# Inflammatory bowel disease in older patients: from gut feeling towards evidence-based medicine

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# Frailty associates with hospitalization and decline in quality of life and functional status in older patients with inflammatory bowel disease

*Submitted*


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## ABSTRACT

**Aims** To study frailty in association with hospitalization and decline in quality of life (QoL) and functional status in older patients with Inflammatory Bowel Diseases (IBD).

**Methods** A prospective multicentre cohort study in IBD patients ≥65 years using frailty screening (G8 Questionnaire) and geriatric assessment, covering domains of somatic, activities of daily living, physical, mental and social functioning. Outcomes were all-cause, acute and IBD-related hospitalization during 18 months, any infection, QoL (EQ5D-3L) and functional decline (Instrumental Activities of Daily Living, (IADL)). Confounders: age, biochemical disease activity (C-reactive protein ≥10 mg/L and/or fecal calprotectin ≥250 µg/g), comorbidity (Charlson Comorbidity Index).

**Results** Out of 405 patients, median age 70 years, 196 (48%) screened at risk for frailty, 160 (39.5%) had 2-3 geriatric deficits, 32 (7.9%) had 4 or 5. All-cause hospitalizations occurred 136 times in 96 patients (23.7%), acute 103 times in 74 (18.3%). Risk of frailty did not associate with all-cause (aHR 1.5, 95% CI 0.9-2.4), but did associate with acute hospitalizations (aHR 2.2, 95% CI 1.3-3.9). Geriatric deficits associated independently with both all-cause and acute hospitalizations. Infections occurred in 86 patients (21.2%) and were not associated with frailty. Decline in QoL was experienced by 108 (30.6%) patients, decline in functional status by 46 (13.3%). Frailty was associated with decline in QoL (aOR 2.1, 95% CI 1.3-3.6) and functional status (aOR 3.6, 95% CI 1.6-8.0).

**Conclusions** Frailty associates with worse health outcomes in older patients with IBD. Further studies are needed to assess feasibility and effectiveness of implementation in routine care.

# INTRODUCTION

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing-remitting inflammatory diseases affecting the gastrointestinal tract. The number of older patients with IBD is rising.[1] Although it has been advised to assess an individual's frailty when making treatment decisions in older patients with IBD, evidence on frailty and its association with outcomes in IBD is still scarce.[2 3]

A geriatric assessment includes an assessment of frailty and functioning in four domains (somatic, functional, mental and social domain). Comprehensive geriatric assessment, which includes geriatric assessment and an integrated care plan and follow-up, has been proven to be effective in improving outcomes of older patients with acute disease[4] and older patients with cancer.[5] Screening for risk of frailty, using validated instruments such as the Fried frailty phenotype[6] or the Geriatric 8 questionnaire[7], could however more feasible in clinical practice as compared to a geriatric assessment.

In the field of IBD, little evidence is available on the association between frailty and negative health outcomes or functional status and (health related) quality of life ((HR)QoL) over time.[3] We recently published a study demonstrating an association between presence of deficits in geriatric assessment and higher disease burden and disease activity in older patients with IBD.[8] It has also been recognised that retrospectively assessed frailty is associated with negative health outcomes such as infections or hospital admissions in IBD patients.[9-11] However, these latter longitudinal studies use frailty scores based on International Classification of Diseases (ICD) coding in administrative databases. Although using ICD coding could be appropriate for large-scale cohorts, they are hard to translate to an individual patient level and are not suitable to aid complex clinical decision making.

The aim of this study is to prospectively research the association between frailty and hospitalization and decline in QoL and functional status in older patients with Inflammatory Bowel Diseases (IBD) over time.

# METHODS

**Study design and patient population**

This is a prospective multicenter cohort study performed in the outpatient departments and day treatment centers of six hospitals in the Netherlands, as previously described in detail.[8] Patients were asked to participate during their regular hospital visit. Baseline visits took place between November 2016 and February 2020. Inclusion criteria were an age of 65 years or older and a confirmed clinical, endoscopic and/or histological diagnosis of CD, UC or IBD-Unclassified (IBD-U). Patients unable or unwilling to participate, sign informed consent,

or unable to speak Dutch or English were excluded. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed.[12]

**Data collection at baseline**

Baseline data were collected face-to-face and were verified using the electronical medical record. Demographic and IBD characteristics included age, sex, weight, height, disease type, disease duration and disease behaviour and location according to the Montreal classification[13] (maximum extent at inclusion), current and previous IBD medications and prior IBD-related surgery. Clinical disease activity was measured through the Harvey Bradshaw Index (HBI) for CD patients[14] and partial Mayo score (pMS)[15] for UC or IBD-U patients. Active disease was defined by a HBI of >4 or a pMS >2. C-reactive protein (CRP)) and fecal calprotectin (FCP) were extracted from the electronical medical record if tests were performed within three months of baseline. Biochemical disease activity was defined by either a CRP ≥10 mg/L or FCP ≥250 µg/g. To further specify biochemical disease activity, elevated FCP levels were reported separately as well. Endoscopic data were used if endoscopy was performed within 6 months of baseline.

Geriatric assessment was performed as previously described.[8] In short; the assessment included five different domains, deficits in 2-3 domains were defined as moderate deficits and deficits in 4-5 domains as severe. The somatic domain comprised comorbidity, measured by Charlson Comorbidity Index (CCI) ( ≥3 points abnormal, age not included)[16], polypharmacy (≥5 non-IBD medications)[17], and malnutrition, measured with Mini Nutritional Assessment (MNA, ≤11 points abnormal)[18]. Activities in daily living comprised Katz Index of Independence in Activities of daily living[19] (≥1 points abnormal, consisting of six items, each scored with zero, one or two points) and Lawton Instrumental Activities of Daily Living[20] (≥1 points abnormal, eight items, each scored with zero to three points, scores derived in a sex-specific manner: questions on food preparation, housekeeping and laundry were not taken into account for the male sex). Physical capacity comprised hand grip strength[21] (stratified by sex and body mass index)[6] and 4-meter gait speed[22] (stratified by sex and height)[6]. The mental domain comprised depression measured with Geriatric Depression Scale[23] (≥6 points abnormal) and cognitive function measured with Six-Item Cognitive Impairment Test[24] (≥8 points abnormal). Social domain was considered impaired when patients did not have a life-partner.[25 26]

The G8 questionnaire was used as a geriatric screening method.[7] The G8 questionnaire consists of eight questions with a total score ranging from zero to seventeen, a score of ≤14 points is indicates a risk of frailty. The G8 screening tool was developed in oncology patients[7] and has also been validated in older adults without cancer.[27]

**Data collection at follow-up**

Patients were contacted for follow-up assessment either at their regular hospital appointment or by phone. During this contact, patients were asked about hospital admissions, infections and malignancies during study period and these data were checked

using the electronical medical record. Also, questionnaires regarding (HR)QoL and functional status were taken (see below). Follow-up assessment was aimed to take place 18 months after baseline. Primary outcome was only noted if occurring within 18 months from baseline. For all patients who were not able to participate in follow-up contact, data regarding primary and secondary outcomes were extracted from the electronical medical record.

