Prevalence and Implications of Frailty in Older Adults with Incident Inflammatory Bowel Diseases: a Nationwide Cohort Study

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Abstract

Aims: We aimed to compare the risk of frailty in older adults with incident inflammatory bowel disease (IBD) and matched non-IBD comparators and assess the association between frailty and future hospitalizations and mortality.

Methods: In a cohort of patients with incident IBD ≥60 years from 2007–2016 in Sweden identified using nationwide registers, we defined frailty using Hospital Frailty Risk Score (HFRS). We compared prevalence of frailty in patients with IBD to age, sex, place-of-residency and calendar-year matched population comparators. In the IBD cohort, we used Cox proportional hazards modeling to examine the associations between frailty risk and hospitalizations or mortality.

Results: We identified 10,590 patients with IBD, 52% female with a mean age of 71 years, matched to 103,398 population-based comparators. Among patients with IBD, 39% had no risk for frailty, 49% had low risk and 12% had higher risk for frailty. Mean HFRS was 1.9 in IBD and 0.9 in matched-comparators ($p<0.01$). Older adults with IBD at higher risk for frailty had a 20% greater risk for mortality at 3 years compared with those who were not frail. Compared to non-frail older patients with IBD, patients at higher risk for frailty had increased mortality (HR:3.22, 95%confidence interval (CI): 2.86–3.61), all-cause hospitalization (HR:2.42,95%CI: 2.24–2.61) and IBD-related hospitalization (HR: 1.50,95%CI: 1.35–1.66). These associations were not attenuated after adjusting for comorbidities.

Conclusion: Frailty is more prevalent in older adults with IBD than matched comparators. Among older patients with IBD, frailty is associated with increased risk for hospitalizations and mortality.

Keywords: geriatric, Crohn's disease, ulcerative colitis, aging

What You Need to Know

Background: Frailty is associated with re-admissions, infections after immunosuppression and mortality in adults of all ages with IBD.

Findings: Adults ≥60 years with incident IBD have a higher prevalence of frailty compared with matched population-based comparators (61% versus 27%). Frailty in older adults with incident IBD is strongly associated with increased risks for mortality and hospitalizations, independent of comorbidities. Frailty is associated with a significantly increased risk of death from digestive, respiratory and cardiovascular diseases.

Implications for Patient Care: These findings support the need to better understand the relationship between frailty and IBD outcomes and to develop a tailored frailty assessment tool that can be implemented in an efficient manner in IBD clinic to risk stratify older patients.

INTRODUCTION

One-quarter of incident IBD diagnoses are in adults ≥60 years.[1, 2] With more effective treatments and decreased disease fatality, the number of people who are aging with IBD is also increasing.[3] It is important to understand geriatric constructs in older patients with IBD. To date, chronologic age and co-morbidity are the most studied geriatric constructs in IBD.[4] However, it is increasingly recognized that age and co-morbidity do not fully approximate risks for adverse outcomes in older adults.[5] Frailty is an age-related decline in multiple physiologic systems that confers significant vulnerability to health-related changes, but does not have a linear relationship with chronologic age.[6] Frailty-related constructs are used to risk stratify patients in fields such as oncology.[7] Frailty is a predictor of outcomes in other chronic inflammatory conditions.[8, 9]

A study in an electronic health record based database demonstrated that frailty was associated with an increased risk for mortality in IBD.[10] However, the studies published to date assess frailty in IBD patients of all ages,[11, 12] without a focused assessment of frailty in older adults. As frailty is an aging-related concept that is more applicable to older adults, describing the prevalence and implications of frailty in older adults with IBD is needed. Furthermore, to date no study has compared the prevalence of frailty in patients with IBD to matched population controls.

We used a nationwide, population-based cohort, to estimate the prevalence of frailty in patients with IBD and compared it with matched adults. We also examined the association between frailty and adverse outcomes, specifically hospitalizations and mortality in older patients with IBD.

METHODS

Data Source

We used the Swedish Patient Registers to achieve our aims. Please see **supplemental methods** for details.

Cohort

Patients with IBD

We identified patients ≥60 years of age with incident IBD between January 1, 2007 – December 31, 2016 to allow for ≥1 full year of follow-up time in the cohort. We defined IBD by those with ≥2 records in the Nationwide Patient Register (NPR), which has a positive predictive value (PPV) of 93%,[13] or 1 record for IBD in the NPR with a biopsy suggestive of IBD from the ESPRESSO cohort, which improves the definition.[14] This combined definition was used in recent studies of IBD in the Swedish Registers (list of codes in **Supplementary Appendix A)**.[15, 16] Follow-up started at the date of the second code for IBD or pathology.

Matched General Population Comparators

We matched incident IBD cases with up to 10 population-based comparators according to age, sex, place of residence and calendar year to account for demographic contributors to frailty and variations in coding practice.

Frailty

We defined frailty using the Hospital Frailty Risk Score (HFRS).[17] Please see **supplemental methods** for more details. If the HFRS was 0, subjects were determined to be non-frail. Based on validated cut-offs of 0 - < 5 and ≥ 5, patients were designated to be at low and higher risk for frailty, respectively.

Covariates

Pertinent covariates were age, sex, type of IBD, IBD medications, health care utilization, country of birth, level of education and geographic location. Please see **supplemental methods** for more details.

