Title

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Journal

Clinical Gastroenterology and Hepatology, 18(11)

ISSN

1542-3565

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Publication Date

2020-10-01

DOI

10.1016/j.cgh.2020.02.048

Peer reviewed

HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2020 October ; 18(11): 2437–2447.e6. doi:10.1016/j.cgh.2020.02.048.

Progression of Elderly-Onset Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis of Population-based Cohort Studies

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Abstract

Background & Aims: The incidence of inflammatory bowel diseases (IBD) in older adults is increasing. We performed a systematic review and meta-analysis to evaluate progression of elderly-onset (EO)-IBD in population-based cohorts and compared it with adult-onset (AO)-IBD.

Methods: In a systematic review through June 1, 2019, we identified population-based cohort studies of EO-IBD reporting cumulative risk of hospitalization, surgery, mortality, treatment patterns, and escalation and/or malignancy. Data were synthesized using random-effects meta-analysis as cumulative risk of events at 1 y, 5 y, and 10 y, and compared with data from patients with AO-IBD in the same cohorts.

Results: We identified 9 studies, comprising 14,765 patients with EO-IBD. In patients with EO-Crohn's disease (CD), the cumulative 5-year risk of surgery was 22.6% (95% CI, 18.7–27.2) and was similar to that of patients with AO-CD (relative risk [RR], 1.04; 95% CI, 0.80–1.34). Overall exposure to corticosteroids was comparable between patients with EO-CD vs AO-CD (5 y risk: 55.4%; 95% CI, 53.4–57.4; RR, 0.88; 95% CI, 0.78–1.00), but exposure to immunomodulators (31.5%; 95% CI, 29.7–33.4; RR, 0.62; 95% CI, 0.51–0.77) or biologic agents (6.5%; 95% CI, 5.6–7.6; RR, 0.36; 95% CI, 0.25– 0.52) was significantly lower for patients with EO-CD than for

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Author Contribution: Study concept and design: SS , Acquisition of data: JJR, SS , Analysis and interpretation of data: JJR, SS , rafting of the manuscript: JJR, SS , Critical revision of the manuscript for important intellectual content: PSD, MF, WJS Approval of the final manuscript: JJR, PSD, MF, WJS, SS
Guarantor of the article: SS

Conflicts of Interest:
Jacob J. Rozich reports no conflicts.

patients with AO-CD. Similarly, in patients with EO-ulcerative colitis (UC), the cumulative 5 y risk of surgery was 7.8% (95% CI, 5.0–12.0), similar to the risk for patients with AO-UC (RR, 1.29; 95% CI, 0.79–2.11). Overall exposure to corticosteroids was comparable between patients with EO-UC vs AO-UC (5 y risk: 57.2%; 95% CI, 55.6–58.7; RR, 0.98; 95% CI, 0.91– 1.06), but exposure to immunomodulators (16.1%; 95% CI, 15.0–17.2; RR, 0.58; 95% CI, 0.54–0.62) or biologic agents (2.0%; 95% CI, 1.6–2.5; RR, 0.36; 95% CI, 0.24–0.52) was significantly lower for patients with EO-UC than for patients with AO-UC. Patients with EO-IBD appeared to have increased mortality, but not malignancy, compared with the general population. There were few data on comorbidities or adverse effects of medications.

Conclusions: In a systematic review and meta-analysis, we found that patients with EO-IBD have a similar risk of surgery as patients with AO-IBD. However, patients with EO-IBD are less likely to receive treatment with immunomodulators or biologic agents.

Keywords

Aged; natural history; prognostic factor; drug

INTRODUCTION

Inflammatory bowel diseases (IBD) are increasing in incidence and prevalence globally.[1–7] While incidence of IBD may have plateaued in many developed countries after increasing for many years, incidence in developing nations continue to rise, contributing to growing worldwide prevalence.[1, 2] In many developed countries, IBD prevalence is greater than 0.3% of the total population (as high as 510 per 100,000 in Canada) and is forecasted to reach as high 0.9% in the coming decade (up to 981 per 100,000 in Canada by 2030).[1, 4, 7] Though the majority of IBD patients are diagnosed as young adults, as many as 10–15% of new IBD diagnoses have been reported to occur in individuals greater than 60 years old, with incidence rates as high as 18.9 per 100,000.[2, 4, 8] The incidence and prevalence of such elderly-onset (EO)-IBD is expected to further increase as the population continues to age.[7, 9]

EO-IBD is often presumed to be milder in severity, and is treated conservatively, in the context of other comorbidities.[10, 11] However, recent population-based studies[12–18] have variably suggested that EO-IBD may have an aggressive course, not dissimilar from adult-onset (AO)-IBD. Prior systematic reviews on EO-IBD have reported differences in disease phenotype at diagnosis and medication utilization, with EO-IBD generally found to have a more frequent left-sided presentation and lower use of antimetabolites and biological therapies.[10, 11] However, these reviews incorporated referral center studies and case series which have an inherent risk of selection and detection bias, tend to over-estimate risks, and may distort true population-level burden of EO-IBD. On the other hand, estimates from population-based studies from unselected cohorts of patients are more representative of the true risk in patients with IBD, and are useful for prognostic information.

Hence, we systematically synthesized the natural history and outcomes of EO-IBD based on true population-based cohorts and compared it to AO-IBD from the same cohorts.

METHODS

This systematic review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) standards and followed an *a priori* protocol.

Selection Criteria

We included only population-based cohort studies (covering all eligible patients within a defined geographical region, over a defined time period) in adults with onset of IBD after the age of 60y (EO-IBD), with at least 1 year follow-up, and reporting natural history (cumulative risk of hospitalization, surgery, mortality, treatment patterns and escalation and/or mortality; at least 1 year follow-up), stratified by Crohn's disease (CD) and ulcerative colitis (UC) separately. Multiple studies from the same cohort were only included if they reported on different outcomes, or risk of outcomes at different time points.

