Journal of Crohn's and Colitis, 2016, 1224–1236
doi:10.1093/ecco-jcc/jjw054
Advance Access publication February 29, 2016
Original Article

Original Article

Systematic Review and Meta-analysis: Phenotype and Clinical Outcomes of Older-onset Inflammatory Bowel Disease

Ashwin N. Ananthakrishnan,[a,*,†] Hai Yun Shi,[b,†] Whitney Tang,[b] Cindy C. Y. Law,[c] Joseph J. Y. Sung,[b] Francis K. L. Chan,[b] Siew C. Ng[b,*]

[a]Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA [b]Department of Medicine and Therapeutics, Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong [c]University of Ottawa School of Medicine, Ottawa, ON, Canada

*They are co-corresponding authors.
[†]These joint first authors contributed equally to the work.

Corresponding author: Siew C Ng, MBBS, MRCP, PhD, Department of Medicine and Therapeutics, Institute of Digestive Disease, State Key Laboratory of Digestive Disease, LKS Institute of Health Sciences, Chinese University of Hong Kong, Hong Kong. Tel: 852 2632 3996; fax: 852 2637 3852; email: siewchienng@cuhk.edu.hk

Abstract

Background: Little is known of the clinical outcome of patients with older-onset inflammatory bowel disease [IBD]. We performed a systematic review to determine phenotype and outcomes of older-onset IBD compared with younger-onset subjects.
Methods: A systematic search of Embase and Medline up to June 2015 identified studies investigating phenotype and outcomes of older-onset [diagnosed at age ≥ 50 years] Crohn's disease [CD] and ulcerative colitis [UC] subjects. Pooled analyses of disease phenotype, medication use, and disease-related surgery were calculated.
Results: We analysed findings from 43 studies comprising 8274 older-onset and 34 641 younger-onset IBD subjects. Compared with younger-onset patients, older-onset CD patients were more likely to have colonic disease (odds ratio [OR] 2.56, 95% confidence interval [CI] 1.88 – 3.48) and inflammatory behaviour [OR 1.19, 95% CI 1.07 – 1.33], and less likely to have penetrating disease or perianal involvement. More older-onset UC patients had left-sided colitis [OR 1.49, 95% CI 1.18 – 1.88]. Although fewer older-onset IBD patients received immunomodulators [CD: OR 0.44; UC: OR 0.60] or biologicals [CD: OR 0.34; UC: OR 0.41], older-onset CD was similar in the need for surgery [OR 0.70, 95% CI 0.40 – 1.22] whereas more older-onset UC patients underwent surgery [OR 1.36, 95% CI 1.18 – 1.57].
Conclusions: Elderly IBD patients present with less complicated disease, but have similar or higher rates of surgery than non-elderly patients. Whether this reflects a non-benign disease course, physicians' reluctance to employ immunomodulators, or both, merits further study which is essential for improving the care of IBD in the elderly.

Key Words: Older-onset IBD; phenotype; natural history; outcomes

1. Introduction

Inflammatory bowel diseases [IBD], including Crohn's disease [CD] and ulcerative colitis [UC], are idiopathic, chronic inflammatory disorders of the gastrointestinal tract, resulting from a combination of genetic predisposition, environmental factors, and abnormal immune response to gut microbiota.[1] The incidence of IBD is

increasing over time around the world.[2] The rise in incidence has been reported across all age groups including in early childhood[3] and, based on recent data, also in the older population.[4] With the ageing of the population, the incidence of older-onset IBD is expected to further increase.[4,5]

Studies have suggested that the phenotype and natural history of disease may differ according to the age of disease onset.[4,6,7,8] As the majority of severe episodes occur during the first few years of disease onset,[9,10] and patients' ability to tolerate underlying activity may diminish with ageing,[5] older-onset patients should be treated differently from older patients with disease onset at a younger age. However, in most studies, these two groups of patients were not clearly distinguished. Some studies have reported that disease course was milder in older-onset patients,[7,8] whereas others[11,12] found that disease outcomes were not so benign, or can be worse in older-onset patients. Identifying age-related differences in the clinical course of older-onset IBD patients could impact on the approach to their management and treatment. With growing adoption of algorithms suggesting early immunosuppressive therapy with biologicals or combination therapy to achieve superior outcomes, defining the natural history of disease in this older-onset IBD population is essential to balance risks of aggressive medical therapy against likelihood of progression of disease. This is particularly pertinent with evidence suggesting that older patients may tolerate immunosuppression less well. There is not yet a comprehensive review of disease phenotype and natural history of older-onset IBD [defined as in individuals diagnosed after age 50]. We conducted a systematic review and meta-analysis of the literature to report disease phenotype and natural history of older-onset IBD patients, and to highlight differences between older-onset and younger-onset IBD patients.

2. Methods

2.1. Literature search

This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] An electronic literature search was conducted on Embase and Ovid MEDLINE using the following combination of keywords: ['crohn' and 'disease'] or ['crohn disease'] or ['ulcerative' and 'colitis'] and ['older' and 'age'] or ['elderly'] or ['elderly' and 'onset']. No start date limit was used and the search was performed until September 2015. Manual search was performed for abstracts published in major international conferences, including the Digestive Disease Week, the United European Gastroenterology Week, and the Asia Pacific Digestive Week, over the past 5 years. Searches of bibliographies of original articles and relevant reviews were subsequently performed to identify further studies for inclusion. The search had no language restrictions. After removal of duplicate references, initial screening of article titles and abstracts was undertaken by two independent teams from the Chinese University of Hong Kong [HYS, WT] and the Massachusetts General Hospital [CYL, AA]. Potentially relevant articles were obtained in full text and reviewed independently. Predefined criteria were used to determine eligibility for inclusion. Authors of papers were contacted as necessary to obtain additional data that were not available in the full manuscript or abstract.

2.2. Selection criteria

Clinical studies investigating the phenotype, clinical outcomes, and natural history of older-onset CD or UC [defined as in patients with disease diagnosed at 50 years of age or older] were included. Members of the two research teams independently conducted an initial screen of citations by titles and abstracts. Citations that were not original data [ie review articles], did not examine older-onset IBD, used a cut-off age younger than 50 years to define the older IBD population, did not separate CD from UC, or did not include information on phenotype or natural history were excluded. Disagreement between the two teams was resolved by discussing through teleconference.

2.3. Data extraction

Eligible citations were randomised into two groups and reviewed separately by the two teams. Data extraction forms were completed by each team, and then combined together. To ensure consistency, data extracted independently from the two teams for a pilot five studies were compared and a consensus was reached. Extracted data included the primary author, year and time of publication, country of origin, study design and setting, study size, population demographics, disease phenotype [disease location and behaviour according to the Montreal classification[14]] and clinical outcomes or natural history [surgery, immunomodulators, and biologics] of older-onset patients. Studies reported either overall proportion of patients using various medical therapies or surgery for their IBD, or reported outcomes at specific time points [ie 1 year, 5 years, 10 years]. If there was a control population with younger-onset IBD, phenotype and natural history of these patients were also collected for comparison.

2.4. Statistical analysis

Statistical analysis was performed using Stata 13.2 [StataCorp, College Station, TX]. We performed analysis in two different steps. First, recognising that a subset of studies did not provide a younger-onset IBD group for comparison but nevertheless provided useful data on phenotype of older-onset IBD patients, we calculated pooled proportions of the distribution of disease location and phenotype in CD and extent in UC according to the Montreal classification. We also calculated the overall proportions of older-onset IBD patients receiving traditional immunomodulator [azathioprine, methotrexate, 6-mercaptopurine] or anti-tumour necrosis factor [TNF] therapy, and IBD-related surgery. Additionally, where information was available, rates of these outcomes at 1 year and 5 years after diagnosis were calculated. The second analysis compared phenotypes and outcomes of older-onset and younger-onset IBD patients. A DerSimonian and Laird random effects model[15] was used to calculate odds ratios [ORs] and 95% confidence intervals [CIs] for outcomes where there was significant heterogeneity between the studies [defined as a Cochrane I2 > 50% or chi-square < 0.05]. For outcomes where there was homogeneity between the various studies, a fixed effects model was used. A p-value of less than 0.05 was considered indicative of statistical significance. Quality of included studies was assessed using the Newcastle Ottawa scale.[16] Meta-regression was performed on each of the outcomes to identify influential variables. A priori specified subgroups included region of origin, year of publication, size of the included cohort, and study quality. The likelihood of publication bias was assessed via Begg's and Egger's tests.