Outcomes

The primary outcome was mortality. Mortality was ascertained from the Causes of Death Register which is 99% complete.[18] Underlying causes of death were defined by ICD codes (listed in **Supplementary Appendix E)**.[19] A secondary outcome was hospitalizations, all-cause hospitalizations and IBD-related, determined by the primary diagnosis code for the hospitalization in the NPR.[20]

Statistical Analysis

We constructed Cox proportional hazard models to estimate hazard ratios (HRs) for the outcomes comparing IBD patients according to risk for frailty (no risk, low risk and higher risk). The models were adjusted for age, sex, calendar year, country of birth and education level prior to diagnosis. We also presented adjusted HRs (aHR) for the following pre-specified sub-groups: sex, age in categories, type of IBD and CCI. We constructed age and sex-weighted Kaplan-Meier curves to determine time to the outcomes by severity of frailty in patients with IBD. For the cause of death analysis, we constructed a competing risk model using the primary cause of death with all the other causes of death as a competing risk. All analyses were conducted in SAS v9.4 (Cary, NC) and Stata v16.0 (College Station, TX).

RESULTS

We identified 10,590 adults ≥60 years with incident IBD between 2007 and 2016 (**Table 1**). Patients with IBD had a mean age of 71 years (range: 60–96 years) and were 52% female. Among patients with IBD, 27% had CD, 59% had UC and 13% had IBD-U. Mean CCI was 0.6 with 16% having a CCI of ≥2. Mean HFRS was 1.9. When examining the severity of frailty, 39% of patients with IBD had a risk score of 0 at diagnosis. Nearly half (49%) were at low risk for frailty and 12% were at higher risk for frailty.

We matched the patients with IBD on age, sex, place of residency and calendar year, to 103,398 non-IBD comparators (**Table 1**). In the non-IBD cohort, mean CCI was 0.4 and mean HFRS was 0.9. The majority of non-IBD comparators (73%) were non-frail, 21% were at low risk for frailty and 6% were at higher risk for frailty.

Mean follow-up in the cohort was 5 years. IBD patients with higher risk for frailty were more likely to be older, female and have less education (**Table 2)**. Mean CCI and healthcare use increased with frailty. Immunosuppression use was the highest in patients with IBD who were at low risk for frailty (**Table 2**).

Non-frail patients with IBD had a mortality rate of 30/1,000 person-years (P-Y), whereas patients with IBD at low risk for frailty had a mortality rate of 51/1,000 P-Y and those at higher risk for frailty had a mortality rate of 153/1,000 P-Y. Incidence rates by sub-groups are presented in **Supplemental Table 1**. Risk differences for mortality between those at higher risk for frailty and non-frail older adults with IBD was 20% at 3 years and 30% at 6 years. After adjusting for all covariates, patients with IBD who were at higher risk for frailty had >3 times the risk of mortality compared with non-frail patients (aHR: 3.22, 95% CI: 2.86–3.61, **Table 3**). Frailty was more strongly associated with mortality in patients with IBD aged 60-69 years (aHR: 5.55, 95% CI:

4.44–6.93) than in those ≥80 years (aHR: 2.07, 95% CI: 1.73–2.47) (p-interaction <0.01). HRs did not markedly vary by strata such as sex, IBD type and CCI. Increasing risk of frailty was associated with a shorter time to all-cause mortality (**Figure 1a**). Additionally, older adults with IBD had a greater risk for all-cause mortality compared with matched non-IBD comparators even when stratified by frailty (**Supplemental Table 3**).

In a competing risk model, higher risk for frailty resulted in statistically significant increases in risk of death from digestive diseases, infections, hematologic conditions, respiratory diseases, endocrine, nutrition and metabolic diseases, diseases of the circulatory system, trauma and diseases of the nervous system compared with those without frailty (**Figure 2**). Lower risk for frailty only conferred increased risk of death from digestive respiratory and cardiovascular diseases compared with older IBD patients without frailty. Notably the risk of death from malignancies was not significantly elevated in frail patients ≥60 years with incident IBD.

The risk differences for all-cause hospitalization between those who are at higher risk for frailty and non-frail older adults with IBD was 31% at 3 years and 24% at 6 years. Older patients with incident IBD who were at higher risk for frailty had a significantly increased risk for all-cause hospitalization (aHR: 2.42, 95% CI: 2.24–2.61) and IBD-specific hospitalization (aHR: 1.50, 95% CI: 1.35–1.66). Frailty was more strongly associated with all-cause hospitalization in patients with IBD aged 60-69 years (aHR: 2.90, 95% CI: 2.57–3.29) than in those ≥80 years older (aHR: 1.73, 95% CI: 1.48–2.02) (p-interaction: <0.01). The relationship between frailty and hospitalizations did not differ by number of serious comorbidities (**Table 4 & Supplemental Table 2**). After weighting for the covariates, being at higher risk for frailty resulted in a decreased time to all-cause hospitalization and IBD related hospitalization **(Figures 1b & 1c)**.

DISCUSSION

In a nationwide, population-based cohort of >10,000 older adults with incident IBD, we demonstrated for the first time that frailty is more prevalent in older adults with IBD than in matched comparators without IBD. Additionally, our data demonstrate that older patients with IBD at higher risk for frailty were significantly more likely to experience adverse outcomes including mortality and hospitalization. Our findings suggest that frailty is a pertinent concept to explore further as a risk stratification modality in patients with IBD. As the population with IBD is rapidly aging, there will be a greater need to develop accurate models for risk stratification to inform shared decision making.

Frailty, function and multi-morbidity are overlapping but distinct geriatric entities, all of which confer increased risk for adverse events, especially to older people.[5] Physical function is difficult to accurately determine using health services data.[21] Comorbidity has long been studied in IBD and recent studies conclude that comorbidity is a better predictor for adverse events than chronologic age alone.[22] Despite overlap and proposed etiologic bi-directionality, frailty and co-morbidity are not fully overlapping constructs.[23] Frailty has been recognized in recent guidelines on multi-morbidity as a critical aspect that confers increased risk for adverse events associated with multi-morbidity.[24] Initial retrospective studies of frailty in IBD also demonstrate that frailty is associated with an increased risk for serious adverse outcomes.[10, 11, 25] Our robust analyses extend prior work by demonstrating the frailty is strongly associated with adverse outcomes even after accounting for comorbidity.