Since our focus was on defining the natural history of EO-IBD, we excluded referral-center studies or registry-based studies (selective inclusion of consenting patients seen at limited practices), studies focusing only on disease phenotype, and not reporting natural history of EO-IBD, studies with follow-up <1y, and where results were not stratified by CD and UC. We opted to exclude comparisons between EO-IBD vs. pediatric-onset IBD, since the pathogenesis of IBD in these populations may be very distinctive, and we wanted to primarily focus on similarities and dissimilarities between EO-IBD and AO-IBD.

Search Strategy

First, we conducted a comprehensive search of Medline, Embase and Cochrane Database of Systematic Reviews, from inception till June 1, 2019, with no language restrictions, and limited to human studies. The search terms used included a combination of keywords and MeSH terms indicating the diseases of interest: 'Crohn(s) disease', 'Ulcerative colitis', 'inflammatory bowel disease', 'regional enteritis' AND age: 'aged', 'older' or 'elderly'. Two study investigators (JJR and SS) independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the research question of interest on the basis of pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article, in consultation with a third investigator (MF). Second, we searched the bibliographies of these selected articles and systematic reviews on the topic to identify any additional studies. Third, we conducted a manual search of abstracts from major gastroenterology conferences (Digestive Disease Week, American College of Gastroenterology annual meeting, European Crohn's and Colitis Organization annual meeting) from 2014 to 2018 to identify additional abstracts on the topic.

Data Abstraction and Quality Assessment

Data on study-, participant-, disease- and treatment-related characteristics were abstracted onto a standardized form, by two authors independently and discrepancies were resolved by consensus, referring to the original article, in consultation with a third reviewer. Risk of bias in included studies were assessed using modified Newcastle Ottawa Scale.

Outcomes

We evaluated the cumulative risk (1-, 5- and 10y) of bowel surgery, hospitalization, mortality, malignancy, treatment patterns (5-aminosalicylates [5-ASA], corticosteroids, immunomodulators [thiopurines and/or methotrexate] and biologic agents including tumor necrosis factor-α antagonists [TNFα antagonists] or others) and escalation. In addition, we evaluated disease phenotype, including location, extent and behavior, and disease progression in EO-IBD. In cohorts that reported similar outcomes in AO-IBD, defined as onset of IBD prior to the age of 60y, we compared risk of bowel surgery, hospitalization, mortality and specific treatment patterns, as well as disease phenotype.

Statistical Analysis

Cumulative risk of outcomes in EO-IBD was calculated using random-effects meta-analysis when reported in 3 or more studies, or summarized as median (range) when inconsistently reported. Similarly, we calculated relative risk (RR) of specific outcomes between EO-IBD vs. AO-IBD using the DerSimonian and Laird random-effects model when reported in 3 or more studies, or synthesized qualitatively as reported in individual studies. In performing this meta-analysis based on Kaplan-Meier curves, we assumed complete follow-up of all patients. Statistical heterogeneity was assessed using the I^2 statistic with a $I^2 \geq 50\%$ considered to be substantial heterogeneity. Due to small number of studies, formal assessment for publication bias or subgroup analyses were not performed.

RESULTS

We identified 5204 unique studies using our search strategy, and after screening titles and abstracts, 51 full texts were reviewed. From this, nine studies representing seven unique population-based cohort studies were included in our synthesis.[12–20] Study selection flowchart is shown in Figure 1.

Study characteristics are summarized in Table 1. Of the seven cohorts, six were based in Europe and one in Canada. Each study compared a cohort of EO-IBD patients vs. one or more cohorts of non-elderly patients, including at least one cohort of AO-IBD patients; three studies also included pediatric cohorts (age<18). Study time periods of inclusion of patients ranged from 4 to 31 years, with a range of mean/median follow up per patient between 4.2 and 9.6 years. EO-IBD was defined as presentation or diagnosis at an age>60y, except for one study that used age >65y.[18] A total of over 70,000 IBD patients were included in all study cohorts. There were between 127 to 6,443 patients in the EO-IBD cohorts, with 21 to 1,937 EO-CD patients and 106 to 3,596 EO-UC patients, compared with 201 and 20,727 AO-CD patients and 733 to 39.224 AOUC patients. Mean/median age ranged from 68 to 73 in the EO-IBD cohorts. Overall, the studies were at low risk of bias, being population-based cohorts, with high degree of follow-up; case ascertainment was based on validated codes and/or chart review in the cohort. Studies ranged from 1977 to 2011 for cohort inclusion, with the majority of studies including patients between 1990s to 2000s; data from more contemporary cohorts was not available.

Disease Phenotype and Progression (Supplementary Table 2, Tables 2 and 3)

All studies utilized the Montreal classification to characterize disease phenotype.[21] At the time of diagnosis, among EO-CD, colonic disease location was the most common (median, 62% [range, 20–67]) and in 3/5 cohorts, rate was higher than that observed for AO-CD. Inflammatory behavior was most common (median, 76% [range, 38–82]), followed by stricturing disease (median, 20% [range, 13–43]); of note, in 2/4 studies, prevalence of stricturing phenotype at diagnosis was higher than that reported in corresponding AO-CD.[15, 17] Perianal disease at diagnosis was reported in 8% patients (range, 4–14). Among EO-UC, left-sided UC was most common (median, 51% [range, 30–61]). Extra-intestinal manifestations were reported in 3–4.9% EO-IBD patients at diagnosis, and 2.2–5.9% patients at follow-up in the Epimad cohort.