3. Results

3.1. Literature search

Our literature search identified 1664 citations from Embase and Medline through June 3, 2015 [1523 citations from Embase, and an additional 141 unique citations from Medline] [Figure 1]. After review of the title and abstracts, a total of 116 citations were selected for full-text review. After excluding studies that did not

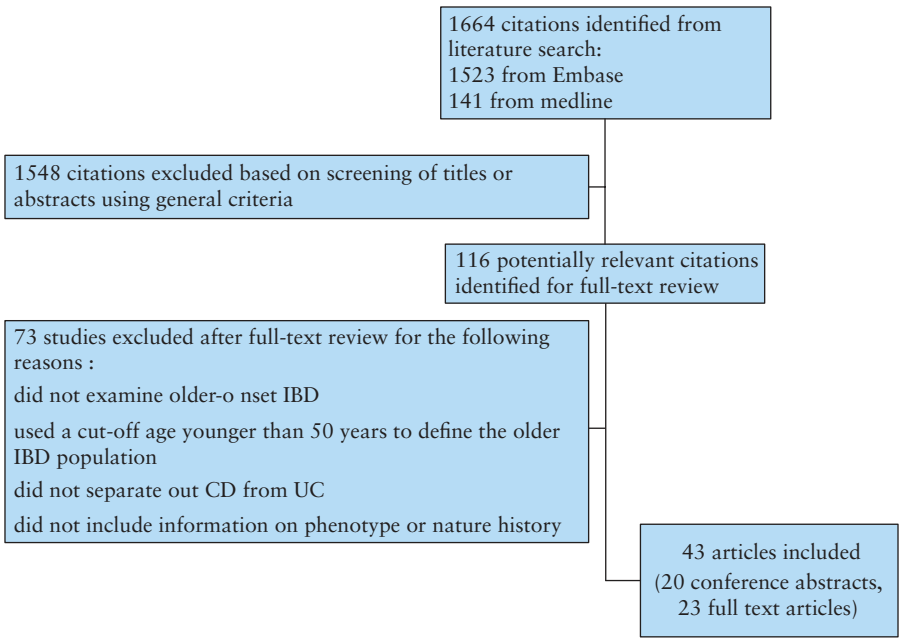


Figure 1. Flowchart depicting search strategy for the systematic review.

examine older-onset IBD, used a cut-off age younger than 50 years to define the older IBD population, did not separate out CD from UC, or did not include information on phenotype or natural history, a total of 43 articles were eventually included in our final analysis [20 conference abstracts, 23 full-text articles]. The years of publication ranged from 1981 to 2015. Most studies [n = 30] were retrospective whereas 10 studies were prospective cohorts. The most common age cut-off to define older-onset IBD was 60 years [30 studies] (range 50 years [6 studies] to 65 years [6 studies]). Most studies were from Europe [n = 19] or North America [n = 13]. There were 32 studies that provided information on CD [Table 1 and Supplementary Table 1 [available as Supplementary data at *ECCO-JCC* online], corresponding to 2981 patients with older-onset CD compared with 17 524 younger-onset CD controls [from 24 studies]. For UC, a total of 25 studies provided information on older-onset disease and included 5293 patients [Table 2 and Supplementary Table 2 [available as Supplementary data at *ECCO-JCC* online]] compared with 17 117 controls [from 21 studies]. The quality of the included studies ranged from 1 to 8 according to the Newcastle Ottawa scale [median 8].

3.2. Phenotype and natural history of older-onset IBD

We first analysed the pooled proportions of disease location and behaviour according to the Montreal classification for older-onset CD patients. From 21 studies that provided estimates of prevalence, the most common disease location in older-onset CD was L2, affecting 44% of patients [95% CI 36 – 52]. In contrast, 32% and 26% had L1 and L3 disease, respectively [Supplementary Table 3, available as Supplementary data at *ECCO-JCC* online]. Upper gastrointestinal involvement was uncommon, with a pooled estimate of 7%. Inflammatory disease behaviour was noted in 68% of older-onset CD [95% CI 61 – 74]; penetrating disease was uncommon [8%]. The pooled frequency of perianal involvement was 12% [95% CI 9 – 15]. The overall rates of surgery, immunomodulators, and biologicals were 32%, 32%, and 15% respectively. Only a small proportion of studies provided estimates of these outcomes at 1 and 5 years [Supplementary Table 3].

In older-onset UC, the most common disease extent was E2 [left-sided] disease, with a pooled estimated of 45% [95% CI 40 – 52]. Both E3 and E1 disease were less common, affecting 31% and 22%, respectively. The overall rates of surgery, immunomodulators, and biologicals were lower than in CD and were 9%, 17%, and 4%, respectively [Supplementary Table 3].

3.3. Comparison of older-onset with younger-onset IBD

3.3.1. Crohn's disease

A total of 18 studies provided sufficient information to compare disease location between older-onset CD and younger-onset CD [as controls]. Patients with older-onset CD were significantly more likely to have L2 disease [OR 2.56, 95% CI 1.88 – 3.48] [$p < 0.001$], though there was significant heterogeneity between the studies with an I^2 of 71% [Figure 2]. In contrast, L3 disease was less common in older-onset CD [OR 0.43, 95% CI 0.33 – 0.57] [Figure 2] whereas there was no difference for L1 [OR 0.87, 95% CI 0.0.68 – 1.12] or upper gastrointestinal [GI] involvement [OR 1.03, 95% CI 0.72 – 1.49]. For disease u older-onset CD was: more likely to be inflammatory [11 studies, OR 1.19, 95% CI 1.07 – 1.33, p = 0.002] though heterogeneity remained between all the studies [I^2 80%]; less likely to be penetrating [OR 0.48, 95% CI 0.33 – 0.69]; and similar in likelihood of stricturing disease [OR 0.90, 95% CI 0.67 – 1.20]. Perianal involvement was less common in older-onset CD compared with younger-onset disease [OR 0.64, 95% CI 0.56 – 0.80], with moderate heterogeneity between the studies [I^2 56%] [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online].

Compared with younger-onset disease, patients with older-onset CD were: less significantly less likely to receive immunomodulators [OR 0.44, 95% CI 0.33 – 0.57] or biologicals [OR 0.34, 95% CI 0.22 – 0.53] therapy; but similar in the need for surgical intervention [OR 0.70, 95% CI 0.40 – 1.22] [Figure 3]. Only two studies provided adequate details to estimate the outcomes at 1 year and confirmed the above findings of similar rates of surgery and lower use of immunomodulator or biological therapy [data not shown]. The pooled rate of surgery at 5 years from four

Table 1. Summary of included studies on older-onset Crohn's disease, stratified by geographical region.