Frailty and functional status have been used to risk stratify older adults with cancer requiring chemotherapy.[26] Similar to oncology, immunosuppressive therapies are the mainstays of modern IBD treatment.[27, 28] As with chemotherapy, age-related changes may impact the tolerance of immunosuppression and shift the risk-benefit ratio for treatment modalities.[29] Our data support the need to evaluate frailty in a prospective manner to determine its utility as a risk stratification modality for patients with IBD.

In Canadian and Swedish studies assess causes of death in older adults with IBD, malignancy was a leading cause of death.[19, 30] Unexpectedly, when stratified by frailty and assessed in a competing risk model we demonstrate that frail older patients with IBD did not have significantly increased risk of death from malignancies. As expected, however, higher risk for frailty increased the risk of death. What may be more notable, however, is that even a lower risk of frailty significantly increased the risk of death from digestive, respiratory and cardiovascular diseases compared with non-frail older patients with incident IBD. Better elucidating how frailty influences cause of death in frail IBD patients may help tailor early interventions for pre-frail older adults with IBD.

Corticosteroid use is known to result in adverse outcomes related to frailty including decreased muscle mass, bone density and even mortality in patients with IBD.[31, 32] Despite this knowledge, a substantial portion (39%) of newly diagnosed older patients with IBD were treated with systemic corticosteroids. It is not known if corticosteroids are immediately useful to ameliorate the frailty syndrome by treating inflammation or if they are worsening frailty. Future studies of frailty in IBD will benefit from assessing trajectories of frailty longitudinally. This will result in better understanding the role of steroid-sparing IBD therapy in modulating frailty.

Our study has a number of strengths. This is the first study of frailty in IBD in a population-based cohort allowing for true comparisons for the prevalence of frailty in unselected cohorts and mitigating selection bias. The cohorts and variables used have been previously validated in a robust manner with excellent test characteristics. Our study has a number of limitations as well. This study does not allow for granular disease level information and markers of inflammation to inform the analyses. Additionally, the use of ICD codes alone to define frailty biases frailty to include those with more co-morbidity burden and fewer functional limitations, however, the HFRS was previously used in studies of frailty in other disease processes, including IBD. It is possible that a healthcare system such as the Swedish one (with universal tax-financed coverage and drug use subsidized by the state) may be influencing prescription patterns and outcomes. This needs to be taken into account when trying to generalize these findings to IBD patients in countries.

In conclusion, in a large nationwide-study of older people, we demonstrate for the first time that frailty is more prevalent in older adults with IBD than population-matched comparators. We also demonstrate that frailty is strongly associated with hospitalizations and mortality in older adults with incident IBD, even after accounting for comorbidities. Understanding the relationship between frailty at diagnosis with medications used to treat IBD will improve the quality of life and overall health of older patients with IBD.

REFERENCES

1. Shivashankar R, Tremaine WJ, Harmsen WS, et al. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clin Gastroenterol Hepatol 2017;15:857-863.
2. Everhov AH, Halfvarson J, Myrelid P, et al. Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. Gastroenterology 2018;154:518-528 e15.
3. Alatab S, Sepanlou SG, Ikuta K, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology & Hepatology 2020;5:17-30.
4. Ananthakrishnan AN, Nguyen GC, Bernstein CN. AGA Clinical Practice Update on Management of Inflammatory Bowel Disease in Elderly Patients: Expert Review. Gastroenterology 2020.
5. Fried LP, Ferrucci L, Darer J, et al. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2004;59:M255-M263.
6. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013;381:752-62.
7. Inamoto T, Matsuyama H, Ibuki N, et al. Risk stratification by means of biological age-related factors better predicts cancer-specific survival than chronological age in patients with upper tract urothelial carcinoma: a multi-institutional database study. Ther Adv Urol 2018;10:403-410.
8. Andrews JS, Trupin L, Yelin EH, et al. Frailty and reduced physical function go hand in hand in adults with rheumatoid arthritis: a US observational cohort study. Clin Rheumatol 2017;36:1031-1039.
9. Legge A, Kirkland S, Rockwood K, et al. Evaluating the Properties of a Frailty Index and Its Association With Mortality Risk Among Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol 2019;71:1297-1307.
10. Kochar B, Cai W, Cagan A, et al. Frailty is independently associated with mortality in 11,001 patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2020;52:311-318.
11. Qian AS, Nguyen NH, Elia J, et al. Frailty Is Independently Associated with Mortality and Readmission in Hospitalized Patients with Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2020.
12. Faye AS, Wen T, Soroush A, et al. Increasing Prevalence of Frailty and Its Association with Readmission and Mortality Among Hospitalized Patients with IBD. Digestive Diseases and Sciences 2021.
13. Jakobsson GL, Sternegård E, Olén O, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). Scandinavian Journal of Gastroenterology 2017;52:216-221.
14. Nguyen LH, Örtqvist AK, Cao Y, et al. Antibiotic use and the development of inflammatory bowel disease: a national case-control study in Sweden. The Lancet Gastroenterology & Hepatology 2020;5:986-995.