In EO-CD vs. AO-CD, rate of disease progression to penetrating and/or stricturing phenotype was either lower[17] or similar[16] based on two studies; overall, this rate varied from 0% to 19.8% at 5 years. In one study,[13] change in disease localization occurred in 8% patients with EO-CD. Cumulative 5- and 10-year rates of proximal extension in EO-UC was 9.5%. (range, 7–12%) and 15% (range, 9–21%), respectively, without any significant difference as compared to AO-UC.[16]

Risk of Surgery and Hospitalization

Surgery in CD patients (Table 2) was generally defined as intestinal surgery, though specific definitions and diagnostic codes varied between studies. On meta-analysis, cumulative 1-, 5- and 10-year risk of surgery in EO-CD was 13.0% (95% CI, 10.7–15.7), 22.6% (18.7–27.2) and 27.8% (19.8–37.5), respectively (Supplementary Figure 1A). As compared to AO-CD, risk of surgery in elderly-onset CD was variably reported as higher,[15, 18] lower[12, 17] or no different (Figure 2A).[16] On meta-analysis, risk of surgery was similar in EO-CD vs. AO-CD at 1-year (RR, 1.01 [0.79–1.29]) and 5-years (RR, 1.04 [0.80–1.34]) (Supplementary Figure 2A). Two studies[13, 16] suggested that patients with ileocolonic disease (vs. isolated ileal disease) and patients with stricturing disease had higher risk of surgery (Supplementary Table 3).

In patients with EO-UC (Table 3), cumulative 1-, 5- and 10-year risk of surgery was 2.1% (1.1–4.0), 7.8% (5.0–12.0) and 9.3% (4.6–18.2), respectively (Supplementary Figure 1B); only 9% patients underwent ileal pouch anal anastomosis.[12] Majority of studies found no significant difference between the risk of surgery in EO-UC vs. AO-UC. On meta-analysis, risk of surgery was similar in EO-UC vs. AO-UC at 1-year (RR, 0.61 [0.29–1.27]) and 5-years (RR, 1.29 [0.79–2.11]), with considerable heterogeneity (I^2>90%) (Supplementary Figure 2B). More extensive disease[13, 16] and corticosteroid use[12, 16] were associated with increased risk of surgery in patients with EO-UC (Supplementary Table 3). In contrast, one study found that extended thiopurine use (>12 months) was associated with a decreased risk of surgery in EO-UC.[12] Approximately 19% patients with EO-IBD experience post-operative complications within 1 month, half of which are serious, and 4% patients die within 30 days of surgery.[22]

Risk of hospitalization (Tables 2 and 3) was reported in three studies.[15, 16, 19] Cumulative risk and number of IBD-related hospitalizations in EO-CD was variably reported as lower or similar to AO-CD (Figure 2B). In contrast, two studies[15, 16] found a higher burden and risk of IBD-related hospitalization in EO-UC, as compared to AO-UC. Neither study reported data on comorbidities, and both limited analysis to IBD-related hospitalizations. Jeuring *et al*[16] observed that more EO-UC patients were hospitalized at diagnosis compared with AO-UC (no difference observed in patients with CD), and patients with extensive and severe disease had an increased risk of hospitalization for both EO-CD and EO-UC (Supplementary Table 3).

Treatment Pattern, Escalation and Discontinuation of Medical Management

Cumulative 1- and 5-year risk of exposure to corticosteroids in EO-CD was 39.0% (37.0–41.0) and 55.4% (53.4–57.4), respectively (Table 2, Figure 2C). On meta-analysis, risk of exposure to corticosteroids was comparable in EO-CD vs. AO-CD (RR, 0.88 [0.78–1.00]) (Supplementary Figure 3A). In contrast, cumulative 1- and 5-year risk of exposure to immunomodulators in EO-CD was 23.2% (21.6–25.0) and 31.5% (29.7–33.4), respectively, and to TNFα antagonists was 3.5% (2.8–4.3) and 6.5% (5.6–7.6), respectively (Table 2, Figure 2D-E). On meta-analysis, risk of exposure to immunomodulators (RR, 0.62 [0.51–0.77]) and TNFα antagonists (RR, 0.36 [0.25–0.52]) was significantly lower in EO-CD vs. AO-CD (Supplementary Figure 3A, Supplementary Table 4). Alexakis *et al*[12] noted lower rates of corticosteroid-dependence in patients with EO-CD vs. AO-CD.

Similarly, cumulative 1- and 5-year risk of exposure to corticosteroids in EO-UC were 40.9% (39.4–42.5) and 57.2% (55.6–58.7), respectively (Table 3, Figure 2C). On meta-analysis, risk of exposure to corticosteroids was comparable in EO-UC vs. AO-UC (RR, 0.98 [0.91–1.06]) (Supplementary Figure 3B). In contrast, cumulative 1- and 5year risk of exposure to immunomodulators in EO-UC was 9.2% (8.4–10.2) and 16.1% (15.0–17.2), respectively, and to TNFα antagonists was 1.0% (0.7–1.3) and 2.0% (1.62.5), respectively (Table 3, Figure 2D-E). On meta-analysis, risk of exposure to immunomodulators (RR, 0.58 [0.54–0.62]) and TNFα antagonists (RR, 0.36 [0.24–0.52]) was significantly lower in EO-UC vs. AO-UC (Supplementary Figure 3A, Supplementary Table 4). Alexakis *et al*[12] noted higher rates of corticosteroid-dependence in patients with EO-UC vs. AO-UC.

Jeuring *et al*[16] reported rates of discontinuation of therapy. They observed no significant difference in rates of discontinuation of immunomodulators and TNFα antagonists between EO-IBD vs. AO-IBD; absolute rate of discontinuation of immunomodulators and TNFα antagonists for patients with EO-CD was 82% and 29%, respectively, and for EO-UC was 66% and 67%, respectively. Most common reason for discontinuation of TNFα antagonists in both EO-IBD and AO-IBD in their cohort was loss of response to therapy (46% vs. 40%, p=0.11), whereas side effects were the most common reason for discontinuing immunomodulators therapy (EO-IBD vs. AO-IBD, 64% vs. 51%, p=0.06).