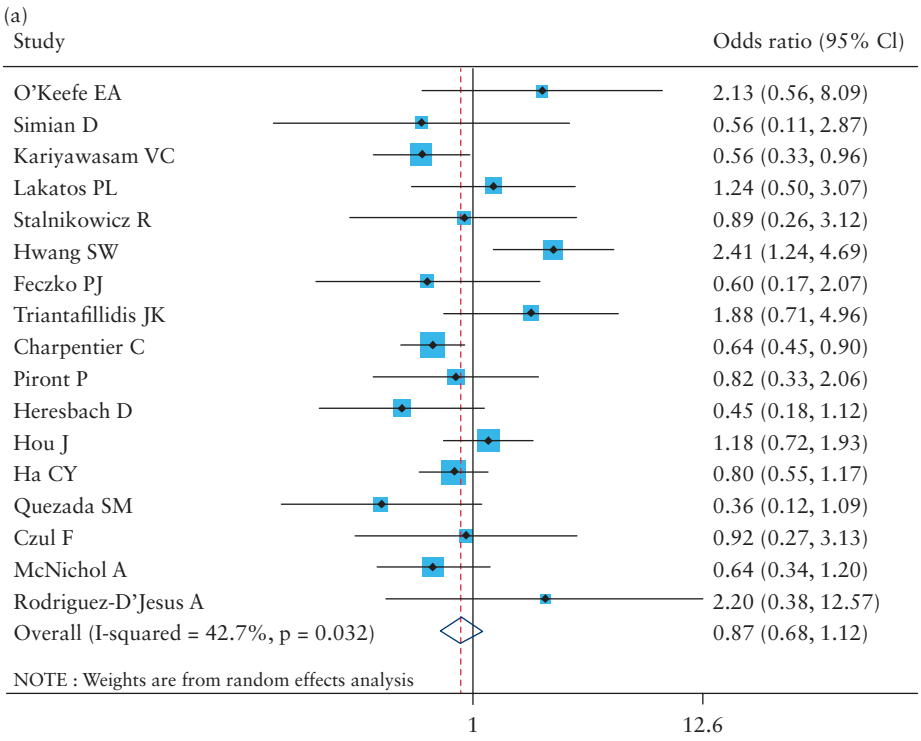
Lead author	Year	Country	Study period	Study type	Cut-off age	Number of patients	Median/mean duration of follow-up [months]	Male [%]	Median/mean age of diagnosis
Europe									
Jeuring S[38]	2015	Netherlands	1991	3	60	136	77		
Cantoro L[39]	2015	Italy	NA	2	60	68	120		
Cheddani H[40]	2014	France	1988–2006	3	60	367	72		
Charpentier C[8]	2014	France	1988–2006	3	60	367		38	70
Viola A[41]	2014	Italy	NA	3	65	113		42	70
McNichol A[42]	2013	UK	NA	1	60	60		17	
Cadilla J[43]	2013	Spain		1	60	90		56	
Lakatos PL[7]	2011	Hungary	1977–2008	3	60	21		52	69
Rodríguez-D'Jesus A[44]	2008	Spain	NA	1	60	8	86	55	67
Heresbach D[45]	2004	France	1994–1997	1	60	63	60	37	72
Triantafillidis JK[46]	2000	Greece	1986	1	60	19	86	63	67
Walmsley RS[47]	1997	UK	NA	1	55	62	120	48	67
Gupta S[48]	1985	UK	1979–1983	1	60	14	60	57	72
Fabricius PJ[49]	1985	UK	1944–1983	1	60	47		53	68
Piront P[50]	2002	Belgium	1993–1996	1	60	23		43	
North America									
Nguyen GC[51]	2015	Canada	1999–2008	1	65	725		38	
Hou J[52]	2014	USA	1999–2014	2	65	92		92	
Saad A[53]	2013	USA	2007-2013	1	60	29		52	71
Saad A[54]	2013	USA	2007–2013	1	60	32	88	53	72
Quezada SM[55]	2013	USA	2004–2010	2	60	22	66	27	
Czul F[56]	2012	USA	2010–2012	1	60	24		46	66
Juneja M[34]	2012	USA	1991–2010	1	65	134			
Ha CY[57]	2012	USA	2003–2010	1	50	160			
Roberts PL[58]	1990	USA	1960–1983	1	50	50	96	36	60
Feczko PJ[59]	1985	USA	1983–1985	1	50	14		43	
Shapiro PA[60]	1981	USA	1966–1979	1	60	33		33	
Asia									
Hwang SW[61]	2014	Korea	1982–2008	1	60	37	62	30	
Pappo I[62]	1997	Israel	NA	1	50	22		46	65
Stalnikowicz R[63]	1989	Israel	1977–1987	1	65	11	64	36	
Australia									
Kariyawasam V[64]	2013	Australia	1977-	3	60	119	84		68
Africa									
O'Keefe EA[65]	1989	South Af	1970–1979	3	60	10			
South America									
Simian D[66]	2015	Chile	1976–2014	1	60	9			

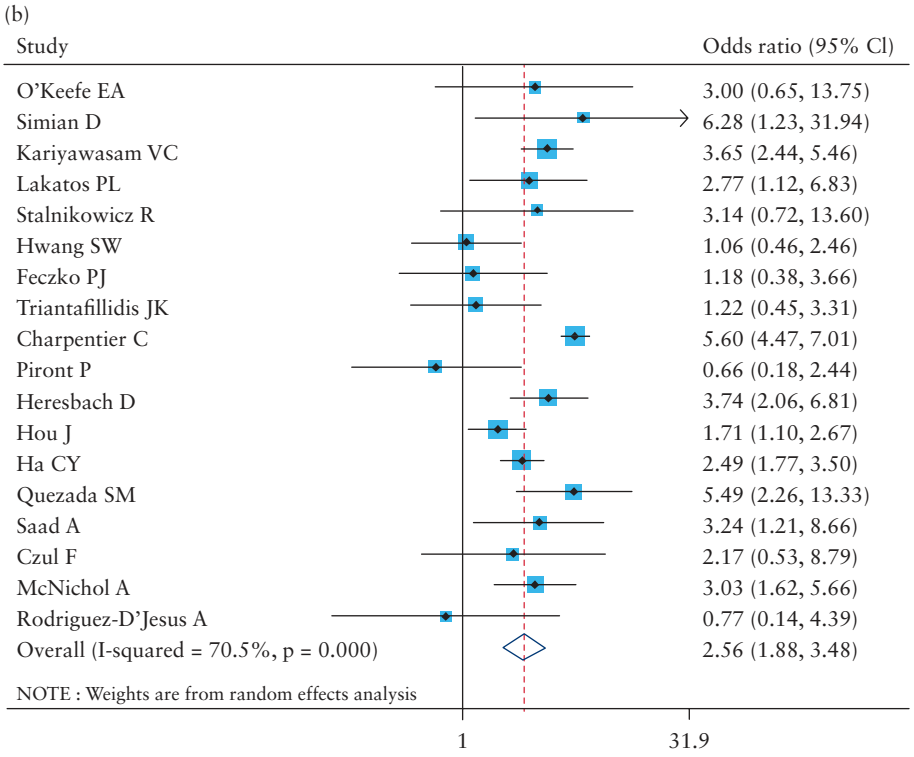
Study type: ,1 retrospective; 2, concurrent cross-sectional; 3, prospective. NA, not available.

Table 2. Summary of included studies on older-onset ulcerative colitis, stratified by geographical region.