15. Olén O, Erichsen R, Sachs MC, et al. Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. The Lancet Gastroenterology & Hepatology 2020;5:475-484.
16. Olén O, Erichsen R, Sachs MC, et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. The Lancet 2020;395:123-131.
17. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018;391:1775-1782.
18. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. European Journal of Epidemiology 2017;32:765-773.
19. Olén O, Askling J, Sachs MC, et al. Mortality in adult-onset and elderly-onset IBD: a nationwide register-based cohort study 1964–2014. Gut 2020;69:453-461.
20. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
21. Branch LG, Meyers AR. Assessing Physical Function in the Elderly. Clinics in Geriatric Medicine 1987;3:29-51.
22. Asscher VER, Van Der Vliet Q, Van Der Aalst K, et al. Anti-tumor necrosis factor therapy in patients with inflammatory bowel disease; comorbidity, not patient age, is a predictor of severe adverse events. International Journal of Colorectal Disease 2020.
23. Vetrano DL, Palmer K, Marengoni A, et al. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. The Journals of Gerontology: Series A 2019;74:659-666.
24. Farmer C, Fenu E, O'Flynn N, et al. Clinical assessment and management of multimorbidity: summary of NICE guidance. BMJ 2016;354:i4843.
25. Kochar B, Cai W, Cagan A, et al. Pretreatment Frailty Is Independently Associated With Increased Risk of Infections After Immunosuppression in Patients With Inflammatory Bowel Diseases. Gastroenterology 2020;158:2104-2111.e2.
26. Cohen HJ, Smith D, Sun C-L, et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer 2016;122:3865-3872.
27. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol 2018;113:481-517.
28. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol 2019;114:384-413.
29. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer 2012;118:3377-3386.
30. Nguyen GC, Bernstein CN, Benchimol EI. Risk of Surgery and Mortality in Elderly-onset Inflammatory Bowel Disease: A Population-based Cohort Study. Inflamm Bowel Dis 2017;23:218-223.
31. Lewis JD, Scott FI, Brensinger CM, et al. Increased Mortality Rates With Prolonged Corticosteroid Therapy When Compared With Antitumor Necrosis Factor-alpha-Directed Therapy for Inflammatory Bowel Disease. Am J Gastroenterol 2018;113:405-417.
32. Ludvigsson JF, Mahl M, Sachs MC, et al. Fracture Risk in Patients With Inflammatory Bowel Disease: A Nationwide Population-Based Cohort Study From 1964 to 2014. Am J Gastroenterol 2019;114:291-304.

Table 1: Baseline characteristics of Swedish patients ≥60 years with incident inflammatory bowel disease (IBD) and matched population-based comparators between 2007-2016

	IBD n (%)	Non-IBD Comparator n (%)
n	10,590	103,398
Female	5,522 (52)	54,014 (52)
Mean age in years (SD)	71 (±8)	71 (±8)
Range of age in years	60-96	60-96
Age in Categories:		
60-69 years	5,425 (51)	53,487 (52)
70-79 years	3,510 (33)	34,277 (33)
≥80 years	1,655 (16)	15,634 (15)
Education Level:		
≤9 years	4,027 (38)	37,340 (36)
10 – 12 years	4,259 (40)	40,788 (39)
>12 years	2,171 (21)	23,979 (23)
Mean follow-up in years (SD)	5 (±3)	5 (±3)
IBD Type:		
Crohn's disease (CD)	2,887 (27)	N/A
Ulcerative colitis (UC)	6,289 (60)	N/A
IBD-unclassified	1,414 (13)	N/A
CD Montreal Classification		
L1/L3/LX	2,422 (84)	
L2	448 (16)	
UC Montreal Classification		
E1/E2	2,665 (42)	
E3	817 (13)	
EX	2,807 (45)	
Mean number of outpatients visits / year (SD)[#]	3.3 (±6.7)	1.7 (±3.6)
Mean number of hospitalizations / year (SD)[#]	0.7 (±1.1)	0.3 (±0.7)
IBD Medications at Index Date		
Local corticosteroids	934 (9)	
Systemic corticosteroids	1,745 (17)	
Systemic 5-ASAs^	2,792 (26)	
Immunomodulators or Anti-TNF agents	275 (3)	
IBD Medications in the Year after Diagnosis		
Local corticosteroids	2,055 (19%)	113 (0.1%)
Systemic corticosteroids	4,106 (39%)	8,602 (8%)
Systemic 5-ASAs^	5,621 (53%)	300 (0.3%)
Immunomodulators	1,365 (13%)	1,496 (1%)
Anti-TNF agents	224 (2%)	105 (0.1%)
Charlson Co-morbidity Index (CCI):		
Range of CCI	0-13	0-15
0	6,462 (61)	79,300 (77)
1	1,515 (14)	9,117 (9)
≥2	2,613 (25)	14,981 (15)
Mean Frailty Risk Score (Range)	1.9 (0-41)	0.9 (0-34)
Severity of Frailty[$]:		
Non-frail	4,156 (39)	75,806 (73)
Low risk for frailty	5,170 (49)	22,071 (21)
Higher risk for frailty	1,264 (12)	5,521 (6)

Comparators are matched on age, sex, place of residence and calendar year

SD: Standard deviation [#]In the 3 years prior to diagnosis TNF: Tumor Necrosis Factor

^5-aminosalicylates [$]Non-frail: frailty risk score of 0, low risk: frailty risk score of >0 - <5, higher risk: ≥5

Table 2: Characteristics of Swedish patients ≥60 years with incident inflammatory bowel disease (IBD) between 2007-2016, stratified by frailty