Risk of Mortality and Malignancy (Tables 2 and 3)

In one study,[18] IBD-specific mortality was higher in EO-CD vs. AO-CD (33.1 vs. 5.6 per 10,000pyr, p<0.01), but standardized mortality ratio was not increased in EO-CD patients

(SMR, 1.12; 95% CI, 0.99–1.26). IBD-specific mortality in patients with UC was lower than that of CD, though rate was relatively higher in EO-UC vs. AO-UC (2.89 vs. 1.33 per 10,000pyr, p=0.25). SMR for EO-UC was not increased (0.98; 95% CI, 0.90–1.06). The leading causes of death for EO-CD and EO-UC was solid malignancy (CD, 26%; UC, 22%), cardiovascular diseases (24% and 17%) and infections (7% and 4%); proportion of deaths due to IBD for CD and UC were 9% and 6%, respectively. In contrast, Olen and colleagues observed that patients with EO-IBD (both patients with CD and UC) had a 1.5 times higher risk of death as compared to age-matched general population, due to all causes, including digestive diseases, malignancy, infections, cardiovascular and respiratory diseases.[20] Cheddani *et al*[14] reported malignancy rates in patients with EO-IBD. In 844 patients with EO-IBD over median follow-up of 6 years, 98 patients developed cancer (IR, 17.6/10,000pyr), and this rate was similar to the general population (SIR, 0.97; 95% CI, 0.80–1.18). While the risk of colorectal cancer was not specifically increased in patients with EO-IBD (SIR, 1.03; 95% CI, 0.62–1.07), the risk of malignant lymphoproliferative (SIR, 2.49; 95% CI, 1.25–4.99) and myeloproliferative disorders (SIR, 2.18; 95% CI, 1.09–4.35) was increased. One hundred fifteen EO-IBD patients were exposed to thiopurines, 12 of whom developed cancer with no significant increased risk over unexposed EO-IBD patients. Of 30 patients exposed to TNFα antagonists, only 2 patients developed cancer (one skin cancer and one pancreatic cancer). Lakatos *et al*[17] likewise observed no increase in risk of UC-related colorectal cancer in EO-UC vs. AO-UC, though they observed a shorter time to developing colorectal cancer in EO-UC.

DISCUSSION

In this systematic review of population-based observational studies on EO-IBD, we made several key observations regarding EO-IBD vs. AO-IBD. First, we observed that risk of surgery, hospitalization and disease progression is similar between EO-IBD and AO-IBD at a population-level. Surgery carries a high risk in older patients; ~10% experience serious complications within the first 30 days, and 4% patients die. Second, while the cumulative use of corticosteroids is high (and comparable to AO-IBD) in EO-IBD, rate of immunomodulator and biologic use is significantly lower in patients with EO-IBD vs. AO-IBD. Risk factors for surgery and hospitalization in EO-IBD were similar to those for AO-IBD, and include early corticosteroid use for UC and more extensive and/or severe disease behavior at diagnosis for both UC and CD. Third, in the few studies where reported, patients with EO-IBD may have a higher risk of all-cause mortality, but not malignancy, as compared to age-matched general population. These patterns are true when EO-IBD is further stratified into elderly (60–69 years) vs. very elderly (≥70 years) patients.[23,24] These data suggest that at a population level, natural history and outcomes in EO-IBD appear to be more similar to AO-IBD, and our treatment approach for elderly-onset disease should reflect this.

The global population is aging.[25] As part of this trend, the number of elderly patients with IBD is also expected to increase, as with any chronic disease[7, 9]; already, these patients comprise the largest group in the U.S. in terms of prevalence.[26] Given the rising burden of IBD in older patients, there are several important considerations for management that are unique to the geriatric population. Elderly patients have a relative immunodeficiency compared to younger patients as well as altered drug metabolism, raising concerns for

increased risk of infection with immunosuppressing agents as well as altered dosing and response to standard drug therapies.[9] Additionally, geriatric patients tend to have an increased number of comorbidities and diminished functional status, often accompanied by detrimental polypharmacy, which can further complicate treatment and measuring response to treatment.[9] We have previously observed that the annual burden and costs of hospitalization is highest in older patients with IBD vs. younger patients, and cardiovascular diseases and infections may be the most common reasons for readmission.[27] In light of these considerations, it is notable that corticosteroids appear to be used just as frequently in elderly-onset disease as in adult-onset disease, while other immunosuppressing agents such immunomodulators and biologic agents are used less frequently. While corticosteroids are effective in symptom control, they are avoided for long-term maintenance due to risk of side effects; exposure to corticosteroids is associated with increased risk of infections, cardiovascular events, and thromboembolic events, though this is under-appreciated by both physicians and patients. Lewis and colleagues recently demonstrated that long-term TNFα antagonist therapy was associated with lower risk of mortality and cardiovascular events as compared to chronic corticosteroid use in patients with IBD, with comparable risk of serious infections.[28] Biologic therapy in older patients may be associated with a higher risk of serious infections and malignancy as compared to its use in younger patients, and biologic exposure (vs. non-exposure) may increase risk of serious infections in a group of older patients.[29] However, risks of therapies should be weighed in the context of risks associated with untreated or under-treated disease, including the risk of surgery and hospitalization. In a recent post hoc analysis of the REACT trial, we have demonstrated that a strategy of early combined immunosuppression is equally effective and safe in older patients vs. younger patients, over conventional management, decreasing the risks of surgery, hospitalization and disease-related complications.[30]