The primary outcome of this study was the occurrence of all-cause hospital admissions during 18 months of follow-up. Hospitalizations were further specified in acute hospitalization and IBD-related hospitalizations. Acute hospitalizations were defined as all non-elective hospital admissions. Secondary outcome was presence of infection during follow-up, which were noted as any infection or serious infection. All infections were noted when occurring between baseline and follow-up contact, or if patient was loss to follow-up between baseline and 18 months after baseline. Serious infections were defined as an infection needing hospital admission. The occurrence of malignancies and mortality were also noted.

Tertiary outcome was decline in (HR)QoL or functional status. HRQoL was assessed using the short Inflammatory Bowel Disease Questionnaire (sIBDQ)[28], a questionnaire containing 10 questions resulting in a score ranging from ten to seventy (high score equals high HRQoL). Decline in QoL was measured with EQ-5D-3L, a standardized questionnaire on QoL developed by the Euroqol group[29] using five health aspects and was scored using the Dutch value set to obtain index values standardized from 0 to 1; 0 representing death and 1 representing full health.[30] A negative difference in HRQoL or QoL at follow-up as compared to baseline was considered a decline. Decline in functional status was measured using the Katz Index of Independence in Activities of Daily Living (ADL)[19] and the Lawton Instrumental Activities of Daily Living (IADL).[20] A decline in ADL or IADL score of ≥1 was considered a decline.



**Statistical analyses**

Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR) and are compared using an independent T-test or Mann Whitney U test, depending on the normality of the distribution of data. Categorical variables are presented as numbers and percentages and compared using a chi-square test or Fisher's exact. Time from baseline to first hospitalization was considered as an outcome and therefore Kaplan-Meier for description and Cox proportional hazards model for association between frailty and primary outcome was used. Proportional hazard assumption was checked by testing each variable's interaction with time and visual inspection of the Schoenfeld residuals. Binary logistic regression analyses were used for secondary and tertiary outcomes. Analyses were performed as complete case analyses. Potential confounders were agreed upon beforehand and included age at baseline (continuous variable), biochemical disease activity (elevated CRP and/or FCP, binary variable) and comorbidity (CCI, continuous variable) for the association between frailty screening and primary and tertiary outcomes. For the association between geriatric deficits and outcomes comorbidity was not considered as a confounder because comorbidity is already included in the geriatric assessment. Regarding

the secondary outcome, baseline IBD medication (oral corticosteroid use, immunomodulator use, biological therapy) was added as potential confounder. No sample size calculation was performed and we aimed to include as many patients as possible to create a representative cohort. A p-value of <.050 was considered statistically significant. Data analyses were performed using IBM SPSS Statistics for Windows, version 25.

We estimated the predictive performance of the multivariate model to predict all-cause hospitalization. Discrimination was quantified by the C-index ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination), internally validated by bootstrapping. Bootstrap analysis was performed using R, version 4.02.

**Ethical considerations**

The study protocol was declared not subjective to the medical research involving human subjects act by the Committee on Research Involving Human Subjects at the LUMC and was approved in all participating centers. All patients provided written informed consent.

## RESULTS

At baseline, 547 patients were eligible for inclusion out of which 405 patients were included in our study, for study flowchart see supplementary figure 1. Baseline characteristics are listed in table 1. Overall median age was 70 years (IQR 67-74), 188 patients were female (46.4%) and 191 patients (47.0%) were diagnosed with CD. Eighty-five patients (21.7%) had clinical IBD disease activity, 93 patients (26.7%) had biochemical disease activity (elevated CRP or FCP), and 68 patients (29.7%) had an elevated FCP. Frailty screening was performed using G8 questionnaire, 196 patients (48.3%) were screened at risk of frailty, in table 1 baseline characteristics are displayed by risk of frailty. Patients at risk of frailty had higher age (median 71.0 versus 70.0, p=.001), were more often female (55.1% versus 37.7%, P<.001) and had a higher percentage of clinical (29.6% versus 14.3%, P<.001) and biochemical (33.5% versus 19.9%, p=.004) disease activity.

Geriatric assessment included five domains: somatic, activities of daily living, physical, mental and social functioning). Deficits in 2-3 domains were defined as moderate deficits and deficits in 4-5 domains as severe. Out of all patients, 160 patients (39.5%) had moderate deficits, 32 patients (7.9%) severe. For details on deficits in geriatric domains at baseline and patient characteristics at baseline displayed by number of deficits in geriatric domains see supplementary table 1 and 2.

We were able to contact 356 patients (87.9%) for follow-up questionnaires, see study flow-chart (supplementary figure 1). Eleven patients died during follow-up, out of which nine were screened frail at baseline (supplementary table 6). Mean duration from baseline to follow-up contact was 560 days (IQR 546-614.5).