	Non-frail	Low risk of Frailty	Higher Risk of Frailty
	n (%)	n (%)	n (%)
n	4,156	5,170	1,264
Female	1,999 (48)	2,796 (54)	727 (58)
Mean age in years (SD)	70 (±7)	71 (±8)	75 (±8)
Age in Categories:			
60-69 years	2,439 (59)	2,596 (50)	390 (31)
70-79 years	1,264 (30)	1,781 (34)	465 (37)
≥80 years	453 (11)	793 (15)	409 (32)
Education Level:			
≤9 years	1,433 (35)	2,037 (39)	557 (44)
10 – 12 years	1,712 (41)	2,061 (40)	486 (38)
>12 years	959 (23)	1,012 (20)	200 (16)
Mean follow-up in years (SD)	6 (±3)	5 (±3)	4 (±3)
IBD Type:			
Crohn's disease	1,079 (26)	1,424 (28)	384 (30)
Ulcerative colitis	2,883 (69)	2,801 (54)	605 (48)
IBD-unclassified	194 (5)	945 (18)	275 (22)
CD Montreal Classification			
L1/L3/LX	910 (84)	1,181 (83)	331 (86)
L2	157 (15)	238 (17)	53 (14)
UC Montreal Classification			
E1/E2	1,400 (49)	1,066 (38)	199 (33)
E3	333 (12)	412 (15)	72 (12)
EX	1,150 (40)	1,323 (47)	334 (55)
Mean number of outpatients visits / year (SD)[#]	1.8 (±2.1)	3.6 (±5.7)	7.1 (±14.3)
Mean number of hospitalizations / year (SD)[#]	0.2 (±0.4)	0.7 (±0.9)	2.2 (±1.9)
IBD Medications at Index Date			
Local corticosteroids	374 (9)	452 (9)	108 (9)
Systemic corticosteroids	662 (16)	881 (17)	202 (16)
Systemic 5-ASAs^	1,372 (33)	1,250 (24)	170 (13)
Immunomodulators or Anti-TNF agents	89 (2)	153 (3)	33 (3)
IBD Medications in the year after diagnosis			
Local corticosteroids	781 (19%)	1,024 (20%)	250 (20%)
Systemic corticosteroids	1,432 (35%)	2,187 (42%)	502 (40%)
Systemic 5-ASAs^	2,472 (60%)	2,722 (53%)	427 (34%)
Immunomodulators	526 (13%)	741 (14%)	98 (8%)
Anti-Tumor Necrosis Factor agents	80 (2%)	127 (3%)	17 (2%)
Charlson Co-morbidity Index:			
0	3,284 (79)	2,914 (56)	264 (21)
1	348 (8)	897 (17)	270 (21)
≥2	524 (13)	1,359 (26)	730 (58)

Non-frail: frailty risk score of 0, low risk: frailty risk score of >0 - <5, higher risk: ≥5
SD: Standard deviation
[#]In the 3 years prior to diagnosis
^5-aminosalicylates

Table 3: Hazard ratios for all-cause mortality in Swedish patients ≥60 years with incident inflammatory bowel disease between 2007-2016

	Adjusted Hazard Ratios* for Mortality (95% CI)	
	Low Risk of Frailty	**Higher Risk of Frailty**
Overall	1.48 (1.35–1.63)	3.22 (2.86–3.61)
Male	1.47 (1.29–1.68)	3.42 (2.90–4.03)
Female	1.49 (1.31–1.71)	3.08 (2.62–3.62)
60–69 years	1.61 (1.35–1.93)	5.55 (4.44–6.93)
70–79 years	1.57 (1.35–1.83)	3.59 (2.99–4.32)
≥80 years	1.28 (1.09–1.51)	2.07 (1.73–2.47)
Crohn's disease	1.39 (1.16–1.66)	2.82 (2.27–3.51)
Ulcerative colitis	1.48 (1.32–1.67)	2.99 (2.56–3.48)
IBD-unclassified	1.89 (1.25–2.86)	5.31 (3.42–8.22)
CCI=0	1.14 (1.00–1.30)	2.10 (1.66–2.65)
CCI=1	1.18 (0.92–1.51)	1.70 (1.27–2.29)
CCI≥2	1.53 (1.28–1.85)	2.83 (2.32–3.44)
Local Corticosteroids*	1.74 (1.20–2.53)	3.15 (1.94–5.13)
Systemic Corticosteroids*	1.37 (1.09–1.73)	3.01 (2.24–4.06)
Systemic 5-ASAs*	1.57 (1.29–1.90)	2.15 (1.58–2.93)
Immunomodulators / Anti-TNF*	1.14 (0.51–2.57)	5.22 (2.06–13.19)

Non-frail: frailty risk score of 0, low risk: frailty risk score of >0 - <5, higher risk: ≥5
Hazard ratios are compared to non-frail IBD patients
CI: Confidence Interval
*At the time of diagnosis
TNF: Tumor Necrosis Factor
All models are adjusted for age, sex, calendar year, country of birth and education prior to diagnosis

Table 4: Hazard ratios for all-cause hospitalization in Swedish patients ≥60 years with incident inflammatory bowel disease between 2007-2016

	Adjusted Hazard Ratios for Hospitalization (95% CI)	
	Low Risk of Frailty	**Higher Risk of Frailty**
Overall	1.37 (1.30–1.44)	2.42 (2.24–2.61)
Male	1.36 (1.27–1.46)	2.43 (2.17–2.73)
Female	1.38 (1.29–1.49)	2.43 (2.19–2.70)
60–69 years	1.40 (1.30–1.50)	2.90 (2.57–3.29)
70–79 years	1.36 (1.25–1.48)	2.57 (2.27–2.90)
≥80 years	1.31 (1.15–1.49)	1.73 (1.48–2.02)
Crohn's disease	1.25 (1.14–1.37)	2.22 (1.93–2.55)
Ulcerative colitis	1.39 (1.31–1.49)	2.40 (2.16–2.68)
IBD-undetermined	1.21 (1.01–1.46)	2.09 (1.66–2.62)
CCI=0	1.29 (1.21–1.37)	1.85 (1.60–2.14)
CCI=1	1.12 (0.92–1.30)	1.71 (1.40–2.08)
CCI≥2	1.29 (1.15–1.45)	2.20 (1.92–2.52)
Local Corticosteroids*	1.74 (1.20–2.53)	3.15 (1.94–5.13)
Systemic Corticosteroids*	1.37 (1.09–1.73)	3.01 (2.24–4.06)
Systemic 5-ASAs*	1.57 (1.29–1.90)	2.15 (1.58–2.93)
Immunomodulators / Anti-TNF*	1.14 (0.51–2.57)	5.22 (2.06–13.19)