The strengths of this review include a focus on population-based cohorts, which minimizes selection and detection bias, and systematic synthesis of a wide range of outcomes. There are also several limitations to this review. First, criteria for defining and reporting phenotype, outcomes and medication exposure varied between studies as a result of both study design and differences in database reporting. None of the studies reported cross-sectional disease activity in EO-IBD vs. AO-IBD using conventional clinical or endoscopic disease activity indices. Second, there was a paucity of data on rates of malignancy, mortality, and adverse medication events, with only two studies reporting on malignancy,[14, 17] two on mortality, [18, 20] and none directly on adverse medication events (though Jeuring *et al*[16] did report on rates of medication discontinuation). There was limited data on the burden of comorbidities and frailty in EO-IBD in the included studies which are important in assessing natural history and outcomes in older patients. Third, the reviewed studies had limited data on biologic therapies in general (as many of the cohorts were initiated before their more widespread use) and in particular had no data on newer, non-TNF biologics (i.e. anti-integrin and anti-IL-12/23 agents) and small molecule inhibitors, and so our review may not completely capture more recent trends in management. Finally, it is difficult to ascertain causality between treatment patterns and outcomes like surgery in EO-IBD with a study-level synthesis. For example, it is unclear whether comparable risks of surgery and hospitalization in EO-IBD vs. AO-IBD, despite less frequent use of disease-modifying

therapy with immunomodulators and/or biologic agents in the former, represents a ‘milder disease’ in EO-IBD. Alternatively, it is likely that these high rates of adverse outcomes like surgery in EO-IBD may be decreased by modifying treatment approach to patients with EO-IBD.

In summary, ased on a systematic review of nine population-based cohort studies, we observed that risks of surgery, hospitalization and corticosteroid exposure in EO-IBD is similar to AO-IBD, whereas immunomodulators and biologic agents are used less frequently. With the increasing burden of IBD in older patients, and high risks associated with prolonged corticosteroid use and surgical complications, there is a critical need to provide evidence-based guidance on safe and appropriate use of

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Research reported in this publication was supported the National Institute of Diabetes and Digestive and Kidney Diseases K23DK117058 to Siddharth Singh. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

Parambir S. Dulai is supported by the American Gastroenterological Association Research Scholar Award, and has received research support from Takeda, Pfizer, Abbvie, Janssen, Polymedco, ALPCO, Buhlmann, Prometheus, and consulting fees from Takeda, Pfizer, Abbvie and Janssen.

Mathurin Fumery received honoraria from AbbVie, MSD, Takeda, Janssen, Pfizer, Ferring, Celgene, Gilead and Boehringer.

William J. Sandborn has received research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, Abbvie, Janssen, Takeda, Lilly, Celgene/Receptos; consulting fees from Abbvie, Allergan, Amgen, Arena Pharmaceuticals, Avexegen Therapeutics, BeiGene, Boehringer Ingelheim, Celgene, Celltrion, Conatus, Cosmo, Escalier Biosciences, Ferring, Forbion, Genentech, Gilead Sciences, Gossamer Bio, Incyte, Janssen, Kyowa Kirin Pharmaceutical Research, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Prizer, Precision IBD, Progenity, Prometheus Laboratories, Reistone, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by Health Academic Research Trust, HART), Series Therapeutics, Shire, Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Takeda, Theravance Biopharma, Tigenix, Tillotts Pharma, UCB Pharma, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals; and stock or stock options from BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals, Ventyx Biosciences, Vimalan Biosciences. Spouse: Opthotech - consultant, stock options; Progenity - consultant, stock; Oppilan Pharma - employee, stock options; Escalier Biosciences - employee, stock options; Precision IBD - employee, stock options; Ventyx Biosciences – employee, stock options; Vimalan Biosciences – employee, stock options.

Siddharth Singh is supported by the American College of Gastroenterology Junior Faculty Development Award and the Crohn’s and Colitis Foundation Career Development Award (#404614), and has received research grant support from AbbVie; has served as a consultant for AbbVie, Takeda and AMAG Pharmaceuticals, and has received honorarium from Pfizer for ad-hoc grant review

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WHAT YOU NEED TO KNOW

Background:

The incidence of inflammatory bowel diseases (IBD) is increasing in older persons. The authors performed a systematic review and meta-analysis of population-based cohorts to learn more about progression and outcomes of elderly-onset (EO)-IBD compared with adult-onset (AO)-IBD.

Findings:

The cumulative risk of surgery at 5 y in patients with EO-Crohn's disease was 23%, and in patients with EO-ulcerative colitis was 8%, with high rates of post-operative complications (10%). Though the cumulative exposure to corticosteroids was comparable between patients with EO-IBD vs AO-IBD, cumulative exposure to immunomodulators and biologic agents was 38%–64% lower in patients with EO-IBD.

Implications for patient care:

Patients with EO-IBD have a similar risk of surgery as patients with AO-IBD, yet patients with EO-IBD are less likely to receive treatment with immunomodulators or biologic agents. Modifying treatment approaches for EO-IBD might improve outcomes. comparable between patients with EO-IBD vs AO-IBD, cumulative exposure to immunomodulators and biologic agents was 38%–64% lower in patients with EO-IBD