**Table 1.** Baseline characteristics by risk of frailty

| | No risk of frailty (n=207) | Risk of frailty (n=196) | p-value |
|---|---|---|---|
| Median age at baseline, years (IQR) | 70.0 (67.0-72.0) | 71.0 (68.0-75.0) | .001 |
| Sex (female) | 78 (37.7) | 108 (55.1) | <.001 |
| Educational level (high) | 64 (31.7) | 57 (31.0) | .881 |
| Current smoker | 23 (11.1) | 16 (8.2) | .317 |
| IBD type | | | .213 |
| CD | 89 (43.0) | 101 (51.5) | |
| UC | 112 (54.1) | 89 (45.4) | |
| IBD-U | 6 (2.9) | 6 (3.1) | |
| Current ostomy | | | .198 |
| No ostomy | 195 (94.2) | 177 (90.3) | |
| Ileostomy | 9 (4.3) | 17 (8.7) | |
| Colostomy | 3 (1.4) | 2 (1.0) | |
| Older-onset IBD | 70 (33.8) | 65 (33.2) | .890 |
| Age at diagnosis, years | | | .730 |
| ≤16 | 4 (1.9) | 5 (2.6) | |
| 17-40 | 72 (34.8) | 74 (37.8) | |
| >40 | 131 (63.3) | 117 (59.7) | |
| Disease location (CD) | | | .193 |
| Ileum | 24 (27.0) | 27 (26.7) | |
| Colon | 21 (23.6) | 14 (13.9) | |
| Ileocolonic | 44 (49.4) | 60 (59.4) | |
| Upper GI involvement (CD) | 6 (6.7) | 5 (5.0) | .598 |
| Disease behavior (CD) | | | .101 |
| Inflammatory | 44 (49.4) | 35 (34.7) | |
| Stricturing | 25 (28.1) | 33 (32.7) | |
| Penetrating | 20 (22.5) | 33 (32.7) | |
| Peri-anal disease (CD) | 22 (24.7) | 24 (23.8) | .878 |
| Disease location (UC/IBD-U) | | | .066 |
| Proctitis | 23 (19.5) | 8 (8.4) | |
| Left-sided colitis | 38 (32.2) | 38 (40.0) | |
| Pancolitis | 57 (48.3) | 49 (51.6) | |
| Median CRP, Mg/L (IQR) | 3.0 (1.2-4.0) | 3.0 (2.0-6.0) | .001 |
| Median FCP, µg/g (IQR) | 82.0 (25.8-233.0) | 141.5 (46.0-414.0) | .007 |
| Elevated FCP (>250 µg/g) | 26 (23.6) | 41 (35.0) | .060 |
| Biochemical disease activity (CRP≥10mg/L and/or ≥250µg/g) | 35 (19.9) | 57 (33.5) | .004 |
| Endoscopic disease activity | 32 (45.7) | 33 (46.5) | .927 |
| Clinical disease activity (HBI>4 or pMS>2) | 29 (14.3) | 55 (29.6) | <.001 |
| Median HBI (IQR) | 2.0 (1.0-3.0) | 3.0 (1.5-5.0) | .001 |
| Median pMS (IQR) | 0.0 (0.0-1.0) | 1.0 (0.0-2.0) | .009 |
| Current IBD therapy | | | |
| No current IBD therapy | 38 (18.4) | 48 (24.4) | .133 |
| Mesalamine | 92 (44.4) | 78 (39.8) | .345 |
| Prednisone or budesonide | 14 (6.8) | 25 (12.8) | .042 |
| Immunomodulator | 40 (19.3) | 39 (19.9) | .885 |
| Biological | 52 (25.1) | 54 (27.6) | .580 |

**Table 1.** Continued.

| | No risk of frailty (n=207) | Risk of frailty (n=196) | p-value |
|---|---|---|---|
| Prior IBD surgery | 70 (33.8) | 86 (43.9) | .038 |

Valid percentages are reported; missing data: educational level, 17; CRP, 81; FCP, 176; biochemical disease activity, 57; endoscopic disease activity, 264; clinical disease activity, 14.
IQR, Interquartile Range; CD, Crohn's disease; UC, Ulcerative Colitis; IBD-U, IBD-Unclassified; CRP, c-reactive protein; FCP, fecal calprotectin; HBI, Harvey-Bradshaw Index; pMS, partial Mayo Score; IBD, inflammatory bowel disease;
High educational level: higher vocational or university.
Only oral IBD therapy was noted.

### Primary outcomes

A total of 136 all-cause hospitalizations occurred during follow-up in 96 patients (23.7%). Out of all hospitalizations, 103 (75.7%) were acute, occurring in 74 patients (18.3%). Forty-one hospitalizations (30.1%) in 28 patients (6.9%) were IBD-related, see supplementary table 3 for details on hospitalization reasons.

Patients at risk of frailty were more often hospitalized during follow-up for all-cause, acute and IBD-related causes (figure 1, figure 2). Risk of frailty was associated with all-cause acute hospitalizations and with IBD-related hospitalizations (figure 1, table 2). Out of patients with 0-1 deficits in geriatric domains, 44 patients (20.7%) were hospitalized, out of patients with moderate (2-3) deficits 37 patients (23.1%) and severe (4-5) deficits 15 patients (46.9%), p=.005. The presence of severe deficits at baseline was independently associated with all-cause hospitalizations (adjusted HR 3.273, 95% CI 1.636-6.550, p=.001, supplementary table 7). Deficits in geriatric domains were also associated with acute and IBD-related hospitalizations (supplementary table 7).

No evidence against the proportional hazard's assumption was found. The internally validated C-index of the prediction model for all-cause hospitalization was 0.653, indicating good discriminatory ability.

**Table 2.** Risk of frailty and its association with all-cause hospitalization during follow-up, univariable and multivariable analyses.

| | HR | 95%CI | p-value | aHR | 95%CI | p-value |
|---|---|---|---|---|---|---|
| **All-cause hospitalization** | | | | | | |
| Risk of frailty | 1.860 | 1.227-2.820 | .003 | 1.530 | .959-2.441 | .074 |
| Age at baseline | 1.006 | .966-1.047 | .784 | .967 | .925-1.011 | .140 |
| Biochemical disease activity | 2.482 | 1.616-3.812 | <.001 | 2.090 | 1.336-3.272 | .001 |
| Comorbidity | 1.340 | 1.174-1.529 | <.001 | 1.274 | 1.103-1.471 | .001 |
| **Acute hospitalization** | | | | | | |
| Risk of frailty | 2.859 | 1.722-4.746 | <.001 | 2.213 | 1.266-3.869 | .005 |
| Age at baseline | 1.020 | .976-1.066 | .386 | .983 | .937-1.030 | .469 |
| Biochemical disease activity | 2.765 | 1.710-4.471 | <.001 | 2.122 | 1.287-3.500 | .003 |
| Comorbidity | 1.451 | 1.259-1.673 | <.001 | 1.309 | 1.121-1.529 | .001 |
| **IBD-related hospitalization** | | | | | | |
| Risk of frailty | 4.069 | 1.650-10.036 | .002 | | | |
| Age at baseline | 1.040 | .972-1.113 | .253 | | | |
| Biochemical disease activity | 3.379 | 1.608-7.102 | .001 | | | |
| Comorbidity | 1.263 | 1.010-1.578 | .040 | | | |

Cox regression analyses. Analyses were performed as complete case analyses; 344 patients were included in multivariable analyses all-cause hospitalizations (n=169 at risk of frailty, n=85 all-cause hospitalization), 345 patients in acute hospitalization multivariable analyses (n=170 at risk of frailty, n=67 acute hospitalization). No multivariable analyses was performed for IBD-related hospitalization due to small number of outcomes. Frailty screening by Geriatric 8 Questionnaire, ≤14 points=risk of frailty. Biochemical disease activity: C-reactive protein ≥10 mg/L and/or fecal calprotectin ≥250 µg/g. Comorbidity measured by Charlson Comorbidity Index, continuous.