Non-frail: frailty risk score of 0, low risk: frailty risk score of >0 - <5, higher risk: ≥5
Hazard Ratios are compared to non-frail patients with IBD
CI: Confidence Interval
*At the time of diagnosis
TNF: Tumor Necrosis Factor
All models are adjusted for age, sex, calendar year, country of birth and education prior to diagnosis

Figure 1: Kaplan-Meier failure curves weighted for age and sex for (A) all-cause mortality (B) all-cause hospitalizations and (C) inflammatory bowel disease (IBD)-related hospitalizations for patients ≥60 years with incident IBD in Sweden

Figure 2: Forrest-Plot for risk of main cause-specific mortality by frailty in Swedish patients ≥60 years with incident inflammatory bowel diseases (IBD) between 2007-2016

Supplemental Table 1: Incidence rates for all-cause mortality overall and by sub-groups in patients ≥60 years with incident inflammatory bowel diseases (IBD) between 2007-2016

	Mortality Rate / 1,000 person-years		
	Non-Frail	Low Risk of Frailty	Higher Risk of Frailty
Overall	30	51	153
Male	31	52	167
Female	29	50	143
60 – 69 years	14	23	80
70 – 79 years	38	62	150
≥80 years	126	164	273
Crohn's disease	31	47	137
Ulcerative colitis	30	51	148
IBD-unclassified	26	56	192
CCI = 0	24	30	80
CCI = 1	46	62	111
CCI ≥ 2	56	99	212

Non-frail: frailty risk score of 0, low risk: frailty risk score of >0 - <5, higher risk: ≥5

Supplemental Table 2: Incidence rates for all-cause hospitalization overall and by sub-groups in patients ≥60 years with incident inflammatory bowel diseases (IBD) between 2007-2016

	Hospitalization Rate / 1,000 person-years		
	Non-Frail	Low Risk of Frailty	Higher Risk of Frailty
Overall	22	33	85
Male	23	34	90
Female	21	32	82
60 – 69 years	17	25	64
70 – 79 years	28	40	95
≥80 years	46	68	106
Crohn's disease	26	35	90
Ulcerative colitis	20	31	80
IBD-undetermined	28	37	90
CCI = 0	19	26	47
CCI = 1	32	40	81
CCI ≥ 2	37	52	119

Non-frail: frailty risk score of 0, low risk: frailty risk score of >0 - <5, higher risk: ≥5

Supplemental Table 3: Incidence rates and hazard ratios for all-cause mortality stratified by degree of frailty in Swedish adults ≥60 years between 2007-2016

	Non-Frail	Low Risk of Frailty	Higher Risk of Frailty
IBD	4,156	5,170	1,264
Mortality n(%)	676 (16)	1,295 (25)	667 (53)
Mortality rate / 1,000 p-y	30	51	153
Non-IBD Comparators	75,806	22,071	5,521
Mortality n(%)	10,254 (14)	5,342 (24)	2,688 (49)
Mortality rate / 1,000 p-y	24	49	131
Hazard Ratio* for adults ≥60 years with Incident IBD (ref: matched non-IBD comparators) & 95% CI	1.36 (1.26 – 1.47)	1.20 (1.12 – 1.27)	1.27 (1.17 – 1.39)

p-y: person-years
CI: confidence interval
*Adjusted for age, sex, calendar year, country of birth and education

Supplemental Table 3: Prevalence of codes associated with frailty in patients ≥60 years with incident inflammatory bowel diseases (IBD) between 2007-2016

ICD-10 Code	Diagnosis	Frailty Score Points	% prevalence in IBD Patients	% prevalence in non-IBD Comparators
Comorbidity Related Diagnoses				
N39	Other disorders of urinary system	3.2	9.33%	11.18%
R31	Hematuria	3	2.66%	3.23%
B96	Other bacterial agents as the cause of diseases classified elsewhere	2.9	2.22%	1.94%
I67	Other cerebrovascular diseases	2.6	0.50%	0.62%
M25	Other joint disorder	2.3	2.38%	3.01%
L03	Cellulitis and acute lymphangitis	2	0.51%	0.43%
K59	Other functional intestinal disorders	1.8	13.52%	3.74%
N17	Acute kidney failure	1.8	1.82%	1.03%
Z22	Carrier of infectious disease	1.7	0.45%	0.34%
B95	Streptococcus, Staphylococcus and Enterococcus as the cause of diseases classified elsewhere	1.7	0.95%	0.89%
L97	Non-pressure chronic ulcer of lower limb	1.6	0.95%	1.04%
K26	Duodenal ulcer	1.6	1.29%	0.75%
N19	Unspecified kidney failure	1.6	1.10%	0.73%
A41	Other sepsis	1.6	2.56%	1.68%
Z87	Personal history of other diseases and conditions	1.5	0.67%	0.51%
J96	Respiratory failure	1.5	1.18%	1.32%
X59	Direct infection of hip in infectious and parasitic diseases	1.5	1.60%	2.12%
E16	Other disorders of pancreatic internal secretion	1.4	0.30%	0.37%
N18	Chronic kidney disease	1.4	3.67%	3.68%
N28	Other disorders of kidney and ureter	1.3	0.37%	0.22%
G45	Transient cerebral ischemic attacks and related symptoms	1.2	2.07%	3.02%
A04	Other bacterial intestinal infections	1.1	2.72%	0.66%
A09	Infectious gastroenteritis and colitis	1.1	6.47%	1.19%
J18	Pneumonia	1.1	4.48%	4.79%
J69	Pneumonitis due to solid and liquids	1	0.26%	0.20%
E55	Vitamin D deficiency	1	0.06%	0.11%
E05	Thyrotoxicosis	0.9	1.18%	1.16%
K92	Other diseases of digestive system	0.8	13.41%	2.52%
I63	Cerebral infarction	0.8	3.47%	5.01%
N20	Calculus of kidney and ureter	0.7	1.63%	2.32%
R00	Abnormalities of heart beat	0.7	2.22%	3.15%
J22	Unspecified acute lower respiratory infection	0.7	0.28%	0.32%
D64	Other anemias	0.4	9.56%	4.16%
K52	Non-infective gastroenteritis and colitis	0.3	41.45%	0.88%
R50	Fever of other and unknown origin	0.1	2.08%	1.49%