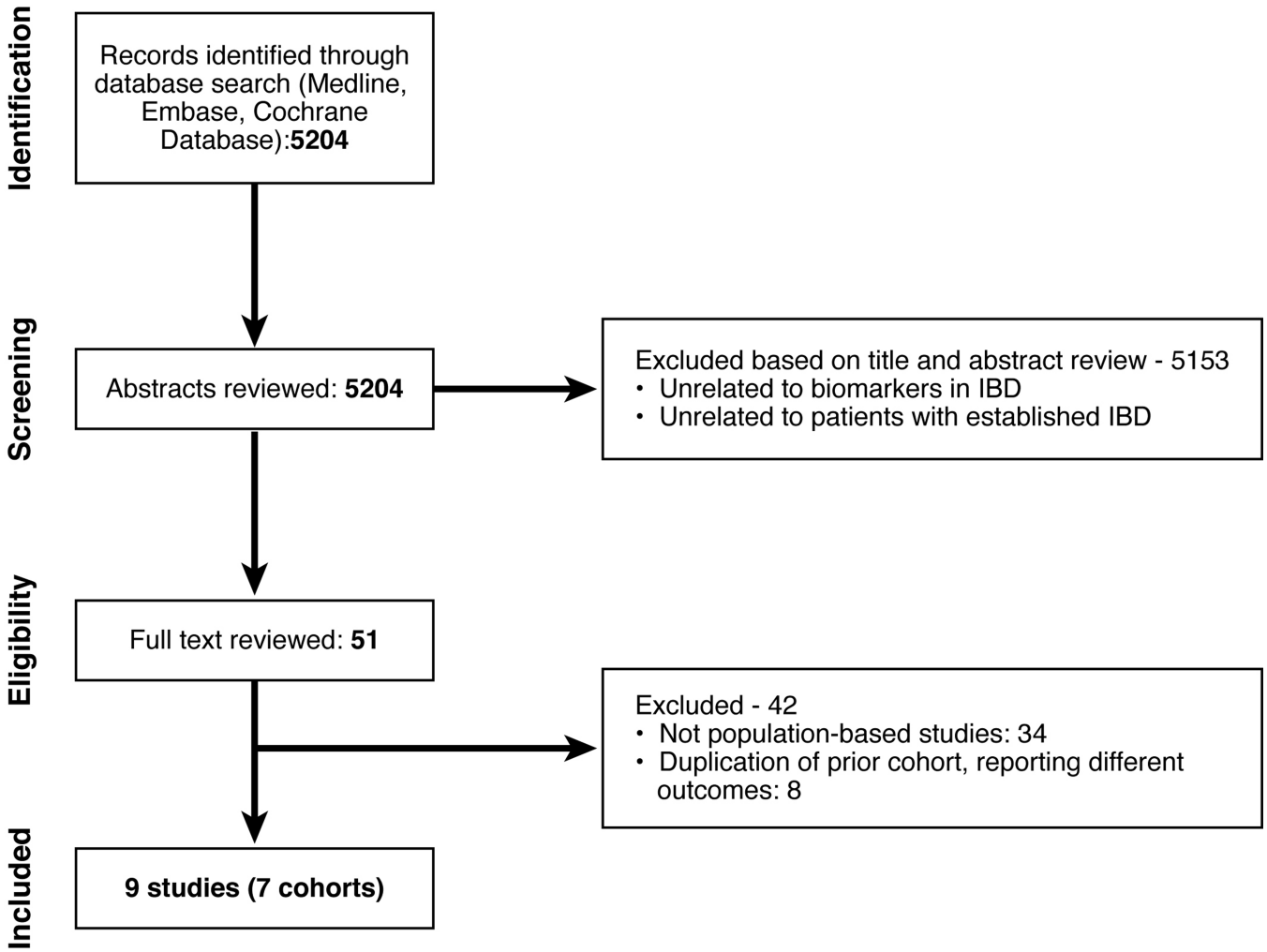

Figure 1:
Study selection flowsheet

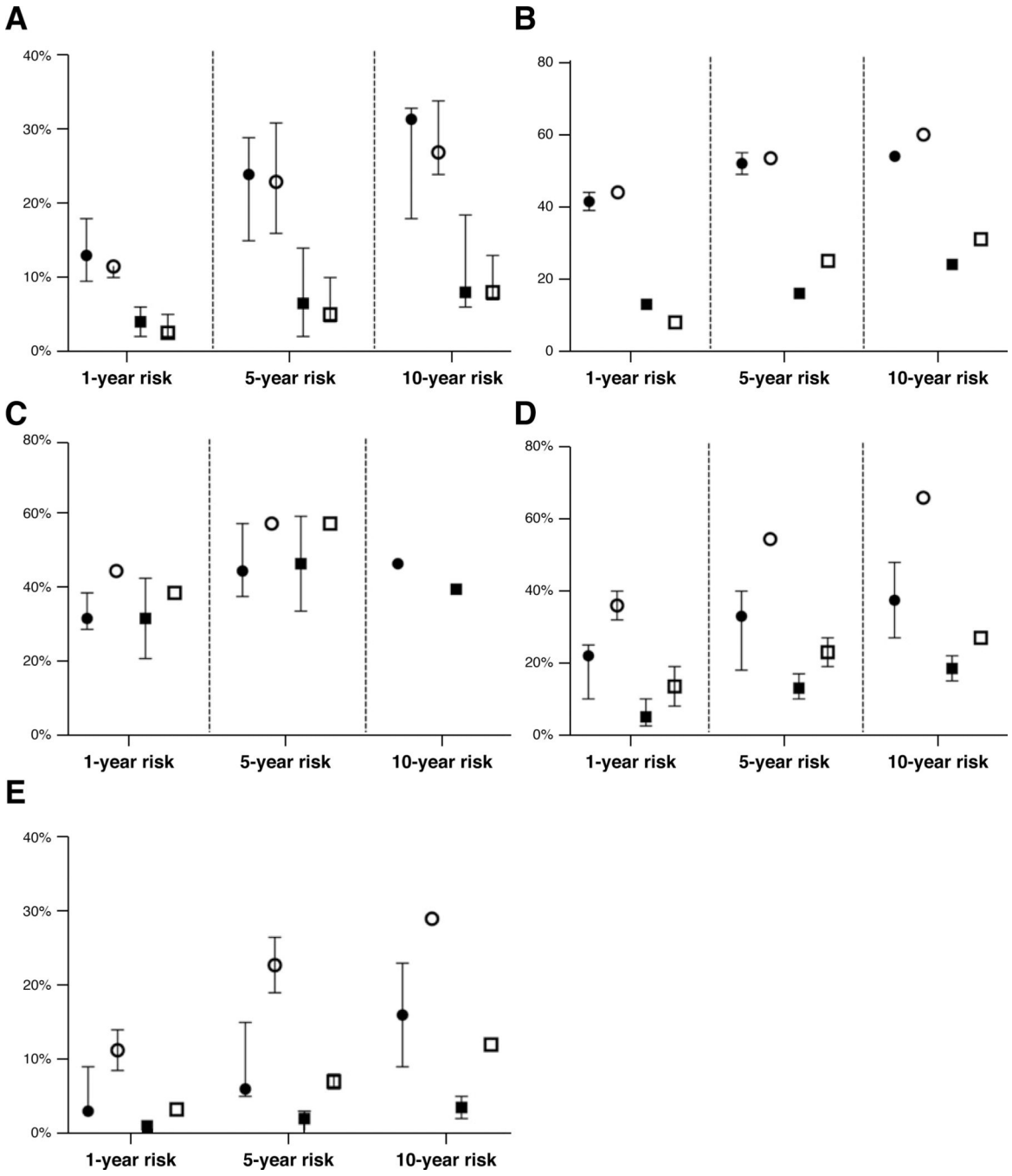

Figure 2:

1-, 5-, 10-year and cumulative risks of (A) surgery*, (B) hospitalization, (C) corticosteroid use, (D) immunomodulator use, and (E) TNFα antagonist use, plotted as median and range. EO-CD=elderly-onset Crohn's disease (solid circle), AO-CD=adult-onset Crohn's disease (clear circle), EO-UC=elderly-onset ulcerative colitis (solid square), AO-UC=adult-onset ulcerative colitis (clear square)

*Adult-onset data for one study (Nguyen) included only 18–40yo patients

Table 1:

Summary of Included Population-based Studies of Elderly-Onset IBD

Study	Year Published	Country	Cohort years	# of patients (EO/AO)	Mean/Median Follow up (years)	Outcome(s). reported
Alexakis[12]	2017	Great Britain	1990–2010	16,005 (2,758/6,757)	4.7–5.6 *	A, D
Epimad [13], [14] (Charpentier, Cheddani)	2014, 2016	France	1988–2006	11,219 (841/9,476)	6	A, D, E, F
Swedish Cohort[15], [20] (Everhov, Olen)	2018	Sweden	2006–2013	27,834 (6,443/18,477)	4.2	A, B, C, D
Jeuring[16]	2016	Netherlands	1991–2011 †	2,823 (509/2,314)	5.6–9.0 *	A, B, D, F
Lakatos[17]	2011	Hungary	1977–2008	1,400 (127/1,144)	NA	A, D, E, F
Nguyen[18]	2017	Canada	1999–2008	10,642 (2,474/8,168)	9.2–9.6 *	A, C
Heresbach[19]	2004	France	1994–1997	264 (63/201)	5	A, B, C, D, E

Primary outcomes: A surgery, B hospitalization, C all-cause mortality, D medication use patterns, E malignancy, F disease progression Other notes:

* range of mean/median follow ups for different subgroups,