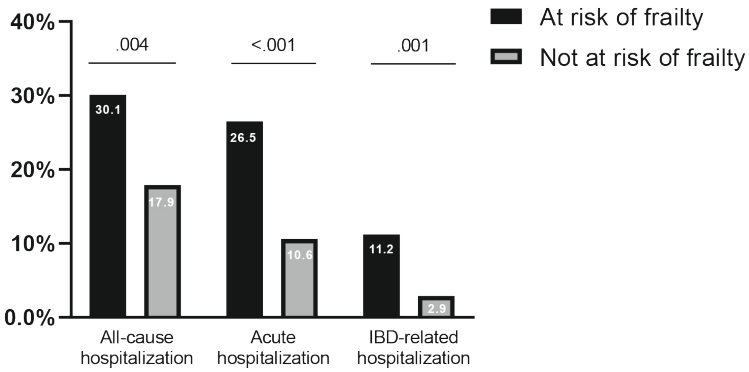



**Figure 1.** Hospitalizations during 18 months follow-up in older patients with Inflammatory Bowel Disease by frailty screening

Percentage of patients hospitalized during 18 months of follow-up. Frailty screening was performed using Geriatric 8 questionnaire. IBD; Inflammatory Bowel Diseases

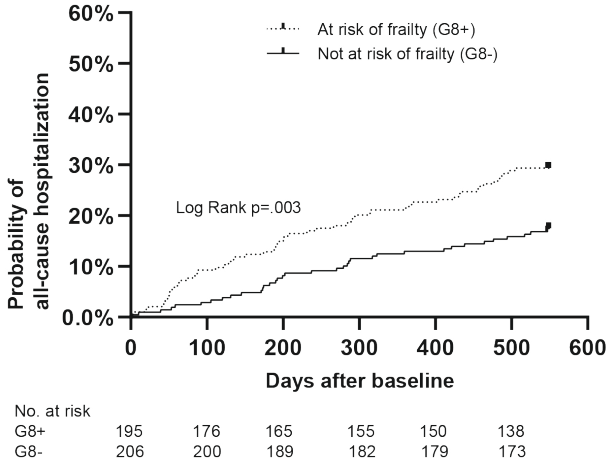



**Figure 2.** Probability of all-cause hospitalization according to frailty screening in older patients with Inflammatory Bowel Disease.
Kaplan Meier figure is displayed, frailty screening was performed using Geriatric 8 questionnaire

### Secondary outcomes

During follow-up 86 patients (21.2%) had any infection, out of which 13 (15.1%) needed hospitalization, see supplementary table 4 for details on infections. Patients screened at risk of frailty did not have a higher infection rate (24.0% versus 18.4%, p=.167). However, the rate of infections needing hospitalization was higher in patients at risk of frailty (11 patients (5.6%) versus 2 patients (1.0%), p=.008). Patients with moderate or severe deficits in geriatric domains did not have higher infection rates as compared to patients without deficits (without deficits: 20.2%, moderate deficits 22.5%, severe deficits 21.8%, overall p-value .860). Rate of infections needing hospitalization was numerically but not statistically significantly higher in patients with moderate (4.3%) and severe (6.3%) deficits, as compared to patients without deficits (1.9%, overall p-value .238).

Frailty screening (table 3) and geriatric deficits (data not shown) did not associate with any infection during follow-up. Patients using biological therapy at baseline (N=107 patients, 26.4%) had a higher risk of any infection during follow-up (table 3). Fifteen patients were diagnosed with a malignancy during follow-up, out of which eight had abnormal frailty screening at baseline (supplementary table 5).

**Table 3.** Risk of frailty and its association with any infection during follow-up, univariable and multivariable analyses

| | OR | 95%CI | p-value | aOR | 95%CI | p-value |
|---|---|---|---|---|---|---|
| Risk of frailty | 1.403 | .867-2.269 | .168 | 1.532 | .890-2.638 | .123 |
| Age at baseline | .963 | .915-1.014 | .154 | .964 | .911-1.019 | .197 |
| Biochemical disease activity | 1.013 | .574-1.789 | .964 | .884 | .478-1.636 | .696 |
| Comorbidity | 1.016 | .853-1.212 | .855 | .936 | .764-1.147 | .523 |
| Oral corticosteroid use | 1.524 | .726-3.202 | .266 | 1.331 | .606-2.923 | .477 |
| Immunomodulator use | .810 | .436-1.504 | .505 | .662 | .341-1.285 | .223 |
| Biological therapy | 2.354 | 1.422-3.897 | .001 | 2.174 | 1.256-3.764 | .006 |

Logistic regression analyses. Analyses were performed as complete case analyses; 346 patients were included in multivariable analyses (n=170 risk of frailty, n=76 any infection). Frailty screening by Geriatric 8 Questionnaire, ≤14 points=risk of frailty. Biochemical disease activity: C-reactive protein ≥10 mg/L and/or fecal calprotectin ≥250 µg/g. Comorbidity measured by Charlson Comorbidity Index , continuous.

### Tertiary outcomes

At follow-up contact, we assessed decline in QoL and functional status (table 4). QoL was measured by EQ5D-3L in 353 patients at both baseline and follow-up, 108 out of 353 patients (30.6%) experienced decline in QoL. Risk of frailty was independently associated with decline in QoL (adjusted OR 2.141, 95% CI 1.266-3.620, p=.005). HRQoL was measured by SIBDQ in 348 patients at both baseline and follow-up, a decline in SIBDQ score was experienced in 135 patients (39.0%). Risk of frailty was not associated with decline in HRQoL.

Decline in functional status was measured by ADL and IADL. ADL was available for 351 patients at both baseline and follow-up, 43 patients (12.3%) had a decline in ADL during follow-up, risk of frailty did not associate with decline in ADL after correcting for confounders. IADL was available for 347 patients at both baseline and follow-up, 46 patients (13.3%) experienced a decline in IADL. Risk of frailty was independently associated with decline in IADL (adjusted OR 3.636, 95% CI 1.653-7.995, p=.001). Deficits in geriatric assessment did not associate with patient reported outcome measures (data not shown).

**Table 4.** Risk of frailty and its association with patient reported outcome measures during follow-up, univariable and multivariable analyses.