Lead author	Year	Country	Study period	Study type	Cut-off age	Number	Median/mean duration of follow-up [months]	Male [%]	Median/mean age of diagnosis
Europe									
Cheddani H[40]	2014	France	1988–2006	3	60	472	72		
Walter F[67]	2014	Italy	NA	1	65	241		61	71
Charpentier C[8]	2014	France	1988–2006	3	60	474		62	68
Jeuring S[38]	2014	Netherlands	1991–?	3	60	373	85		
McNichol A[42]	2013	UK	NA	1	60	102			
Cadilla J[43]	2013	Spain		1	60	162		64	
Lakatos PL[7]	2011	Hungary	1977–2008	3	60	106		52	69
Rodríguez-D'Jesus A[44]	2008	Spain	NA	1	60	25			
Triantafillidis JK[46]	2001	Greek	NA	1	60	51	112	55	64
Riegler G[68]	2000	Italy	1998	3	50	386		67	
Gupta S[48]	1985	UK	1979–1983	1	60	17	60	35	69
Pironi P[50]	2002	Belgium	1993–1996	1	60	30		60	
North America									
Nguyen GC[51]	2015	Canada	1999–2008	1	65	1749		45	
Hou J [52]	2014	USA	1999–2014	2	65	159		92	
Juneja M[34]	2012	USA	1991–2010	1	65	87			
Ha CY[57]	2012	USA	2003–2010	1	50	254			
Quezada S[69]	2010	USA	2004–2010	3	60	17			
Ha CY[70]	2010	USA	2001–2008	1	50	140	12	50	
Asia									
Shi HY[71]	2015	China	1981–2013	1	60	157	96	61	66
Matsumoto S[12]	2013	Japan	2009–2011	1	60	23	97	57	66
Kalkan I[72]	2013	Turkey	1995–2011	1	60	56	92	79	65
Mizuno M[73]	2012	Japan	2010–2012	1	60	22			
Parlak E[74]	2000	Turkey	NA	1	60	41			
Australia									
Kariyawasam V[64]	2013	Australia	1977–	3	60	144	84		68
South America									
Simian D[66]	2015	Chile	1976–2014	1	60	5			

Study type: 1, retrospective; 2, concurrent cross-sectional; 3, prospective. NA, not available.





included studies was also not significantly different between older-onset and younger-onset CD [OR 0.89, 95% CI 0.61 – 1.29].

3.3.2. Ulcerative colitis

Older-onset UC was modestly more likely to be left-sided in location [OR 1.49, 95% CI 1.18 – 1.88] [Figure 4] when compared with younger-onset IBD, whereas there was no statistically significant difference for either E1 [OR 0.83, 95% CI 0.67 – 1.03] or E3 location [0.99, 95% CI 0.87 – 1.11]. Similar to the findings observed in CD, patients with older-onset UC were less likely to receive immunomodulator [OR 0.60, 95% CI 0.45 – 0.79] or biological therapies [OR 0.41, 95% CI 0.27 – 0.62] [Figure 5]. However in contrast, older-onset UC patients were significantly more likely to undergo surgery [OR 1.36, 95% CI 1.18 – 1.57, $p < 0.001$] with no heterogeneity between the studies [I^2 44%, $p = 0.11$] [Figure 5]. Analysis at 1 year after diagnosis revealed that the differences in the rates of surgery

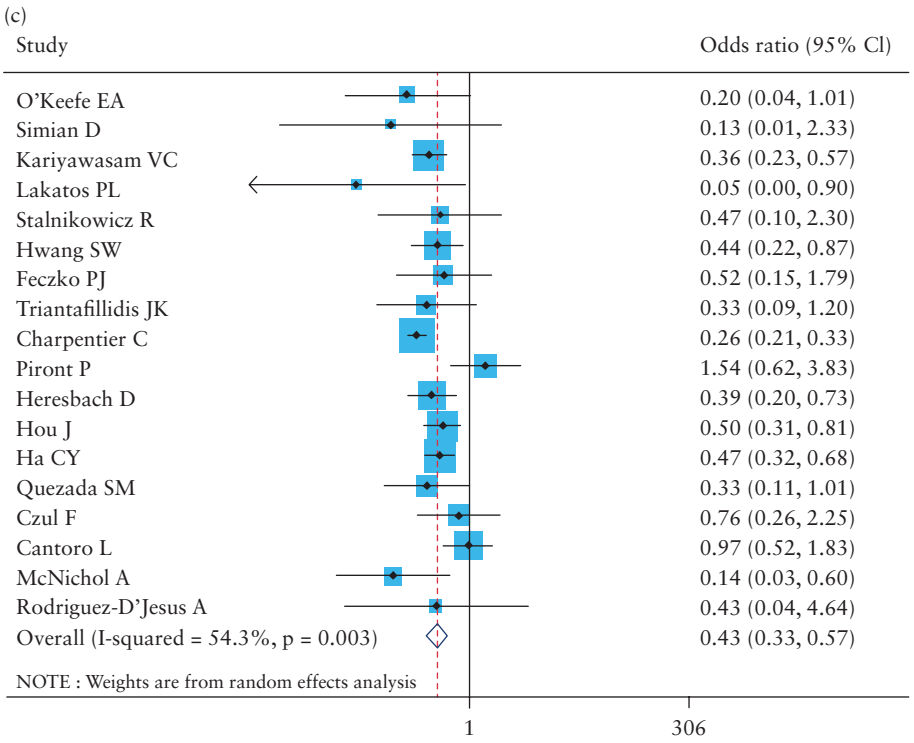


Figure 2. Comparison of disease location in older-onset and younger-onset Crohn's disease. [a] Ileal disease [L1]. [b] Colonic disease [L2]. [c] Ileocolonic disease [L3].

[OR 1.33, 95% CI 1.19 – 1.57], immunomodulator [OR 0.50, 95% CI 0.25 – 1.00] and biological use [OR 0.48, 95% CI 0.28 – 0.84] were already apparent at this time and persisted through the 5-year follow-up period.

3.4. Analysis restricted to full-text manuscripts

In an analysis restricted to full-text manuscripts alone, our results remain mostly unchanged. In Crohn's disease, compared with young-onset IBD patients, those with onset at an older age were more likely to have L2 disease [OR 1.84, 95% CI 1.44 – 2.34] and less likely to have L3 disease [OR 0.56, 95% CI 0.41 – 0.75] without any difference in likelihood of L1 or upper GI disease. There was no difference in disease phenotype, with similar proportions of B1 [OR 1.14, 95% CI 0.84 – 1.55], B2 [OR 0.89, 95% CI 0.37 – 2.14], and B3 disease [OR 0.60, 95% CI 0.25 – 1.43]. Similar to the main analysis, older-onset CD was no different from younger-onset disease in requiring surgery [OR 0.80, 95% CI 0.47 – 1.38], but less likely to receive immunomodulators [OR 0.54, 95% CI 0.31 – 0.93] or biological therapy [OR 0.19, 95% CI 0.04 – 0.99]. In UC, older-onset IBD was more likely to be E2 [OR 1.26, 95% CI 1.07 – 1.49] but no different in E1 or E3. Older-onset UC patients were more likely to undergo surgery [OR 1.29, 95% CI 1.14 – 1.47] but less likely to receive immunomodulator [OR 0.77, 95% CI 0.60 – 0.99] but not biological therapy [OR 0.48, 95% CI 0.20 – 1.14].

3.5. Additional analysis

Meta-regression was performed on each of the outcomes to identify influential variables. Study quality score, region, year of publication, whether the manuscript was a full-text manuscript or conference abstract, age cut-off for definition of older-onset IBD, and number of older IBD patients included did not influence the difference between older-onset and younger-onset IBD patients [$p > 0.10$ for all]. Year of initiation of cohort was weakly associated with a greater difference between older- and younger-onset CD patients [OR 1.02, 95% CI 1.00 – 1.04]. The Egger test showed evidence of weak publication bias [$p = 0.047$] for immunomodulator use, biological use, and disease location in CD, and disease extent and surgery in UC [< 0.05].

4. Discussion

Up to one-fifth of all new diagnoses of IBD may occur after 60 years of age.[17,18,19] With evolution of therapeutic algorithms into recommendation for early, aggressive immunosuppressive therapy to achieve better outcomes, yet recognition that widespread use of this practice is limited by concerns about safety and long-term durability, accurate determination of the natural history of disease is essential to balance risks and benefits in specific patient subpopulations. Literature on outcomes of older-onset IBD is both sparse and heterogeneous, further limited by the frequent grouping together of those with true older-onset disease and those diagnosed at a younger age who have now attained the age of 60 years. In this systematic review and meta-analysis, we demonstrated that older-onset CD and UC have specific phenotypic characteristics distinct from younger-onset disease, with less utilisation of conventional immunomodulators and biological therapy. In contrast, they have comparable or even higher rates of IBD-related surgery.

