this was not a universal finding. In Hungary, in a population-based inception cohort, the prevalence of UGI involvement was 15.8% in patients diagnosed in 1977–2011.[30] Interestingly, in the new Hungarian national registry cohort UGI involvement was 29.9% in patients diagnosed in 2007–2009,[31] which may represent different attitude to perform upper endoscopies. Of note however, the indication of gastroscopy is much wider in the adult setting and partly an overinterpretation of minute lesions by paediatric gastroenterologists can contribute to the observed differences.

Second, complicated behaviour at maximal follow-up is more prevalent in early- than in late-onset CD.[28,32,33] Indeed, more than 50% of children are expected to develop complicated behaviour.[4] Of note, in a head-to-head comparison the rate of disease progression was not different in paediatric vs. adult onset CD in a recent study from Hungary. In contrast, the rate of disease progression was linked to the era of diagnosis, location and presence of perianal disease.[34] Also, in an European multicentre inception cohort the majority of patients, both adult and paediatric, were diagnosed with B1 behaviour and[16,35] recent studies found that elderly-onset CD is characterized by an unexpected rarity of behaviour progression. Disease behaviour was reported to remain stable in 91% of patients, after a median follow-up of 6 years.[14]

In an Australian study describing differences in the natural history between an elderly-onset IBD cohort and a younger-onset cohort (16 to 40 years of age), the cumulative probability of introducing IM, having intestinal resection and disease progression was significantly lower compared to younger-onset patients.[36]

The less aggressive course of elderly-onset IBD should thus be taken into account when making therapeutic decisions. In paediatric-onset CD, perianal disease was also found to be more prevalent than in late-onset CD, increasing from 9% of patients at diagnosis to 27% at follow-up.[4] In elderly-onset CD, perianal disease prevalence increased from 8% to 17% at follow-up in the French cohort.[14]

3.2. Ulcerative colitis

Generally, the natural course of paediatric UC is considered to be more severe than that of older patients.[37] Paediatric-onset UC is characterized by widespread location at diagnosis and a high rate of disease extension.[25,35–38]

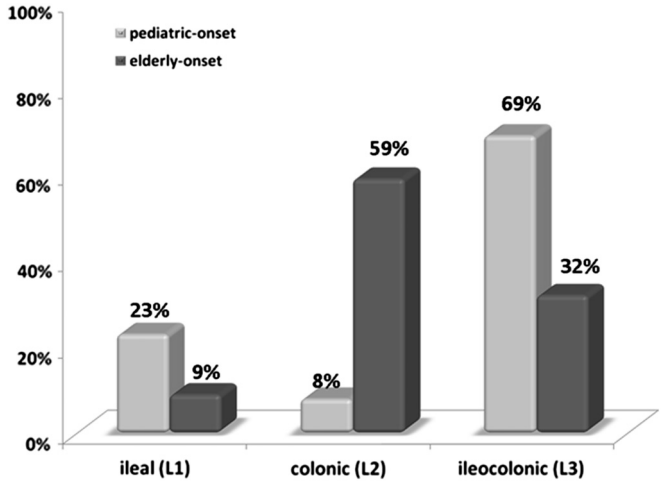

Figure 1 Comparison of Crohn's disease (CD) location on diagnosis between elderly-onset patients (n = 367) and paediatric-onset patients (n = 689). Disease site was recorded according to the Montreal classification with slight modification (ileal location with cecal involvement was considered as a L3 location). (Gower-Rousseau et al. Dig Liv Dis 2013;45:89–94; ref [28]).