† cohort subgroup with different range of years, NA none given. Study by Nguyen et al included other patients also

Table 2:

Risk of Disease Progression, Hospitalization, Surgery, and Mortality in Elderly-Onset CD

Study	Disease/Therapy Progression	Hospitalization	Surgery	Cancer/Mortality
Alexakis[12]	NR	NR	1-yr risk: *9.5%* 5-yr risk: *15%* 10-yr risk: *18%* Crude rate: *13%* HR vs AO: 0.8, 95% CI 0.68–0.94	NR
Charpentier[13]	From B1 to B2/B3: 9% Any change in localization: 8% CS exposure - 1-yr risk: 32% - 5-yr risk: 45% - 10-yr risk: 47% IM exposure - 1-yr risk: 10% - 5-yr risk: 18% - 10-yr risk: 27% TNF exposure - 1-yr risk: 3% - 5-yr risk: 5% - 10-yr risk: 9%	NR	1-yr risk: 18% 5-yr risk: 27% 10-yr risk: 32% Total rate: 28%	NR
Everhov[15], Olen[20]	CS exposure - 1-yr risk: 39% - 5-yr risk: 58% IM exposure - 1-yr risk: 25% - 5-yr risk: *33%* TNF exposure - 1 -yr risk: 3% - 5-yr risk: *6%*	Mean #/yr: 1.2 Median #/yr: 0 IRR vs AO: 0.88, 95% CI 0.78–0.99	1 -yr risk: **12%** 5-yr risk: **22%**	Mortality: 32 per 1000py (HR vs. general population, 1.6 [1.5–1.6])
Jeuring[16]	From B1 to B2 or B3: - 5-yr risk: 19.8% - 10-yr risk: 29.9% - HR vs AO: 0.81, 95% CI 0.52–1.25 IM exposure - 1 -yr risk: 22% - 5-yr risk: *40%* - 10-yr risk: *48%* - HR vs AO: 0.74, 95% CI 0.76–0.97 TNF exposure - 1 -yr risk: 9% - 5-yr risk: *15%* - 10-yr risk: *23%*	Rate at dx: 30.2% HR vs AO at dx: 1.14, 95% CI 0.82–1.58 1 -yr risk: 42% 5-yr risk: 49% 10-yr risk: 55% Total proportion during f/u: 56.8% HR during f/u: 1.02, 95% CI 0.78–1.32	Risk at dx: **14%** HR at dx: 1.88, 95% CI 1.12–3.15 5-yr risk: 29% 10-yr risk: 33% HR during f/u vs AO: 1.19, 95% CI 0.85–1.67	NR