There are several interesting findings from our meta-analysis. First, we found that in comparison with younger-onset CD, disease diagnosed after the age of 50 years more frequently had isolated colonic distribution, was predominantly inflammatory, and infrequently presented with perianal involvement. Whereas older-onset UC was more similar to younger-onset disease, there was a modestly greater likelihood of left-sided colitis but not pancolitis. The

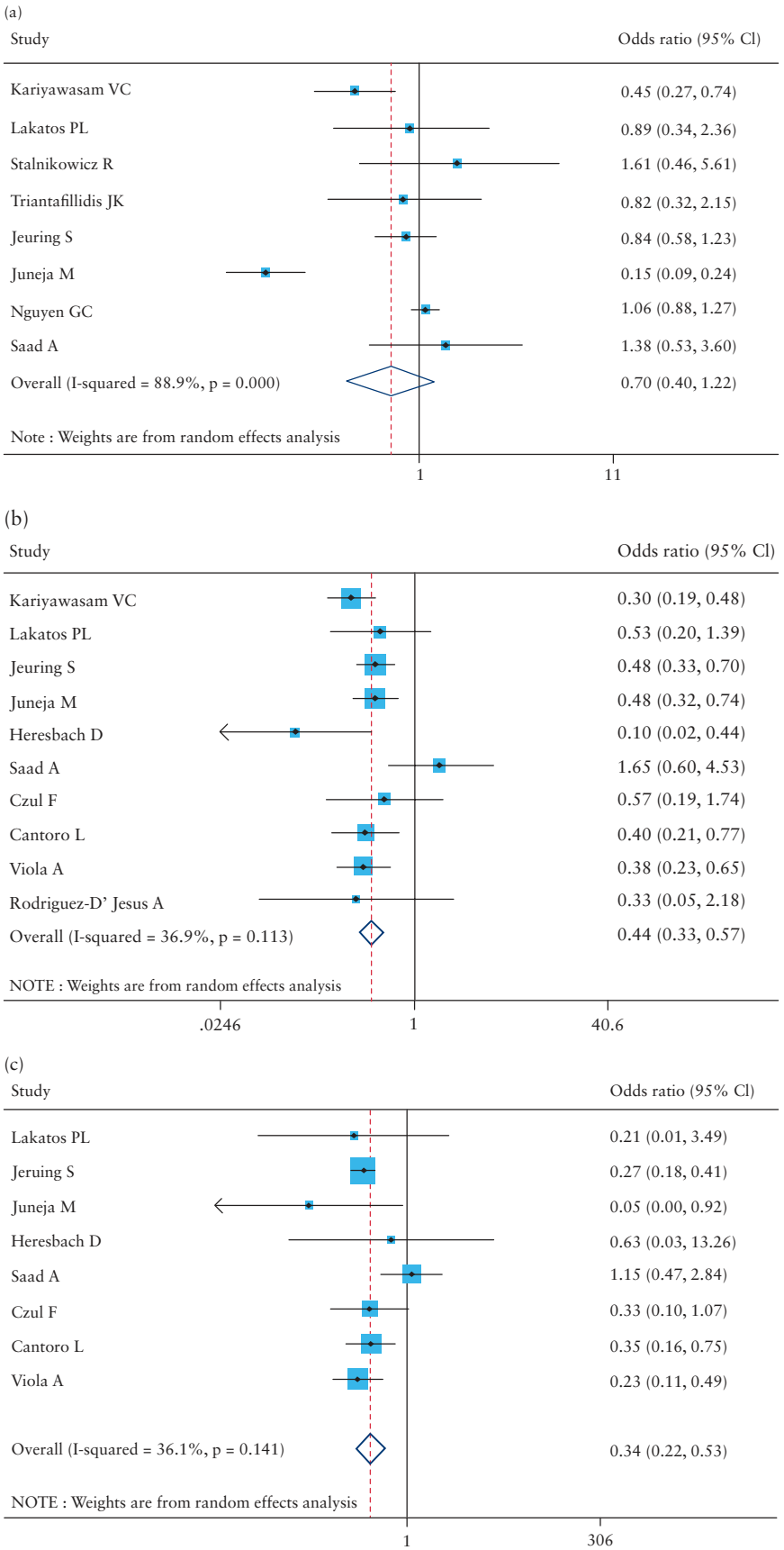


Figure 3. Comparison of outcomes in older-onset and younger-onset Crohn's disease. [a] Surgery. [b] Immunomodulator use. [c] Biological [anti-tumour necrosis factor α] agents.

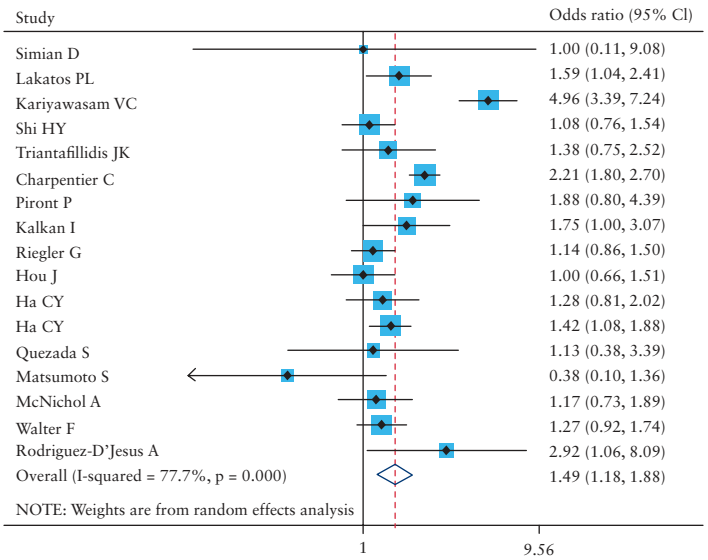


Figure 4. Comparison of frequency of left-sided involvement in older-onset and younger-onset ulcerative colitis.

difference in phenotype based on younger compared with older patients could reflect underlying genetic predisposition, distinct dominant genetic pathways, or the effect of environmental influences. WAlthoughthe genetics of very early-onset and paediatric IBD have been robustly studied,[20,21] few studies have specifically examined the genetics of the older-onset IBD population. In several cohorts, age of diagnosis was inversely associated with genetic predisposition to IBD.[22,23] Some of the risk alleles associated with earlier age at diagnosis, like the *NOD2* gene,[23,24] are more frequently associated with ileal involvement and penetrating complications,[25,26] thereby potentially explaining the lower frequency of such phenotypes in older-onset IBD. Additionally, the distribution of disease phenotypes may also represent the effect of varying environmental exposures. This has not been as widely examined, but evidence suggests that some environmental influences such as smoking may predispose to specific disease locations or behaviour. For example, in a population-based cohort by Lindberg *et al.*, lifetime cumulative cigarette smoking was associated with ileocolonic or ileal CD and a greater likelihood of penetrating or stricturing complications.[27]

In contrast to disease phenotype which is easier to define, analysis of the severity and natural course of older-onset compared with younger-onset disease has been challenging. In addition to being a reflection of the biological evolution of disease, it may also be influenced by physician behaviour and patient acceptance of various medical or surgical therapies, particularly in the context of significant non-IBD comorbidity. A few previous population-based cohorts and expert opinions have suggested a more benign course of disease in older-onset IBD.[4,8,19] In this meta-analysis, although this held true if defined by lower frequency of conventional immunomodulator or biological therapy use in both CD and UC, severe disease as defined by the need for IBD-related surgery, arguably a harder endpoint, was equally common in older- and younger-onset CD, and more common both overall and as early as within 1 year of diagnosis in older-onset UC. Although there is lower utilisation of immunosuppressive therapy in older-onset IBD patients, there remain a lack of data on both efficacy and safety of therapies. Older patients are frequently excluded from drug clinical trials; observational cohorts suggest that older patients have lower rates of response to medical therapies[28,29] and higher rates of infections and discontinuation of therapy,[28,30] potentially contributing to the reluctance to use such treatments. However, the lower rates of response in older patients may also be in part due to inclusion of those with prolonged disease duration wherein fibrostenosis or other consequences of chronic inflammation may impair therapeutic response. Thus, there is an important need for contemporary data specifically on the efficacy and safety of these medications in those with older-onset IBD who may still be susceptible to the early aggressive course of new-onset IBD. Second, the observation of more frequent use of systemic corticosteroids in older IBD patients[31,32,33,34] may be associated with significant adverse outcomes including steroid-related adverse events and non-IBD comorbidities.