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In a recent paediatric study, 60% of patients had extensive colitis after a median follow-up of 6.5 years.[37] A comparable rate of progression was also reported in a study from Denmark after 15 years of follow-up.[25] Similarly, significantly higher proximal progression rates were reported in patients with proctitis or left-sided colitis from Hungary in paediatric *vs* adult-onset population (paediatric-onset UC: 26% and 40.6% vs adult-onset UC: 12.8% and 20.2% after 5 and 10 years)[30] while more paediatric-onset had at least one acute severe episode compared to patients with an adult-onset (19.3% vs 8.2%, $P = 0.001$). In adults with UC, extension from initial location was reported to vary from 10% to 19% of patients after 5 years of disease, and from 11% to 28% after 10 years.[39] Among elderly UC patients with proctitis at diagnosis, only 8% progressed to left-sided colitis, and 3% to extensive colitis, whereas among patients with left-sided colitis at diagnosis, 5% progressed to extensive colitis.[14] Thus, UC location appears to remain stable in more than 80% of elderly-onset patients, as compared with the 49% rate of extension reported in the paediatric population.[14,37]

IBD presentation and natural course are strikingly different according to age at onset of symptoms. Indeed, disease extension occurs more frequently in paediatric-onset IBD as compared with adult and elderly age groups. In paediatric CD, the most frequent location at maximal follow-up remained the ileocolonic distribution, and the changing pattern of location is characterized by an extension of the digestive involvement, including upper GI involvement and in addition complicated disease behaviour. In paediatric UC half of patients will present a colonic extension during the 5 first years of the disease course. In adult and elderly-onset, the natural history of IBD seems less aggressive.
The age of onset of IBD has an important weight in the natural course of these diseases.

4. Medical treatment according to age at IBD diagnosis: paediatric- and elderly-onset

The majority of the guidelines on medical therapy in IBD suggest a partly different therapeutic and monitoring strategy in paediatric onset-IBD[40,41] including an earlier use of IM and biologicals in parallel with the findings on more aggressive disease phenotypes and a more rapid disease progression in paediatric-onset patients discussed above, which is partly based on the results of the landmark trial by Markowitz et al.[42] Another difference is the frequent use of initial enteral nutrition in paediatric-onset CD, which was less efficacious compared to steroids in adult-onset patients.[43,44] The benefit of early aggressive therapy (e.g. on decline surgical rates) and complex patient management including tight monitoring is however still uncertain.

According to Pigneur et al.,[32] patients with childhood-onset CD had more severe disease, increased frequency of active periods, and increased need for IM in the MICISTA registry in referral CD patients. Cumulative steroid, azathioprine (AZA), methotrexate (MTX) and biological requirements were significantly higher in paediatric-onset (96%, 72%, 19% and 26%) patients compared to patients with an adult-onset (91%, 61%, 10% and 13%) between 2000 and 2007.

Data from population-based cohorts on both early- and elderly-onset patients are only available thus far from the EPIMAD cohort from France and from the Veszprem cohort in Hungary.[4,6,14,31,34,37] In the EPIMAD cohort, steroid exposure and early AZA use were frequent in patients with a paediatric-onset disease: 85% of the 404 patients received corticosteroid therapy (steroid dependency: 24%, steroid resistant: 5% at 1 year). In addition, 61% received IM, intolerance and failure rates were 10% and 29%. Exposure to IM (regular use from 1995) increased over observation period, with a 5-year cumulative probability of prescription of 0.32 (95% CI: 0.2–0.44) in the 1988–1994 cohort and 0.68 (95% CI: 0.6–0.76) in the 1995–2002 cohort ($P < 0.01$). A total of 24% of paediatric-onset CD patients received infliximab therapy (initial success rate: 79%, intolerance: 14%, and failure 7%), reimbursed after 1999. The 5-year cumulative probability of prescription of infliximab rose from 0.15 (95% CI: 0.05–0.25) in 1988–1998 to 0.35 (95% CI: 0.19–0.51) in 1999–2002 ($P < 0.01$).[4] In UC, besides 5-ASA, 68% received oral or IV steroid therapy. At one year, 26% were steroid-dependent and 13% were steroid-resistant. Twenty five percent received IM, the 5-year cumulative probability of prescription was 0.11 in the 1988–1994 cohort and 0.34 in the 1995–2002 cohort, while only one patient received infliximab.[37]