Function Related Diagnoses				
G81	Hemiplegia & hemiparesis	4.4	0.98%	1.04%
R29	Other signs and symptoms involving nervous and musculoskeletal systems	3.6	0.51%	0.70%
W19	Fall	3.2	5.16%	8.97%
S00	Superficial injury of head	3.2	0.58%	1.25%
R26	Abnormalities of gait and mobility	2.6	0.34%	0.42%
R56	Convulsions	2.6	0.65%	0.79%
T83	Complications of genitourinary prosthetic devices, implants and grafts	2.4	0.25%	0.42%
S06	Intracranial Injury	2.4	1.12%	1.87%
S42	Fracture of shoulder and upper arm	2.3	1.54%	2.93%
E87	Other disorders of fluid, electrolyte and acid-base balance	2.3	3.84%	2.43%
E86	Volume depletion	2.3	2.66%	1.15%
R54	Age-related physical debility	2.2	0.00%	0.01%
Z50	Care involving use of rehabilitation procedures	2.1	0.73%	1.20%
W18	Slipping, tripping, stumbling and falls	2.1	0.65%	0.80%
Z75	Problems related to medical facilities and other healthcare	2	0.31%	0.28%
S80	Superficial injury of knee and lower leg	2	0.68%	1.19%
E53	Deficiency of other B group vitamins	1.9	0.36%	0.18%
Z60	Problems related to social environment	1.8	0.14%	0.14%
G20	Parkinson's Disease	1.8	1.76%	2.21%
R55	Syncope and collapse	1.8	2.98%	3.98%
S22	Fracture of rib, sternum and thoracic spine	1.8	1.15%	1.59%
L89	Pressure ulcer	1.7	0.65%	0.50%
I95	Hypotension	1.6	1.51%	1.74%
M19	Osteoarthritis	1.5	2.55%	4.00%
G40	Epileptic seizures related to external causes	1.5	1.54%	2.31%
M81	Osteoporosis	1.4	2.98%	3.01%
S72	Fracture of femur	1.4	2.28%	3.79%
S32	Fracture of lumbar spine and pelvis	1.4	1.18%	1.28%
R94	Abnormal results of function studies	1.4	0.09%	0.13%
R33	Retention of Urine	1.3	2.95%	3.89%
R69	Illness	1.3	3.02%	2.62%
R32	Urinary incontinence	1.2	0.58%	0.79%
Y95	Nosocomial condition	1.2	0.06%	0.03%
S09	Injury of head	1.2	0.14%	0.29%
R45	Symptoms and signs involving emotional state	1.2	0.14%	0.16%
Z74	Problems related to care provider dependency	1.1	0.12%	0.08%
M79	Non-traumatic compartment syndrome	1.1	8.66%	11.06%
W06	Fall from bed	1.1	0.30%	0.36%
S01	Open wound of head	1.1	1.27%	2.65%
Z93	Artificial opening status	1	2.25%	0.84%
R02	Gangrene	1	0.02%	0.01%

R63	Symptoms and signs concerning food and fluid intake	0.9	1.21%	0.42%
W10	Fall on and from stairs and steps	0.9	1.29%	1.67%
W01	Fall on same level from slipping, tripping and stumbling	0.9	8.02%	13.41%
M41	Scoliosis	0.9	0.23%	0.25%
R13	Aphagia and dysphagia	0.8	1.73%	1.92%
Z99	Dependence on enabling machines and devices	0.8	0.95%	0.91%
U80	Agent resistant to penicillin and related antibiotics	0.8	0.03%	0.04%
M80	Osteoporosis with current pathological fracture	0.8	1.31%	1.53%
F10	Alcohol related disorders	0.7	1.87%	2.83%
Y84	Other medical procedures as the cause of abnormal reaction of the patient	0.7	0.68%	0.66%
Z73	Problems related to life management difficulty	0.6	0.05%	0.15%
R79	Other abnormal findings of blood chemistry	0.6	0.37%	0.41%
Z91	Personal risk factors	0.5	0.20%	0.28%
S51	Open wound of elbow and forearm	0.5	0.16%	0.38%
M48	Other spondylopathies	0.5	3.54%	4.67%
E83	Disorders of mineral metabolism	0.4	0.67%	0.49%
M15	Polyosteoarthritis	0.4	0.75%	0.82%
L08	Other local infections of skin and subcutaneous tissue	0.4	1.06%	0.99%
R11	Nausea and vomiting	0.3	3.02%	1.89%
Cognition Related Diagnoses				
F00	Alzheimer's Dementia	7.1	0.67%	1.90%
G30	Alzheimer's Disease	4	0.78%	2.31%
I69	Sequellae of Cerebrovascular Disease	3.7	4.37%	5.60%
F05	Delirium due to known physiologic condition	3.2	0.34%	0.36%
R41	Other symptoms and signs involving cognitive function and awareness	2.7	1.37%	2.12%
R40	Somnolence, stupor and coma	2.5	0.22%	0.21%
F03	Dementia	2.1	0.90%	2.20%
F01	Vascular dementia	2	0.28%	0.95%
G31	Degenerative diseases of nervous system	1.2	0.16%	0.29%
F32	Depressive episode	0.5	3.02%	3.52%
Sensory Related Diagnoses				
H54	Blindness and low vision	1.9	0.50%	0.66%
R44	Other symptoms and signs involving general sensations and perceptions	1.6	0.12%	0.20%
R47	Speech disturbances	1	0.76%	0.90%
H91	Hearing loss	0.9	1.01%	2.12%