Though medical therapies are used less frequently, this does not imply a more benign natural history, as our analysis suggests similar rates of surgical intervention in older-onset CD and higher rates of colectomy in older-onset UC when compared with younger-onset disease. Two factors may contribute to this finding. It may be due to reluctance to use long-term immunosuppressive therapy in older patients and preference towards more definitive surgery, particularly in older-onset UC patients. However, it may also represent a biologically more aggressive disease course in older-onset UC patients. Supporting this hypothesis is that differences in rates of surgery were apparent as early as 1 year after diagnosis, a period of time whereby even aggressive medical therapy may have only modest benefits in reduction of rates of colectomy. There are few comparative studies of medical and surgical therapy in IBD, let alone in an older-onset population. In a retrospective study of Medicare and Medicaid patients, surgical therapy was associated with greater survival compared with medical therapy in UC, particularly in those older than 50 years.[35] However, intestinal surgery in older patients may also be associated with greater short-term and long-term complications.[36,37] Thus, studies of comparative outcomes of medical and surgical therapies in older-onset IBD are essential to optimise management algorithms in this cohort.

There are several implications to our findings. First, our confirmation of different phenotypic patterns in older-onset IBD patients should serve as a trigger for future studies of genetic and environmental contributions to disease pathogenesis and phenotype in this population.

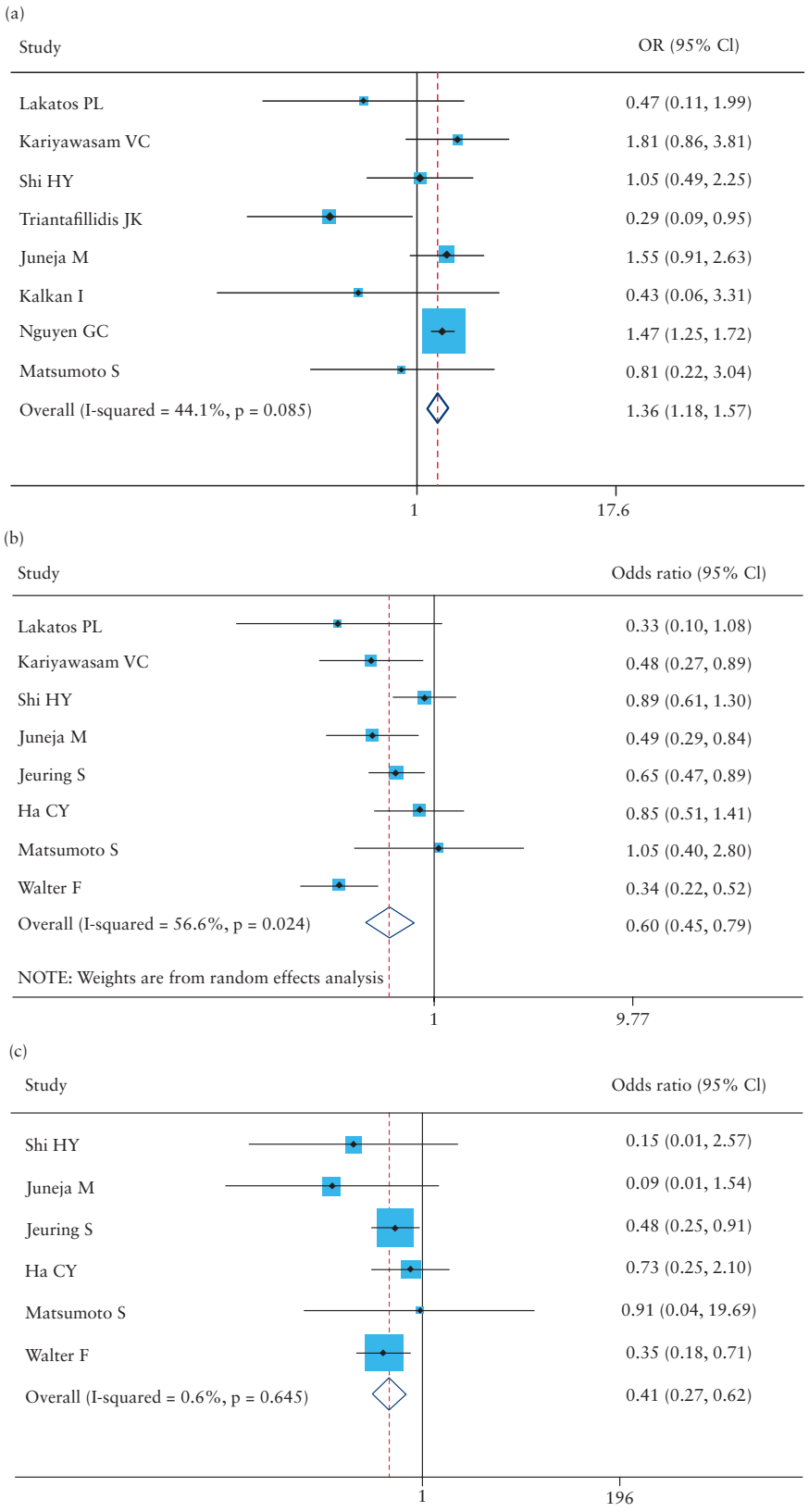


Figure 5. Comparison of outcomes in older-onset and younger-onset ulcerative colitis. [a] Surgery. [b] Immunomodulator use. [c] Biological [anti-tumour necrosis factor α] agents.

With a growing armamentarium of medical therapies targeting different mechanisms of inflammation, such analyses may identify alternative pathways of inflammation in older-onset IBD patients, highlighting opportunities for safer and more effective therapies. Second, and more importantly, the less frequent use of immunomodulators and biologicals in older-onset IBD patients was not supported by lower rates of surgical therapy, and indeed the rate of surgery was higher in older-onset UC patients. Consequently, the natural history of older-onset IBD is not more benign than younger-onset disease, and shared decision making between the provider and patient should acknowledge the potential for aggressive disease behaviour in late-onset but newly diagnosed IBD while determining appropriate medical or surgical therapies. Additionally, comparative studies on the short-term and long-term impact of both medical and surgical treatments on outcomes must also necessarily include other parameters such as health-related quality of life and physical functioning, including independence in activities of daily living that may be more important in older patients.