In contrast, in the 841 elderly-onset IBD (>60-years) patients in the EPIMAD cohort[14] the medical strategy was significantly different. 5ASA-s was prescribed often in both CD and UC (cumulative probability: 68%, 77% and 80% in CD and 65%, 78% and 84% in UC at 1-, 5- and 10-years). Steroids (cumulative probability: 32%, 45% and 47% in CD and 21%, 34% and 40% in UC at 1-, 5- and 10-years) and IM (cumulative probability: 10%, 18% and 27% in CD and 2.5%, 10% and 15% in UC at 1-, 5- and 10-years) were prescribed at a lower rate. The cumulative use of anti-TNFs was 5% and 9% at 5- and 10-years in CD while this was exceptional in UC in patients diagnosed between 1988 and 2006.[14]

In concordance, in the Hungarian population-based inception cohort the need for AZA was more common in the paediatric and adult-onset CD populations compared to patients with an elderly onset disease (68.9%, 42.6% vs. 28.6%, $P < 0.001$) after a median 11 years of follow-up. Exposure to anti-TNF agents was absent in the elderly-onset population, while in patients with non-elderly-onset, it was 9.5%. Age at diagnosis, presence of perianal disease and disease behaviour at diagnosis were independent predictors for the need for immunosuppression during follow-up.[6] Similarly to the French data, there was a change in the prescription of IM from the early 1990s. Time-to initiation of AZA was largely dependent on the decade of diagnosis with an earlier and more frequent use from 1977 to 2008.[45] Of note, a much more aggressive therapeutic strategy was reported in the Hungarian national paediatric-onset registry in inception CD patients diagnosed in a different era, diagnosed in 2007–2009.[31] AZA was started directly after diagnosis in 42.5% and 54.6% of CD patients within 3- and 12-months after

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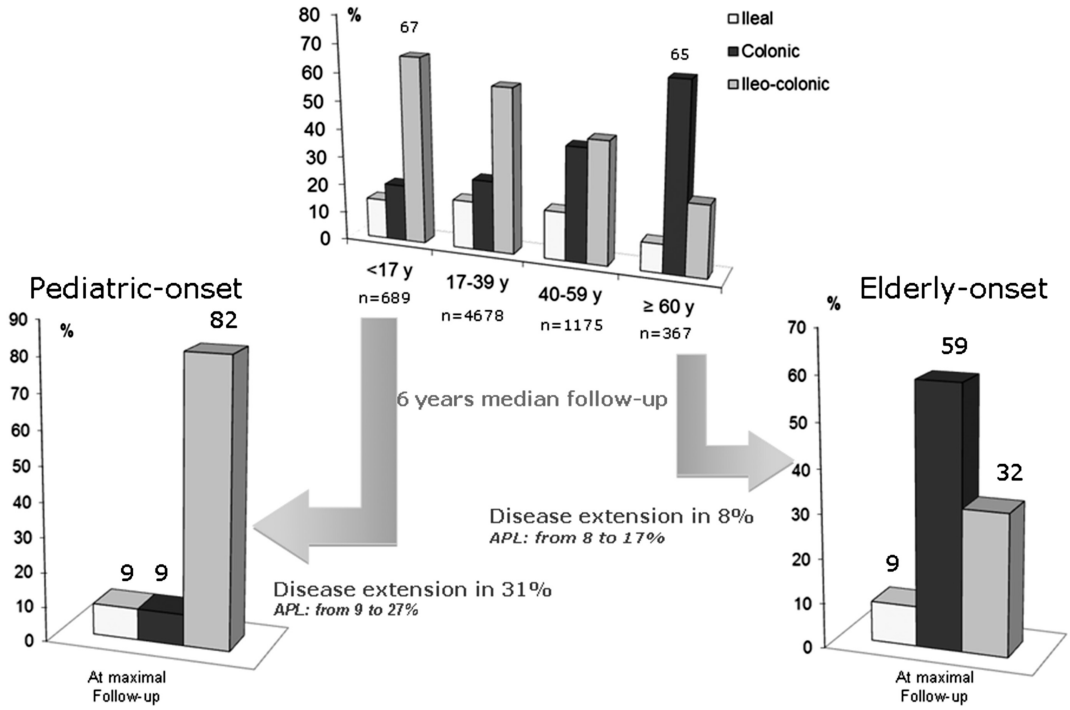

Figure 2 Comparison of digestive location during a 6-year follow-up between elderly-onset patients (n = 367) and paediatric-onset patients (n = 689). Disease site was recorded according to the Montreal classification with slight modification (ileal location with cecal involvement was considered as a L3 location). (Gower-Rousseau et al. Dig Liv Dis 2013;45:89–94; ref [28]).

diagnosis. Infliximab was started in 14% (33 out of 238) of CD patients within one year from diagnosis. This is the only inception cohort that reported also the frequency of exclusive early enteral nutrition. This was the therapy of choice only in the minority of the patients (n = 6).