SUPPLEMENTAL METHODS

Data Source

The Swedish healthcare system offers universal access to clinical care, including prescription coverage. The Swedish National Board of Health and Welfare has collected individual patient level data nationally since 1987.[1] Each record is organized according to the individual's personal identity number and includes age, sex, hospitalization diagnoses with International Classification of Disease (ICD) codes.[2] In 2001, this register was expanded to include outpatient care as well and together encompass the Nationwide Patient Register.[1] Patients with incident IBD were identified using the Nationwide Patient Register.[3] The diagnosis of IBD was supported by histology suggestive of IBD in the Epidemiology Strengthened by histoPathology REports in Sweden (ESPRESSO).[4] Medication use was identified using the Prescribed Drug Register, the National Patient Register and the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG).[5-7] Matched comparators were identified using the Total Population Register, held by Statistics Sweden.[8] Education level as well as country of birth were derived from the Longitudinal Integrated database for health insurance and labour market studies.[9]

Frailty

This score is based on 109 ICD-10 codes that were twice as prevalent in frail older adults than in non-frail older adults. Please see **Supplementary Appendix B** for a complete list of codes. The score is a weighted sum of the codes based on how common the condition is among frail individuals. For ease of interpretation, the regression coefficients are multiplied by 5 to create a point system. This frailty index was validated in a population of adults ≥75 years in the United Kingdom who were hospitalized to identify those who are at higher risk for adverse outcomes. A recent study assessing the HFRS in a sample of community dwelling adults found that it compares

well to other widely used frailty measures as well as predicts mortality similarly.[10] This frailty index has been previously used in studies of older adults in European nations, including Sweden.[11-13] Furthermore, this score has been used in previous studies of patients with IBD.[14-16] We assessed frailty in the 3 years prior to IBD diagnosis (or 3 years prior to entry into the cohort for the non-IBD comparators).

Covariates

We included IBD-related medications in the following categories: locally acting corticosteroids, systemic corticosteroids, systemic aminosalicylates (5-ASAs), immunomodulators and anti-tumor necrosis factor (TNF)-α agents (ATC code in **Supplementary Appendix C**). We also reported health care utilization prior to entry into the cohort and a version of the Charlson Co-morbidity index (CCI) adapted for the Swedish Register studies (codes in **Supplementary Appendix D**).[17]

References:

1. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
2. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European Journal of Epidemiology 2009;24:659-667.
3. Jakobsson GL, Sternegård E, Olén O, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). Scandinavian Journal of Gastroenterology 2017;52:216-221.
4. Ludvigsson JF, Lashkariani M. Cohort profile: ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden). Clinical Epidemiology 2019;Volume 11:101-114.
5. Wettermark B, Hammar N, Michaelfored C, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and Drug Safety 2007;16:726-735.
6. Bröms G, Söderling J, Sachs MC, et al. Capturing biologic treatment for IBD in the Swedish Prescribed Drug Register and the Swedish National Patient Register – a validation study. Scandinavian Journal of Gastroenterology 2021:1-12.
7. Ludvigsson JF, Andersson M, Bengtsson J, et al. Swedish Inflammatory Bowel Disease Register (SWIBREG) – a nationwide quality register. Scandinavian Journal of Gastroenterology 2019;54:1089-1101.
8. Statistics Sweden: Statistics Sweden, 2021.
9. Ludvigsson JF, Svedberg P, Olén O, et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. European Journal of Epidemiology 2019;34:423-437.
10. Mak JKL, Kuja-Halkola R, Wang Y, et al. Frailty and comorbidity in predicting community COVID -19 mortality in the UK Biobank: the effect of sampling. Journal of the American Geriatrics Society 2021.
11. Mak JKL, Kuja-Halkola R, Wang Y, et al. Frailty and comorbidity in predicting community COVID-19 mortality in the U.K. Biobank: The effect of sampling. J Am Geriatr Soc 2021;69:1128-1139.
12. Szilcz M, Wastesson JW, Johnell K, et al. Unplanned hospitalisations in older people: illness trajectories in the last year of life. BMJ Support Palliat Care 2021.
13. Gunnarsdottir GM, Helgadottir S, Einarsson SG, et al. Validation of the Hospital Frailty Risk Score in older surgical patients: A population-based retrospective cohort study. Acta Anaesthesiol Scand 2021;65:1033-1042.
14. Kochar B, Cai W, Cagan A, et al. Frailty is independently associated with mortality in 11,001 patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2020;52:311-318.
15. Kochar B, Cai W, Cagan A, et al. Pretreatment Frailty Is Independently Associated With Increased Risk of Infections After Immunosuppression in Patients With Inflammatory Bowel Diseases. Gastroenterology 2020;158:2104-2111.e2.
16. Qian AS, Nguyen NH, Elia J, et al. Frailty Is Independently Associated with Mortality and Readmission in Hospitalized Patients with Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2020.

17. Ludvigsson JF, Appelros P, Askling J, et al. Adaptation of the Charlson Comorbidity Index for Register-Based Research in Sweden. Clinical Epidemiology 2021;Volume 13:21-41.