We acknowledged a few limitations to the literature contributing to our meta-analysis. Not all studies provided detailed disease phenotypes and outcomes, or a younger-onset IBD cohort for comparison. Information on systemic corticosteroid use was provided only by a few studies and inconsistently, and data on other disease=related complications were sparse. Second, the time of phenotype assessment may have differed between the various studies. In IBD, where there is a progressive evolution over time, different time points for phenotyping may have introduced a bias. However, we feel this is less likely to have influenced comparative studies of younger- and older-onset IBD patients, given likely similar protocols for phenotyping the two populations within the context of a single study. Additionally, surgery and medication use outcomes were also assessed at fixed time points 1 and 5 years after diagnosis. Whereas many more studies than were included in our study examined outcomes of IBD in older patients, these often grouped together both older-onset IBD patients and those who may have had disease that was diagnosed at a younger age and had now attained the age of 60 years. The course of IBD is often most aggressive within the first year of disease onset,[10] and consequently the natural history of true older-onset IBD may be distinct from those with younger-onset disease who are now older. Endpoints anchored to specific time points in the natural history of disease [1, 5, or 10 years] were also available only in a small subgroup of studies, and a larger body of literature is essential to more robustly quantify these. We also noted heterogeneity in the age cut-offs used to define older-onset IBD, and although within the range we examined this did not influence our findings on meta-regression, it is important for the field to arrive at a consensus cut-off [commonly 60 years] to ensure homogeneity in future studies. In addition to common disease-related endpoints, older patients may have specific concerns like continence and functional independence in activities of daily living, and it is important for future studies to look at this. We also did not have information on severity of disease. Ideally, a study able to adjust for severity would help to definitively address the question of whether older-onset IBD is more severe and if the increased rates of surgery within 1 year of diagnosis in UC is a reflection of patient and provider treatment preference, due to comorbidities or polypharmacy, or a reflection of the underlying biology of the disease. Most of the studies did not provide description of use of systemic steroids and consequently this need to be addressed in future studies.

In conclusion, in a comprehensive systematic review of literature examining phenotype and outcomes of older-onset IBD patients, we demonstrated that older-onset disease, particularly CD, is more likely to have an isolated colonic location and inflammatory phenotype with less frequent penetrating or perianal disease. In contrast to some prevailing opinions, we did not identify a consistently more benign natural history in older-onset IBD patients, and in particular, demonstrate a higher rate of colectomy with older-onset UC. Whether this reflects a non-benign disease course, physicians' reluctance to employ immunomodulators, or both, merits further study which is essential for improving the care of IBD in the elderly. Informing clinicians of the expected natural history in this select population may help guide appropriate therapeutic choices and trigger future studies of comparative effectiveness and outcomes of medical and surgical therapies in this population, in order to optimise patient outcomes.

Funding

AA is supported by funding from the US National Institutes of Health [K23 DK097142].

Conflict of Interest

AA has served on scientific advisory boards for Abbvie, Cubist, and Exact Sciences.

Author Contributions

All authors have contributed to the study concept and design. AA, HYS, WT, and CL searched and retrieved the data. All authors critically revised the manuscript and all authors approved the final version of the manuscript.

Supplementary Data

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

References

1. Abraham C, Cho J. Inflammatory bowel disease. *N Engl J Med*. 2009;**361**:206678.
2. Molodecky NA, Soon IS, Rabi DM, *et al*. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46–54 e42; quiz e30.
3. Benchimol EI, Fortinsky KJ, Gozdyra P, *et al*. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;**17**:423–39.
4. Ruel J, Ruane D, Mehandru S, *et al*. IBD across the age spectrum: is it the same disease? *Nat Rev Gastroenterol Hepatol* 2014;**11**:88–98.
5. Ha CY, Katz S. Clinical implications of ageing for the management of IBD. *Nat Rev Gastroenterol Hepatol* 2014;**11**:128–38.
6. Gower-Rousseau C, Vasseur F, Fumery M, *et al*. Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry [EPIMAD]. *Dig Liver Dis* 2013;**45**:89–94.
7. Lakatos PL, David G, Pandur T, *et al*. IBD in the elderly population: results from a population-based study in Western Hungary, 1977–2008. *J Crohns Colitis* 2011;**5**:5–13.
8. Charpentier C, Salleron J, Savoye G, *et al*. Natural history of elderly-onset inflammatory bowel disease. A population-based cohort study. *Gut*. 2014;**63**:423–32.
9. Henriksen M, Jahnsen J, Lygren I, *et al*. Clinical course in Crohn's disease: results of a five-year population-based follow-up study [the IBSEN study]. *Scand J Gastroenterol* 2007;**42**:602–10.
10. Solberg IC, Lygren I, Jahnsen J, *et al*. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort [IBSEN Study]. *Scand J Gastroenterol* 2009;**44**:431–40.
11. Lee JH, Cheon JH, Moon CM, *et al*. Do patients with ulcerative colitis diagnosed at a young age have more severe disease activity than patients diagnosed when older? *Digestion* 2010;**81**:237–43.