In UC, significantly more paediatric (57.3%, $P < 0.001$, OR: 6.58) and adult (39.8%, $P < 0.001$, OR: 3.24) patients required systemic steroids during follow-up compared to the elderly-onset (17%) population in Hungary.[6] In multivariate analysis, age at diagnosis ($P < 0.001$, OR: 0.39) and disease extent at diagnosis ($P < 0.001$, OR: 2.80) were independent predictors of need for systemic steroids. In contrast, AZA use was relatively infrequent (paediatric-onset: 9.3%, adult-onset: 7.8% and elderly onset 2.8%; $P < 0.01$) between adult- onset and elderly-onset. In addition, in the Hungarian national paediatric registry cohort, the rate of corticosteroid use was 50% at diagnosis, while 15.3% and 22.5% of the patients received steroids and AZA one-year after the diagnosis. Infliximab was not available in paediatric UC during this period.[31]

The aggressive medical strategy in the paediatric-onset patients was reported also from other population-based cohorts. These data are confirming a change in the treatment/management strategy in the last decade. A good example is the recent Danish population-based paediatric cohort diagnosed in 2007–2009.[23] The median follow-up was approximately 18-months and systemic steroid, AZA and biological use was 92.3%, 61.5% and 24.6% in CD and 85.5%, 33.9% and 17.7% in UC. The authors reported an increased early AZA use (29.0 versus 69.2 per 100 person-years within the first year, $P < 0.001$) compared to the previous cohort (diagnosed in 1998–2000). In concordance, increasing early exposure to IM was reported in Canada. The use of these drugs within three years of diagnosis increased from 19.6% and 17.0% to 37.8% and 31.3% in patients diagnosed in 1994 and 1997 compared to those diagnosed in 2001 and 2004 in CD and UC.[46] Anti-TNFs within three years of diagnosis were prescribed only in 7.6% of CD patients diagnosed in 2001 and 2004. Data were largely similar in recent paediatric-onset inception cohorts from Wisconsin, US[47] in paediatric-onset IBD patients diagnosed between 2000 and 2007. Eighty-five percent and 40% of patients with paediatric onset CD were treated with IM and biologics, compared with 62% and 30% of patients with UC, respectively.

The therapeutic strategy is significantly different according to age at onset, with earlier and more prevalent use of immonusuppressives and to some extent biologicals compared to the elderly-onset patients, especially in patients with Crohn's disease. Recent data indicate that up to 65% and 40% of the patients with paediatric onset Crohn's disease may be exposed to immunosuppressives and biologicals within 5-years from the diagnosis. Comparable figures in elderly onset patients are 20%–30% and less than 10%. The above changes can be at least partially explained by the recent advances in patient management strategy.

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5. Impact of age on surgery in patients with IBD

5.1. Crohn's disease

In a Hungarian population-based study of incidence cases diagnosed between 1977 and 2008, the risk of intestinal surgery five years after diagnosis was not different comparing paediatric (≤18 years), adult and elderly (>60 years) patients (33.8% vs. 30.7% vs. 28.6%, P = NS).[6] This result was likely influenced by high rate of complicated (mainly stricturing) disease phenotype in elderly population than in paediatric and adult ones (61.9% vs. 37.8% vs. 19.5%). This is supported by analyses of inflammatory disease behaviour only which showed lower probability of resective surgery in older population than in paediatric and adult ones (log-rank test: P = 0.032). Furthermore age at diagnosis was the only significant predictor of the time to bowel resection.[6]