Study	Disease/Therapy Progression	Hospitalization	Surgery	Cancer/Mortality
	- HR vs AO: 0.61, 95% CI 0.38–0.96			
Lakatos[17]	5-yr risk of behavior change: 0% OR of behavior change at 5 yrs, AO vs EO: 1.25, 95% CI 1.18–1.32	NR	5-yr rate: 29% Reoperation rate: 16.7% HR (vs. AO-CD): 0.41 (0.29–0.79)	NR
Nguyen[18]	NR	NR	1 -yr risk: 14% 5-yr risk: 24% 10-yr risk: 31% HR (vs. AO-CD): 1.18 (1.00–1.38)	CD-specific: **33.1/10Fk pyr** CD SMR: 1.12, 95% CI 0.99–1.26
Heresbach[19]	CS exposure 1 -yr risk: 29% 3-yr risk: 33% 5-yr risk: 38%	1 -yr risk: 39% 3-yr risk: 52% 5-yr risk: 55%	Overall risk: 14% 1 -yr risk: 13% 3-yr risk: 15% 5-yr risk: 21%	

Risk reported as cumulative risk by Kaplan-Meier analysis unless otherwise specified. EO=elderly onset, AO=adult onset, NR=not reported, HR=adjusted hazard ratio, OR=odds ratio, CS=corticosteroid, IM=immunomodulator, TNF=anti-TNFα biologic, SMR=standardized mortality ratio, pyr=person-year, dx=diagnosis, f/u=follow-up, IRR=incidence risk ratio, CI=confidence interval. **Bold**=significantly greater than comparison group, *Italics*=significantly less than comparison group.

Table 3:

Risk of Disease Progression, Hospitalization, Surgery, and Mortality in Elderly-Onset UC

Study	Disease/Therapy Progression	Hospitalization	Surgery	Cancer/Mortality
Alexakis[12]	NR	NR	1 -yr risk: 2% 5-yr risk: 4.5% 10-yr risk: 6% Crude rate: *3.9%* HR vs AO: 0.94, 95% CI 0.75–1.18	NR
Charpentier[13]	Progression E1 to E2: 8% Progression E1 to E3: 3% Progression E2 to E3: 5% 5-ASA exposure - 1 -yr risk:65% - 5-yr risk: 78% - 10-yr risk: 84% CS exposure - 1 -yr risk: 21% - 5-yr risk: 34% - 10-yr risk: 40% IM exposure - 1 -yr risk: 2.5% - 5-yr risk: 10% - 10-yr risk: 15% TNF exposure - 1 -yr risk: 0% - 5-yr risk: 0.4% - 10-yr risk: 2%	NR	1 -yr risk: 4% 5-yr risk: 8% 10-yr risk: 8% Total rate: 7%	Cancer - IR: 17.6/1000pyr - SIR: 0.97 (0.80–1.18)
Everhov[15], Olen[20]	5-ASA exposure - 1 -yr risk: 70% - 5-yr risk: 80% CS exposure - 1 -yr risk: 43% - 5-yr risk: 60% IM exposure - 1 -yr risk: 10% - 5-yr risk: *17%* TNF exposure - 1 -yr risk: 1 % - 5-yr risk: *2%*	Mean #/yr: 1.2 Median #/yr: 0 IRR vs AO: 1.49, 95% CI 1.33–1.67	1 -yr risk: **4**% 5-yr risk: 13%	Mortality: 81 per 1000py (HR vs. general population, 1.5 [1.4–1.5])
Jeuring[16]	From E1 to E2 or E3: - 5-yr risk: 12% - 10-yr risk: 21% - HR vs AO: 0.96, 95% CI 0.71–1.3	Rate at dx: **5.7%** HR vs AO at dx: 1.89, 95% CI 1.10–3.24 1 -yr risk:	Risk at dx: 0.5% 5-yr risk: 7% 10-yr risk: 8% HR during f/u vs AO:	NR

Study	Disease/Therapy Progression	Hospitalization	Surgery	Cancer/Mortality
	IM exposure - 1-yr risk: *5%* - 5-yr risk: *13%* - 10-yr risk: *22%* - HR vs AO: 0.66, 95% CI 0.5–0.87 TNF exposure - 1 -yr risk: *1%* - 5-yr risk: *3%* - 10-yr risk: *5%* - HR vs AO: 0.42, 95% 0.25–0.72	**0–20**% 5-yr risk: **20–30**% 10-yr risk: **20–30**% Total proportion during f/u: 56.8% HR during f/u: 1.29 95% CI 1.01–1.63	0.88, 95% CI 0.53–1.46	
Lakatos[17]	Proximal extension 5-yr: 7% Proximal extension 10-yr: 9%	NR	5-yr risk: 1.9%	5-yr risk of UC-related CRC: 2.5%
Nguyen[18]	NR	NR	1 -yr risk: **6%** 5-yr risk: **14%** 10-yr risk: **18.5%**	UC-specific: 2.89/10k pyr UC SMR: 0.98, 95% CI 0.90–1.06

Risk reported as cumulative risk by Kaplan-Meier analysis unless otherwise specified. EO=elderly onset, AO=adult onset, NR=not reported, HR=adjusted hazard ratio, IR=incidence rate, OR=odds ratio, CRC=colorectal cancer, CS=corticosteroid, IM=immunomodulator, TNF=anti-TNFα biologic, CA=cancer, SMR=standardized mortality ratio, SIR=standardized incidence rate, pyr=person-year, dx=diagnosis, f/u=follow-up, IRR=incidence risk ratio, CI=confidence interval. **Bold**=significantly greater than comparison group, *Italics*=significantly less than comparison group.