| | OR | 95%CI | p-value | aOR | 95%CI | p-value |
|---|---|---|---|---|---|---|
| **Decline in QOL** | | | | | | |
| Risk of frailty | 2.546 | 1.597-4.058 | .000 | 2.141 | 1.266-3.620 | .005 |
| Age at baseline | 1.065 | 1.017-1.116 | .008 | 1.044 | .992-1.100 | .101 |
| Biochemical disease activity | 1.359 | .787-2.347 | .271 | 1.092 | .610-1.953 | .768 |
| Comorbidity | 1.155 | .977-1.365 | .091 | 1.035 | .856-1.251 | .722 |
| **Decline in HRQOL** | | | | | | |
| Risk of frailty | 1.293 | .838-1.996 | .245 | 1.531 | .932-2.515 | .092 |
| Age at baseline | .964 | .919-1.010 | .122 | .949 | .901-1.001 | .053 |
| Biochemical disease activity | .655 | .379-1.133 | .130 | .655 | .368-1.167 | .151 |
| Comorbidity | .895 | .755-1.062 | .205 | .902 | .7450-1.094 | .295 |
| **Decline in ADL** | | | | | | |
| Risk of frailty | 1.963 | 1.023-3.767 | .042 | 1.837 | .897-3.763 | .096 |
| Age at baseline | 1.007 | .943-1.075 | .836 | .988 | .920-1.062 | .751 |
| Biochemical disease activity | .847 | .383-1.875 | .682 | .751 | .328-1.719 | .498 |
| Comorbidity | 1.110 | .882-1.398 | .374 | 1.036 | .803-1.336 | .787 |
| **Decline in IADL** | | | | | | |
| Risk of frailty | 4.362 | 2.128-8.941 | .000 | 3.636 | 1.653-7.995 | .001 |
| Age at baseline | 1.077 | 1.015-1.142 | .014 | 1.037 | .971-1.107 | .281 |
| Biochemical disease activity | 1.898 | .941-3.830 | .073 | 1.437 | .675-3.061 | .347 |
| Comorbidity | 1.094 | .873-1.371 | .437 | .921 | .714-1.188 | .525 |

Frailty screening by Geriatric 8 Questionnaire, ≤14 points=risk of frailty. Biochemical disease activity: C-reactive protein ≥10 mg/L and/or fecal calprotectin ≥250 µg/g. Comorbidity measured by Charlson Comorbidity Index, continuous. QoL=Quality of Life; measured with EQ5D-3L. HRQoL=Health Related Quality of Life; measured with Short Inflammatory Bowel Disease Questionnaire. Functional decline measured with Katz Index of Independence in Activities of Daily Living (ADL) and the Lawton Instrumental Activities of Daily Living (IADL), 20 A decline in ADL or IADL score of ≥1 was considered a decline.
Logistic regression analyses were performed as complete case analyses. QoL; 298 patients included in analyses (n=140 risk of frailty, n=94 decline in QoL), HRQoL; 296 patients included in analyses (n=140 risk of frailty, n=119 decline in HRQoL), ADL; 297 patients included in analyses (n=139 risk of frailty, n=39 decline in ADL), IADL; 292 patients included in analyses (n=137 risk of frailty, n=39 decline in IADL).

## DISCUSSION

In the present study we found that frailty, measured by both frailty screening and geriatric assessment, independently associates with hospitalizations over time in older patients with IBD. Second, frailty screening associated with a higher risk of decline in QoL and functional status over time.

The number of older patients with IBD is increasing due to both a rising prevalence and a rising incidence.[31 32] In other research fields (such as rheumatology and hepatology) frailty, a state of increased vulnerability,[6 33] it has been proven that frailty can successfully function

as risk stratification in treatment of older patients.[34-36] Also in the IBD research field, the population of older patients is gaining attention and several papers have called for action or described possible mechanisms interplaying between IBD and frailty.[3 37-39] Recently, a number of studies were published on the association between frailty and outcomes in patients with IBD. These studies provided evidence on the association between frailty and mortality[9 40], readmission[9], and infections in patients treated with immunosuppression[10]. A paper by Singh et al. researched the association between frailty and serious infections in biologic-treated patients, but did not find an independent association.[41] In these papers frailty was retrospectively measured ICD codes or applying hospital frailty risk scoring systems in administrative databases.

In the present study we researched the association between prospectively assessed frailty and negative health outcomes in older patients with IBD. An independent association was found between frailty and hospitalization over time. Risk of frailty associated independently with acute hospitalizations, however not with all-cause hospitalizations. This can be explained due to the fact that hospitalizations due to semi-planned surgeries were included in all-cause hospitalizations. These semi-planned hospitalizations are more related to comorbidity then to frailty.

Frailty did not associate with infections during follow-up, although patients at risk of frailty had more serious infections. In the above-mentioned study performed by Singh et al.[41] in anti-TNF and vedolizumab treated patients with IBD of all ages the authors also found a higher rate of serious infections in frail patients, however after adjusting for confounders this risk was no longer significant.

Next, we researched decline in (HR)QoL and functional status during follow-up. Risk of frailty was independently associated with a decline in both QoL and functional status. In other studies concerning older patients at the emergency department[42] or in oncology[43] this association has already been established. In older patients, outcomes regarding functional status and quality of life could be more important than established IBD-related outcomes such as mucosal healing.[44]

Important strengths of this study are its prospective nature and the inclusion of both referral and general hospitals. Furthermore, we used valid and robust measurements for frailty, namely a validated frailty screening tool and a geriatric assessment. . Last, we included outcomes which are important in an older patient population such as functional status and quality of life.[3 45] However, there are also some limitations. First, it could be that our results are subjected to ascertainment bias as frail patients, patients with (biochemical) disease activity or patients treated with biologicals will have more contacts with their physician or scheduled hospital visits and therefore, more outcomes are noted in the electronical medical record. To limit the chance of bias, we not only checked the electronical medical record for outcomes but also planned follow-up contacts via phone or during regular hospital visits.

Second, biochemical disease activity and endoscopic disease activity were not measured for study purposes. Therefore, these baseline data are not complete. However, by choosing to do so, we created a low barrier for patients to participate and were able to create a large cohort of older patients with IBD

Future studies should focus on developing a prediction model which could identify patients at risk for hospitalization or decline in (HR)QoL and functional status. A prediction model with the current data predicting all-cause hospitalization including frailty screening, biochemical disease activity and comorbidity as predictors yielded a C-index of .653. The size of the current cohort and lack of a validation cohort made the development of a fully clinically applicable model less reasonable in our study.

Other research should focus on assessing frailty at multiple time points and investigating the relationship between frailty and biochemical disease activity. A study by Lai et al.[46] in patients with liver cirrhosis found that worsening of frailty was significantly associated with death and delisting of transplantation list, whereas patients with improvements in frailty had a lower risk of death or delisting. Besides, as frailty consists of modifiable elements such as nutritional status, depression and physical status, studies could focus on ameliorating frailty status, for example prior to start of medical treatment. This concept is already being researched in surgery, for example prior to esophagogastric cancer resection[47] or colorectal surgery.[48] Another option could be to select different therapy strategies in frail patients as compared to fit older patients with IBD to minimize negative health outcomes. In our study, we found that frailty screening associated with negative health outcomes, independent of biochemical disease activity, thereby suggesting that that optimizing frailty status could be as useful as treating IBD.