Two population-based studies from northern France evaluated the natural history of elderly (>60 years at diagnosis) and paediatric (<17 years at diagnosis) onset IBD in patients diagnosed and included in the EPIMAD registry in the period 1988–2006 and 1988–2002, respectively.[4,14] The cumulative probability of intestinal surgery in elderly onset CD was 18% (95% CI: 14%–23%) at 1 year, 27% (95% CI: 23%–32%) at 5 years and 32% (95% CI: 27%–38%) at 10 years since diagnosis.[14] The corresponding surgical cumulative probabilities in paediatric cohort were 7% (95% CI: 5%–9%), 20% (95% CI: 16%–24%) and 34% (95% CI: 30%–40%) at 1, 3 and 5 years, respectively.[4] In elderly population complicated disease phenotype (B2 or B3) increased the risk of 1st intestinal resection while exposure to corticosteroids decreased this risk.[14] On the contrary, corticosteroid use in paediatrics as well as stricturing phenotype was associated with elevated risk of operation, while the use of azathioprine reduced the surgical risk.[4]

Another French population-based inception cohort (1994–1997) compared the individuals diagnosed with CD at age ≥60 years and below 60 years.[48] The five year follow-up data revealed no difference in probability of abdominal surgery. Nevertheless, the rate of small bowel and/or ileocaecal resection was significantly lower in older patients (1.6% vs. 13.9%, $P < 0.01$) which corresponds to predominant colonic localisation of CD in older individuals.

Several population-based studies evaluated the disease course in paediatric IBD.[22,49–51] A study from southeastern Norway included the incidence cases of CD (n = 16) and indeterminate colitis (n = 3) diagnosed in 1990–1993 at age <16 years.[50] During the five year follow-up 26.3% of children underwent bowel surgery. In another inception paediatric cohort (<18 years at diagnosis) from Finland (1987–2003) 16% of CD children received surgical procedure during a median follow-up of 3.1 years.[51] A Danish population-based study compared paediatric (<15 years) and adult cohort (≥18 years) diagnosed in 2001–2006 and 2003–2004, respectively.[49] No significant difference in 5-year cumulative probability of bowel resection was observed between paediatric and adult onset disease (18% vs. 21.2%, P = 0.1) which is in accordance with the results of an older unselected cohort from the same area.[22,52]

Several other population-based studies reported on impact of age on surgical risk, however not specifically comparing paediatric and elderly onset IBD.[53–55] While some reported lower surgical risk in older patients (cut-off 40 or 50 years) others did not find any age-related difference.[53–55]

5.2. Ulcerative colitis

In a population-based Hungarian inception cohort (1977–2008) the 5-year colectomy rate in paediatric (≤18 years at diagnosis), adult (19–60 years) and elderly (>60 years) UC patients was 8.1%, 4.1% and 1.9%, respectively.[6] There was a trend to statistical significance comparing paediatric and elderly individuals (P = 0.06). Nevertheless, survival analysis did not reveal age at onset as a predictor of time to colectomy.

Population based-study from northern France (EPIMAD) evaluated the disease course of elderly-onset UC patients (>60 years) diagnosed in 1988–2006.[14] Cumulative probability of colectomy at 1, 5 and 10 years after diagnosis was 4% (95% CI: 2%–6%), 8% (5%–11%) and 8% (6%–12%), respectively. Only 9% of colectomized patients underwent construction of ileo-pouch anal anastomosis (IPAA), while 41% of operated had ileorectal anastomosis and in half of the individuals definite ileostomy was performed. A paediatric (<17 years) inception cohort (1988–2002) from the same geographic area reported cumulative probability of colectomy 8% (95% CI: 4%–15%), 11% (6%–17%), 15% (1%-23%) and 20% (13%–29%) at 1, 2, 3 and 5 years, respectively.[37] The majority of children, 63%, underwent IPAA construction and the rest had ileorectal anastomosis. In elderly-onset population, use of corticosteroids was associated with increased risk of colectomy while presence of extraintestinal manifestations at diagnosis and progression to extensive disease phenotype were risk factors for surgery in paediatric population.[14,37]