12. Matsumoto S, Miyatani H, Yoshida Y. Ulcerative colitis: comparison between elderly and young adult patients and between elderly patients with late-onset and long-standing disease. *Dig Dis Sci* 2013;**58**:1306–12.
13. McLeroy K, Northridge M, Balcazar H, *et al.* Reporting guidelines and the American Journal of Public Health's adoption of Preferred Reporting Items for Systematic reviews and Meta-Analyses. *Am J Public Health*. 2012;**102**:780–4.
14. Satsangi J, Silverberg MS, Vermeire S, *et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
16. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**:603–5.
17. Gisbert JP, Chaparro M. Systematic review with meta-analysis: inflammatory bowel disease in the elderly. *Aliment Pharmacol Ther* 2014;**39**:459–77.
18. del Val JH. Old-age inflammatory bowel disease onset: a different problem? *World J Gastroenterol* 2011;**17**:2734–9.
19. Taleban S, Colombel JF, Mohler MJ, *et al.* Inflammatory bowel disease and the elderly: a review. *J Crohns Colitis* 2015;**9**:507–15.
20. Cutler DJ, Zwick ME, Okou DT, *et al.* Dissecting allele architecture of early onset IBD using high-density genotyping. *PLoS One* 2015;**10**:e0128074.
21. McGovern DP, Kugathasan S, Cho JH. Genetics of inflammatory bowel diseases. *Gastroenterology* 2015;**149**:1163–76 e2.
22. Ananthakrishnan AN, Huang H, Nguyen DD, *et al.* Differential effect of genetic burden on disease phenotypes in Crohn's disease and ulcerative colitis: analysis of a North American cohort. *Am J Gastroenterol* 2014;**109**:395–400.
23. Weersma RK, Stokkers PC, van Bodegraven AA, *et al.* Molecular prediction of disease risk and severity in a large Dutch Crohn's disease cohort. *Gut* 2009;**58**:388–95.
24. Connelly TM, Berg AS, Harris L 3rd, *et al.* Genetic determinants associated with early age of diagnosis of IBD. *Dis Colon Rectum* 2015;**58**:321–7.
25. Abreu MT, Taylor KD, Lin YC, *et al.* Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology* 2002;**123**:679–88.
26. Cleynen I, Gonzalez JR, Figueroa C, *et al.* Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. *Gut* 2013;**62**:1556–65.
27. Lindberg E, Jarnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and clinical course. *Gut* 1992;**33**:779–82.
28. Desai A, Zator ZA, de Silva P, *et al.* Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:309–15.
29. Lobaton T, Ferrante M, Rutgeerts P, *et al.* Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2015;**42**:441–51.
30. Cottone M, Kohn A, Daperno M, *et al.* Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;**9**:30–5.
31. Johnson SL, Bartels CM, Palta M, *et al.* Biological and steroid use in relationship to quality measures in older patients with inflammatory bowel disease: a US Medicare cohort study. *BMJ Open* 2015;**5**:e008597.
32. Parian A, Ha CY. Older age and steroid use are associated with increasing polypharmacy and potential medication interactions among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;**21**:1392–400.
33. Brassard P, Bitton A, Suissa A, *et al.* Oral corticosteroids and the risk of serious infections in patients with elderly-onset inflammatory bowel diseases. *Am J Gastroenterol* 2014;**109**:1795–802; quiz 1803.
34. Juneja M, Baidoo L, Schwartz MB, *et al.* Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. *Dig Dis Sci* 2012;**57**:2408–15.
35. Bewtra M, Newcomb CW, Wu Q, *et al.* Mortality associated with medical therapy versus elective colectomy in ulcerative colitis a cohort study. *Ann Intern Med* 2015;**163**:262–70.
36. Shung DL, Abraham B, Sellin J, *et al.* Medical and surgical complications of inflammatory bowel disease in the elderly: a systematic review. *Dig Dis Sci* 2015;**60**:1132–40.
37. De Silva S, Ma C, Proulx M, *et al.* Postoperative complications and mortality following colectomy for ulcerative colitis. *Clin Gastroenterol Hepatol* 2011;**9**:972–80.
38. Jeuring S, Van Den Heuvel T, Zeegers M, *et al.* Disease course, phenotype, and medication use in elderly-onset Crohn's disease patients - a population-based IBD-SL cohort study. *Gastroenterology* 2015;**1**:S477.
39. Cantoro L, Papi C, Cicala M, *et al.* Early and late onset Crohn's disease: Different phenotype and course, an Italian cohort study. *Dig Liver Dis* 2015;**47**:e73.
40. Cheddani H, Dauchet L, Charpentier C, *et al.* Cancer in elderly-onset inflammatory bowel disease: A population-based study. *Gastroenterology* 2014;**1**] S-101.
41. Viola A, Cantoro L, Monterubbianesi R, *et al.* Crohn's disease [CD] in the elderly: an IG-IBD study. *J Crohns Colitis* 2014;**8**:S293-4.
42. McNichol A, Din S, Porteous M, *et al.* Definition of phenotypic characteristics of late-onset IBD. *J Crohns Colitis* 2013;**7**:S114-5.
43. Cadilla J, Ferreiro R, Ollero V, *et al.* Clinical characteristics of inflammatory bowel disease in elderly patients. *J Crohns Colitis* 2013;**7**:S276.
44. Rodriguez-D'Jesus A, Casellas F, Malagelada JR. [Epidemiology of inflammatory bowel disease in the elderly.] [Spanish] Epidemiologia de la enfermedad inflamatoria intestinal en el paciente de edad avanzada. *Gastroenterol Hepatol* 2008;**31**:269–73.
45. Heresbach D, Alexandre JL, Bretagne JF, *et al.* Crohn's disease in the over-60 age group: A population based study. *Eur J Gastroenterol Hepatol* 2004;**16**:657–64.
46. Triantafillidis JK, Emmanouilidis A, Nicolakis D, *et al.* Crohn's disease in the elderly: Clinical features and long-term outcome of 19 Greek patients. *Dig Liver Dis* 2000;**32**:498–503.
47. Walmsley RS, Gillen CD, Allan RN. Prognosis and management of Crohn's disease in the over-55 age group. *Postgrad Med J* 1997;**73**:225–9.
48. Gupta S, Saverymuttu SH, Keshavarzian A, *et al.* Is the pattern of inflammatory bowel disease different in the elderly? *Age Ageing* 1985;**14**:366–70.
49. Fabricius PJ, Gyde SN, Shouler P. Crohn's disease in the elderly. *Gut* 1985;**26**:461–5.
50. Piront P, Louis E, Latour P, *et al.* Epidemiology of inflammatory bowel diseases in the elderly in the province of Liege: A three-year prospective study. *Gastroenterol Clin Biol* 2002;**26**:157–61.
51. Nguyen GC, Sheng L, Benchimol EI. Health care utilization in elderly onset inflammatory bowel disease: a population-based study. *Inflamm Bowel Dis* 2015;**21**:777–82.
52. Jason H, Linda F, Akbar W. Characteristics and behaviour of elderly-onset inflammatory bowel disease: A multi-center U.S. study. *Inflamm Bowel Dis* 2014;**20**:S40-1.
53. Saad A, Czul-Gurdian F, Sakuraba A, *et al.* Age of diagnosis is associated with the severity of adverse effects to therapy in Crohn's disease patients. *Inflamm Bowel Dis* 2013;**19**:S55.
54. Saad A, Czul-Gurdian F, Sakuraba A, *et al.* Age of diagnosis is associated with disease phenotype and behavior in Crohn's disease patients. *Am J Gastroenterol* 2013;**108**:S537-8.
55. Quezada SM, Steinberger EK, Cross RK. Association of age at diagnosis and Crohn's disease phenotype. *Age Ageing* 2013;**42**:102–6.
56. Czul F, Yarur A, Deshpande A, *et al.* Diagnosis of Crohn's disease aft er age 60 is associated with lower prevalence of penetrating phenotype. *Am J Gastroenterol* 2012;**107**:S676-7.
57. Ha CY, Bayless TM, Bitton A, *et al.* Late adult-onset inflammatory bowel disease patients require surgery earlier during their disease course compared to early adult-onset patients. *Gastroenterology* 2012;**1**:S253-4.

58. Roberts PL, Schoetz DJ Jr, Pricolo R, *et al.* Clinical course of Crohn's disease in older patients. A retrospective study. *Dis Colon Rectum* 1990;**33**:458–62.
59. Feczko PJ, Barbour J, Halpert RD, *et al.* Crohn disease in the elderly. *Radiology* 1985;**157**:303–4.
60. Shapiro PA, Peppercorn MA, Antonioli DA. Crohn's disease in the elderly. *Am J Gastroenterol* 1981;**76**:132–7.
61. Hwang SW, Chun J, Lim JH, *et al.* Age at diagnosis and clinical characteristics of Crohn's disease in Korea: A KASID multicentre study. *J Crohn's Colitis* 2014;**8**:S182-3.
62. Pappo I, Zamir O, Freund HR. Is Crohn's disease different in the elderly? [Hebrew]. *Harefuah* 1997;**132**:86–8, 151.
63. Stalnikowicz R, Eliakim R, Diab R, *et al.* Crohn's disease in the elderly. *J Clin Gastroenterol* 1989;**11**:411–5.
64. Kariyawasam VC, Huang TD, Lunney PC, *et al.* Natural history of elderly onset inflammatory bowel disease - Sydney IBD cohort [1942–2012]. *Gastroenterology* 2013;**1**:S634-5.
65. O'Keefe EA, Wright JP, Froggatt J, *et al.* Medium-term follow-up of Crohn's disease in Cape Town. *S Afr Med J* 1989;**76**:139–41.
66. Simian D, Estay C, Kronberg U, *et al.* [Differences by age in clinical features of inflammatory bowel disease]. *Rev Med Chil* 2015;**143**:689–96.
67. Walter F, Viola A, Manetti N, *et al.* Ulcerative colitis [UC] diagnosed over-age 65 years an IG-IBD study. *Gastroenterology* 2014;**1**:S-440.
68. Riegler G, Tartaglione MT, Carratu R, *et al.* Age-related clinical severity at diagnosis in 1705 patients with ulcerative colitis: A study by GISC [Italian Colon-Rectum Study Group]. *Dig Dis Sc* 2000;**45**:462–5.
69. Quezada S, Cross R. Impact of age at diagnosis and ulcerative colitis disease extent. *Am J Gastroenterol* 2010;**105**:S468.
70. Ha CY, Newberry RD, Stone CD, *et al.* Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. *Clin Gastroenterol Hepatol* 2010;**8**:682–7.e1.
71. Shi HY, Ng SC, Leung WK, *et al.* Natural history of elderly-onset ulcerative colitis in Chinese: A population-based cohort study. *Gastroenterology* 2015;**1**:S23-4.
72. Kalkan IH, Dagli U, Oztas E, *et al.* Comparison of demographic and clinical characteristics of patients with early vs. adult vs. late onset ulcerative colitis. *Eur J Intern Med* 2013;**24**:273–7.
73. Mizuno M, Sasaki M, Okaniwa N, *et al.* Clinical features of ulcerative colitis in Japanese elderly. *J Gastroenterol Hepatol* 2012;**27**:187.
74. Parlak E, Tezel A, Ulker A, *et al.* Ulcerative colitis in the elderly in Turkey. *Turk J Gastroenterol* 2000;**11**:45–8.