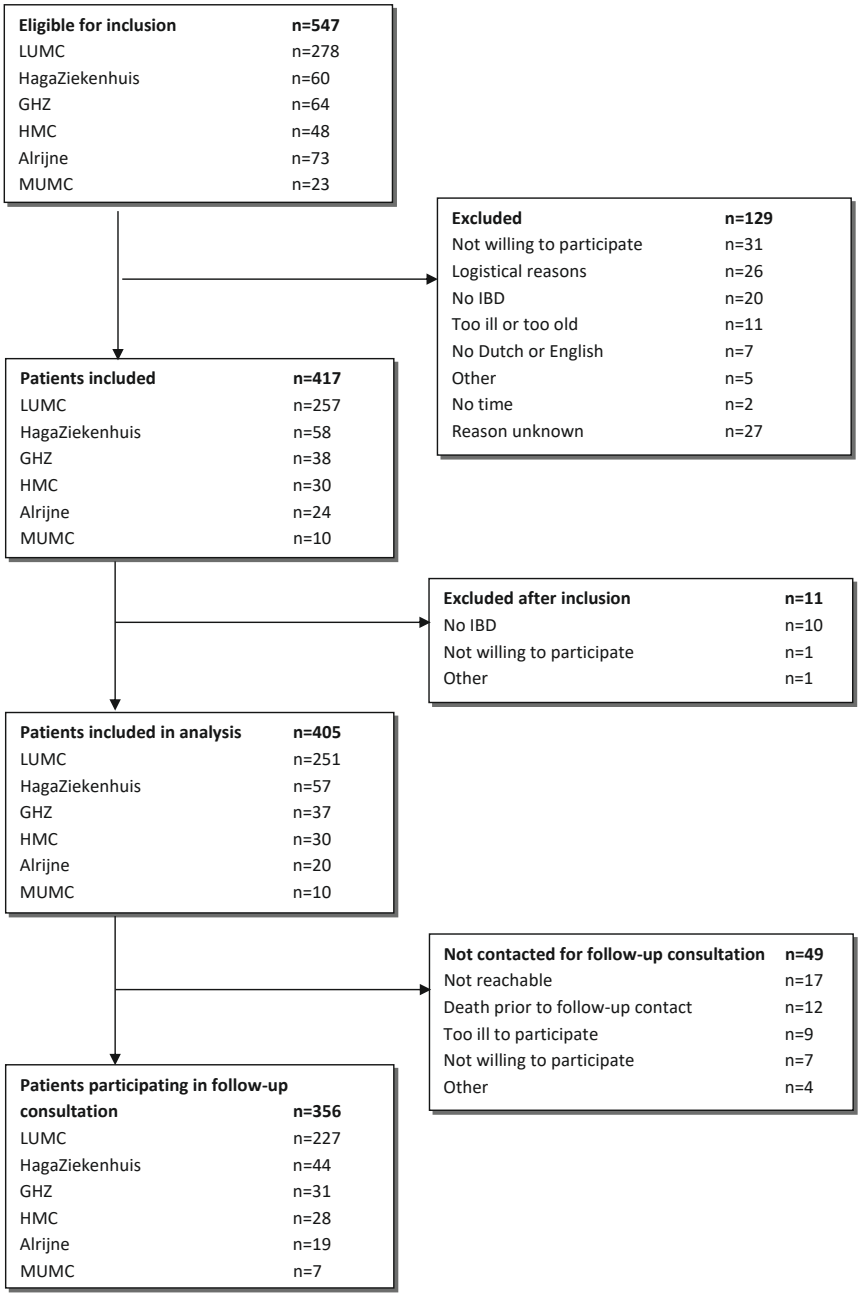
In conclusion, the findings of this paper emphasize the importance of assessing frailty in older patients with IBD. Patients with frailty are at higher risk for both hospitalization and decline in QoL and functional status. Future studies should focus on implementation of frailty in routine care and the effectiveness of interventions to improve outcomes in older patients with frailty.

## REFERENCES


1. Coward S, Clement F, Benchimol EI, et al. Past and Future Burden of Inflammatory Bowel Diseases Based on Modeling of Population-Based Data. *Gastroenterology* 2019;156(5):1345-53 e4. doi: 10.1053/j.gastro.2019.01.002 [published Online First: 2019/01/15]
2. Sturm A, Maaser C, Mendall M, et al. European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly. *J Crohns Colitis* 2017;11(3):263-73. doi: 10.1093/ecco-jcc/jjw188 [published Online First: 2016/11/01]
3. Asscher VER, Lee-Kong FVY, Kort ED, et al. Systematic review: components of a comprehensive geriatric assessment in inflammatory bowel disease - a potentially promising but often neglected risk stratification. *J Crohns Colitis* 2019 doi: 10.1093/ecco-jcc/jjz082 [published Online First: 2019/04/20]
4. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017;9:CD006211. doi: 10.1002/14651858.CD006211.pub3 [published Online First: 2017/09/13]
5. Mohile SG, Mohamed MR, Xu H, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. *Lancet* 2021;398(10314):1894-904. doi: 10.1016/S0140-6736(21)01789-X [published Online First: 2021/11/07]
6. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56(3):M146-56. doi: 10.1093/gerona/56.3.m146 [published Online First: 2001/03/17]
7. Bellera CA, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 2012;23(8):2166-72. doi: 10.1093/annonc/mdr587 [published Online First: 2012/01/18]
8. Asscher V, ; Waars, S,; van der Meulen-de Jong, A. . Deficits in Geriatric Assessment Associate With Disease Activity and Burden in Older Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2021;S1542-3565(21)00643-1 doi: 10.1016/j.cgh.2021.06.015
9. 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 doi: 10.1016/j.cgh.2020.08.010 [published Online First: 2020/08/18]
10. Kochar B, Cai W, Cagan A, et al. Pre-treatment Frailty Is Independently Associated With Increased Risk of Infections After Immunosuppression in Patients with Inflammatory Bowel Diseases. *Gastroenterology* 2020 doi: 10.1053/j.gastro.2020.02.032 [published Online First: 2020/02/28]
11. Kochar B, Jylhävä J, Söderling J, et al. Prevalence and Implications of Frailty in Older Adults with Incident Inflammatory Bowel Diseases: a Nationwide Cohort Study. *Clin Gastroenterol Hepatol* 2022 doi: 10.1016/j.cgh.2022.01.001 [published Online First: 2022/01/10]
12. https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_cohort.pdf. *Accessed January 9, 2020*
13. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55(6):749-53. doi: 10.1136/gut.2005.082909 [published Online First: 2006/05/16]
14. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;1(8167):514. doi: 10.1016/s0140-6736(80)92767-1 [published Online First: 1980/03/08]
15. Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008;14(12):1660-6. doi: 10.1002/ibd.20520 [published Online First: 2008/07/16]

16. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. [published Online First: 1987/01/01]
17. Wang J, Nakamura TI, Tuskey AG, et al. Polypharmacy is a risk factor for disease flare in adult patients with ulcerative colitis: a retrospective cohort study. *Intest Res* 2019 doi: 10.5217/ir.2019.00050 [published Online First: 2019/10/12]
18. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;56(6):M366-72. doi: 10.1093/gerona/56.6.m366 [published Online First: 2001/05/31]
19. Katz S, Ford AB, Moskowitz RW, et al. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. *JAMA* 1963;185:914-9. doi: 10.1001/jama.1963.03060120024016 [published Online First: 1963/09/21]
20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-86. [published Online First: 1969/01/01]
21. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011;40(4):423-9. doi: 10.1093/ageing/afr051 [published Online First: 2011/06/01]
22. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging* 2009;13(10):881-9. [published Online First: 2009/11/20]
23. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *Int J Geriatr Psychiatry* 1999;14(10):858-65. [published Online First: 1999/10/16]
24. Tuijl JP, Scholte EM, de Craen AJ, et al. Screening for cognitive impairment in older general hospital patients: comparison of the Six-Item Cognitive Impairment Test with the Mini-Mental State Examination. *Int J Geriatr Psychiatry* 2012;27(7):755-62. doi: 10.1002/gps.2776 [published Online First: 2011/09/16]
25. Sherman SM, Cheng YP, Fingerman KL, et al. Social support, stress and the aging brain. *Soc Cogn Affect Neurosci* 2016;11(7):1050-8. doi: 10.1093/scan/nsv071 [published Online First: 2015/06/11]
26. Hoogendijk EO, Smit AP, van Dam C, et al. Frailty Combined with Loneliness or Social Isolation: An Elevated Risk for Mortality in Later Life. *J Am Geriatr Soc* 2020 doi: 10.1111/jgs.16716 [published Online First: 2020/07/24]
27. Cavusoglu C, Deniz O, Tuna Dogrul R, et al. Validity and reliability of the G8 screening test in older non-cancer patients. *Eur Geriatr Med* 2020 doi: 10.1007/s41999-020-00404-0 [published Online First: 2020/10/02]
28. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol* 1996;91(8):1571-8. [published Online First: 1996/08/01]
29. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37(1):53-72. doi: 10.1016/0168-8510(96)00822-6 [published Online First: 1996/06/06]
30. Lamers LM, Stalmeier PF, McDonnell J, et al. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *Ned Tijdschr Geneeskd* 2005;149(28):1574-8. [published Online First: 2005/07/26]
31. Katz S, Pardi DS. Inflammatory bowel disease of the elderly: frequently asked questions (FAQs). *Am J Gastroenterol* 2011;106(11):1889-97. doi: 10.1038/ajg.2011.271 [published Online First: 2011/08/25]
32. Jeuring SF, van den Heuvel TR, Zeegers MP, et al. Epidemiology and Long-term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age-An Increasing Distinct Entity? *Inflamm Bowel Dis* 2016;22(6):1425-34. doi: 10.1097/MIB.0000000000000738 [published Online First: 2016/03/05]

33. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381(9868):752-62. doi: 10.1016/S0140-6736(12)62167-9 [published Online First: 2013/02/12]
34. Li G, Chen M, Li X, et al. Frailty and risk of osteoporotic fractures in patients with rheumatoid arthritis: Data from the Ontario Best Practices Research Initiative. *Bone* 2019;127:129-34. doi: 10.1016/j.bone.2019.06.006 [published Online First: 2019/06/12]
35. Sinclair M, Poltavskiy E, Dodge JL, et al. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. *World J Gastroenterol* 2017;23(5):899-905. doi: 10.3748/wjg.v23.i5.899 [published Online First: 2017/02/23]
36. Lai JC, Rahimi RS, Verna EC, et al. Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multicenter Study. *Gastroenterology* 2019;156(6):1675-82. doi: 10.1053/j.gastro.2019.01.028 [published Online First: 2019/01/23]
37. Singh S, Picardo S, Seow CH. Management of Inflammatory Bowel Diseases in Special Populations: Obese, Old or Obstetric. *Clin Gastroenterol Hepatol* 2019 doi: 10.1016/j.cgh.2019.11.009 [published Online First: 2019/11/13]
38. Lovatt J, Selinger CP. Letter: recognising frailty in patients with inflammatory bowel disease is crucial for appropriate personalised treatment. *Aliment Pharmacol Ther* 2020;52(5):908-09. doi: 10.1111/apt.15995 [published Online First: 2020/08/28]
39. Tran V, Limketkai BN, Sauk JS. IBD in the Elderly: Management Challenges and Therapeutic Considerations. *Curr Gastroenterol Rep* 2019;21(11):60. doi: 10.1007/s11894-019-0720-7 [published Online First: 2019/11/30]
40. 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 doi: 10.1111/apt.15821 [published Online First: 2020/06/17]
41. Singh S, Heien HC, Sangaralingham L, et al. Frailty and Risk of Serious Infections in Biologic-treated Patients With Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2020 doi: 10.1093/ibd/izaa327 [published Online First: 2020/12/17]
42. van Dam CS, Hoogendijk EO, Mooijaart SP, et al. A narrative review of frailty assessment in older patients at the emergency department. *Eur J Emerg Med* 2021;28(4):266-76. doi: 10.1097/mej.0000000000000811 [published Online First: 2021/04/23]
43. Jespersen E, Winther SB, Minet LR, et al. Frailty screening for predicting rapid functional decline, rapid progressive disease, and shorter overall survival in older patients with gastrointestinal cancer receiving palliative chemotherapy - a prospective, clinical study. *J Geriatr Oncol* 2021;12(4):578-84. doi: 10.1016/j.jgo.2020.10.007 [published Online First: 2021/04/09]
44. S. Waars VA, A. Pieterse, A. van der Meulen-de Jong, S. Mooijaart, J. Maljaars. P702 Treatment decisions in older inflammatory bowel disease patients: Applying gut feeling in an evidence-based era? A qualitative study. ECCO 2020. Vienna, 2020.
45. Kochar B, Kalasapudi L, Ufere NN, et al. Systematic Review of Inclusion and Analysis of Older Adults in Randomized Controlled Trials of Medications Used to Treat Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2021 doi: 10.1093/ibd/izab052 [published Online First: 2021/03/12]
46. Lai JC, Dodge JL, Kappus MR, et al. Changes in frailty are associated with waitlist mortality in patients with cirrhosis. *J Hepatol* 2020 doi: 10.1016/j.jhep.2020.03.029 [published Online First: 2020/04/03]
47. Minnella EM, Awasthi R, Loiselle SE, et al. Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. *JAMA Surg* 2018;153(12):1081-89. doi: 10.1001/jamasurg.2018.1645 [published Online First: 2018/09/08]
48. Gillis C, Buhler K, Bresee L, et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. *Gastroenterology* 2018;155(2):391-410.e4. doi: 10.1053/j.gastro.2018.05.012 [published Online First: 2018/05/12]




**Supplementary figure 1.** Flowchart patient inclusion.
Logistical reasons are researcher- or hospital-related logistical reasons such as no consulting room available or due to different hospital locations. No time means patient had no time; too ill or too old means patient thinks he or she is too ill or too old to participate. GHZ, Groene Hart Ziekenhuis; HMC, Haaglanden Medical Centre; LUMC, Leiden University Medical Centre; MUMC, Maastricht University Medical Centre.