Paediatric (<16 years) population-based study from southeastern Norway (diagnosed in 1990–1993) reported 5 year colectomy rate of 21% for medically refractory UC.[50] Another population-based study from Finland (1987–2003) described that 25% of children (<18 years) underwent colectomy within a median follow-up of 3.1 years.[51] Danish population-based study comparing paediatric (<15 years) and adult (≥18 years) IBD patients did not find any significant difference in 5-year cumulative risk of colectomy (5% vs. 9.2%; HR 0.5, 95% CI: 0.1–5.0)[46] which is in agreement with previous unselected cohort from the same region.[22]

Similarly to CD, several population-based studies analyzed the impact of age on colectomy rates in UC although not specifically looking at childhood and elderly-onset disease.[53,56,57] Likewise in CD, the results were conflicting. Differences in age cut-offs and length of follow-up might have contributed to this heterogeneity.

The results of population-based studies on the impact of age on surgery rate in Crohn´s disease as well as ulcerative colitis are conflicting. While some studies suggest lower surgical risk in elderly onset disease compared to younger patients, others don't show any difference. There is a need for more studies of unselected cohorts specifically focused on impact of age on disease course and prognosis with regard to surgery. Moreover, the influence of current treatment on operation rate should be evaluated.

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6. Cancer risk and mortality according to age at IBD diagnosis

Studies on risk of cancer and mortality in patients with IBD from tertiary specialist centers often suffer from selection bias resulting in worryingly high risk estimates, which are not applicable to the average IBD patient. The tradition for population-based studies of unselected cohorts was started by Truelove and colleagues from Oxford, UK, in the 1960s and has been followed up by a number of prognostic cohort studies mainly from Europe, in particular Scandinavia, and North America.[52,58–64] Many of these studies also provide evidence of a potential effect of age at diagnosis on prognosis in IBD.

6.1. Age and intestinal cancer risk

The risk of small bowel cancer (SBC) and colorectal cancer (CRC) in patients with CD remains debated. A meta-analysis based on population-based cohort studies exclusively (n = 6), found a pooled standardized incidence ratio (SIR) of CRC of 1.9 (95% CI, 1.4–2.5), whereas the SIR for SBC was 27.1 (95% CI, 14.9–49.2).[62] Of note, the latter estimate was based on very few cases (i.e. a very low absolute risk), which only resulted in the high 27-fold increased relative risk due to the extremely rare occurrence of SBC in the general population.[65] The meta-analysis did not assess impact of age at diagnosis of CD on risk of cancer and the underlying studies either did not report on impact of age or had limited power per se to show any consistent impact. A recent nationwide Danish cohort study suggested a tendency towards increase in risk among patients diagnosed at young age,[66] whereas a recent regional population-based study from North Jutland County, Denmark did not suggest an impact of age on risk of CRC in CD.[67]

The risk of colorectal cancer in UC was markedly increased in a debated meta-analysis of both selected and unselected studies — with cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years and high numbers for those diagnosed at young age as well.[68] However, a recent meta-analysis based explicitly on population-based studies showed an overall pooled SIR of 2.4 (95% CI, 2.1–2.7) with relatively low absolute numbers (1.1%–2.5% at 20 years in studies with sufficiently long follow-up time).[69] In this meta-analysis, three studies from US,[70] Denmark,[61] and Canada[71] reported risk of CRC according to age at UC diagnosis. The pooled standardized incidence ratio suggested a significantly increased risk of CRC in young patients, being 8.6 (95% CI, 3.8–19.5) in the 0–29 year age group; 2.1 (95% CI, 1.3–3.3) in the 30–49 year age group; and 1.7 (95% CI, 1.2–2.4) in patients aged 50+ years at diagnosis. In accordance, recent cohort studies from Sweden[72] and Denmark[66] suggesting decreased risk of CRC in UC over calendar time still reported a fairly high relative risk of CRC in patients diagnosed at young age (0–19 years; RR, 42.8; 95% CI, 25.0–73.1; 20–39 years, RR, 2.41; 95% CI, 1.67–3.49).[66] However, the absolute risk of CRC was limited, also among young individuals.[66]

In contrast to intestinal cancer risk, a recent study from North Jutland, Denmark[67] of cancer *in general* among patients with IBD suggested that young age at diagnosis of IBD only plays a role in CD (0–19 years; HR, 2.17; 95% CI, 1.15–3.71; 20–39 years; HR, 1.75; 95% CI, 1.29–2.33), but not UC.

In France, in a large population-based cohort of paediatric-onset IBD patients with a median follow-up of more than 11 years there was a significant 3-fold increased risk of neoplasia with heterogeneous locations.[73]

6.2. Age at IBD diagnosis and mortality

In a meta-analysis of mortality in UC based on population-based studies (n = 10) no increased overall mortality (standardized mortality ratio, SMR, 1.1; 95% CI, 0.9–1.2) was found.[74] However, mortality from gastrointestinal diseases, non-alcoholic liver diseases, pulmonary embolisms, and pneumonia was increased, whereas mortality from pulmonary cancer was reduced.[74] Three of the studies included in the meta-analysis presented SMRs stratified for age at diagnosis. No pooled estimate for age 0–18 years could be calculated as two of the studies reported values of 0, whereas the pooled estimates for patients aged 20–29 years (SMR 0.9, 95% CI 0.5–1.5), 30–49 years (SMR 0.9, 95% CI 0.7–1.1), and 50+ years (SMR 1.0, 95% CI 0.9–1.1) at diagnosis did not suggest an effect of age on mortality in UC.[74] In France, in a large population-based cohort of paediatric-onset IBD patients with a median follow-up of more than 11 years, global mortality risk was increased 1.4 fold but did not significantly differ from that of the general population.[73] A recent nationwide Danish study found decreasing overall mortality among patients with UC during the last three decades, primarily explained by decreased mortality from CRC.[75] The study suggested, however, that patients diagnosed at age 0–19 years (HR, 2.15; 95% CI, 1.67–2.76) or 20–39 years (HR, 1.07; 95% CI. 0.97–1.19) were at significantly increased risk of dying relative to patients diagnosed at age 60–79 years.[75]

In a meta-analysis of mortality in CD based exclusively on population-based studies (n = 9), the pooled SMR was 1.39 (95% CI, 1.30–1.49) due to increased mortality from cancer, pulmonary disease, gastrointestinal disease, and genitourinary disease.[76] Meta-regression analysis revealed no significant impact of age at diagnosis of CD on mortality. In contrast, a recent nationwide Danish data showed 50% increased mortality in CD and this number did, of note, not decrease over time.[75] The Danish study also suggested that patients diagnosed with CD at age 0–19 years (HR, 1.62; 95% CI, 1.25–2.09) or age 20–39 years (HR, 1.31; 95% CI, 1.16–1.50) had a significantly higher risk of dying relative to patients diagnosed at age 60–79 years.[75] This is in contrast to findings from the EC-IBD study, where CD patients aged >40 years at diagnosis had higher mortality (SMR, 1.99; 95% CI, 1.37–2.80) than patients aged <40 years (SMR, 1.29; 95% CI, 0.26–3.78).[77]

The risk of CRC is increased in patients with IBD but not as high as previously reported and not in all patients. The risk of CRC is significantly higher in patients with longer disease duration, extensive disease, and IBD diagnosis at young age.

Among unselected patients with IBD, overall mortality was slightly but significantly higher than in the general population but meta-regression analysis revealed no significant impact of age at diagnosis of IBD on mortality.

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7. Conclusion

In all aspects highlighted in this review including epidemiology, clinical characteristics, natural history, cancer risks and therapeutic strategies, many differences were outlined between paediatric-, adult- and elderly-onset IBD, showing the disease heterogeneity according to age of onset. We showed in this review that early-onset IBD does differ from late-onset IBD in all these aspects. The disease heterogeneity regarding the change in disease pattern and behaviour is rather suggestive of different pathways leading to diverging phenotypes according to age of onset. However, differences in the clinical approach including treatment guidelines and strategies between paediatric and adult gastroenterologists also influence on disease course and might contribute to the observed differences.

Conflict of Interest Statement

We declare no conflicts of interest.

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