**Supplementary table 1.** Deficits in geriatric domains at baseline in older patients with inflammatory bowel diseases.

| **Impaired in somatic domain** | **N (%)** | **209 (51.6)** |
|---|---|---|
| Comorbidity | N (%) | 56 (13.8) |
| Polypharmacy | N (%) | 163 (40.2) |
| Nutritional status | | |
| -at risk of malnutrition | N (%) | 73 (18.1) |
| -malnutrition | N (%) | 8 (2.0) |
| **Impaired in activities of daily living** | **N (%)** | **174 (43.0)** |
| Impaired in ADL | N (%) | 121 (29.9) |
| Impaired in IADL | N (%) | 94 (23.2) |
| **Impaired in physical capacity** | **N (%)** | **92 (22.7)** |
| Low handgrip strength | N (%) | 77 (19.9) |
| Low gait speed | N (%) | 24 (6.0) |
| **Impaired in mental domain** | **N (%)** | **67 (16.5)** |
| Cognitive impairment | N (%) | 41 (10.1) |
| Depressive symptoms | N (%) | 35 (8.7) |
| **Impaired in social domain** | **N (%)** | **96 (23.7)** |
| No life-partner | N (%) | 96 (23.7) |

Comorbidity defined by Charlson Comorbidity Index ≥3; Polypharmacy defined as ≥5 non-IBD medications; Nutritional status defined as 'at risk of malnutrition' (Mini Nutritional Assessment (MNA) 8-11) or 'malnutrition' MNA≤7; Impaired in Activities of Daily Living (ADL) defined as ADL ≥1; Impaired in Instrumental Activities of Daily Living (IADL) ≥1, corrected for sex. Low handgrip strength corrected for sex and body mass index (Fried criteria); Low gait speed in m/s corrected for sex and height (Fried criteria). Cognitive impairment defined as 6-Cognitive Impairment Test ≥8; Depressive symptoms defined as Geriatric Depression Scale-15 ≥6;

Valid percentages are reported: missing data: nutritional status 2; handgrip strength: 18; gait speed 7; cognition 1, depressive symptoms 1; partner: 3.

**Supplementary table 2.** Baseline characteristics by number of geriatric deficits

| | No deficits in geriatric assessment (0-1) (n=213) | Moderate deficits in geriatric assessment (2-3)(n=160) | Severe deficits in geriatric assessment (4-5) (n=32) | P-value |
|---|---|---|---|---|
| Median age at baseline, years (IQR) | 69.0 (67.0-72.0) | 71.0 (68.0-75.0) | 72.5 (70.3-79.8) | <.001 |
| Sex (female) | 82 (38.5) | 81 (50.6) | 25 (78.1) | <.001 |
| Educational level (high) | 75 (36.1) | 45 (29.6) | 1 (3.6) | .002 |
| Current smoker | 20 (9.4) | 11 (8.8) | 5 (15.6) | .435 |
| IBD Type | | | | .029 |
| CD | 85 (39.9) | 86 (53.8) | 20 (62.5) | |
| UC | 121 (56.8) | 69 (43.1) | 12 (37.5) | |
| IBD-U | 7 (3.3) | 5 (3.1) | 0 (0.0) | |
| Current ostomy | | | | .132 |
| No ostomy | 200 (93.9) | 148 (92.5) | 26 (81.3) | |
| Ileostomy | 11 (5.2) | 10 (6.3%) | 5 (15.6) | |
| Colostomy | 2 (0.9) | 2 (1.3) | 1 (3.1) | |
| Older-onset IBD | 64 (30.0) | 58 (36.3) | 14 (43.8) | .213 |
| Age at diagnosis, years | | | | .908 |
| ≤16 | 5 (2.3) | 3 (1.9) | 1 (3.1) | |
| 17-40 | 79 (37.1) | 58 (36.3) | 10 (31.3) | |
| >40 | 129 (60.6) | 99 (61.9) | 21 (65.5) | |
| Disease location (CD) | | | | .623 |
| Ileum | 23 (27.1) | 25 (29.1) | 3 (15.0) | |
| Colon | 18 (21.2) | 13 (15.1) | 4 (20.0) | |
| Ileocolonic | 44 (51.8) | 48 (55.8) | 13 (65.0) | |
| Upper GI involvement (CD) | 6 (7.1) | 4 (4.7) | 1 (5.0) | .818 |
| Disease behaviour (CD) | | | | .718 |
| Inflammatory | 39 (45.9) | 32 (37.2) | 8 (40.0) | |
| Stricturing | 24 (28.2) | 30 (34.9) | 5 (25.0) | |
| Penetrating | 22 (25.9) | 24 (27.9) | 7 (35.0) | |
| Peri-anal disease (CD) | 24 (28.2) | 19 (22.1) | 3 (15.0) | .432 |

**Supplementary table 2.** Continued.

| | No deficits in geriatric assessment (0-1) (n=213) | Moderate deficits in geriatric assessment (2-3)(n=160) | Severe deficits in geriatric assessment (4-5) (n=32) | P-value |
|---|---|---|---|---|
| Disease location (UC/IBD-U) | | | | .281 |
| Proctitis | 19 (14.8) | 10 (13.5) | 2 (16.7) | |
| Left-sided colitis | 40 (31.3) | 29 (39.2) | 7 (58.3) | |
| Pancolitis | 69 (53.9) | 35 (47.3) | 3 (25.0) | |
| Median CRP, mg/L (IQR) | 3.0 (1.7-4.0) | 3.0 (2.0-6.0) | 3.0 (2.0-9.6) | .027 |
| Median FCP, µg/g (IQR) | 82.0 (26.3-187.5) | 172 (51.0-484.0) | 108 (32.0-244.0) | .004 |
| Elevated FCP (≥250 µg/g) | 23 (21.3) | 41 (40.2) | 4 (21.2) | .007 |
| Biochemical disease activity (CRP≥10 mg/L and/or FCP≥250 µg/g) | 31 (17.1) | 52 (37.7) | 10 (34.5) | <.001 |
| Endoscopic disease activity | 35 (46.7) | 24 (42.9) | 6 (60.0) | .627 |
| Clinical disease activity (HBI>4 or pMS>2) | 31 (14.9) | 43 (27.7) | 11 (39.9) | .001 |
| Median HBI (IQR) | 2.0 (1.0-3.0) | 3.0 (2.0-5.0) | 3.0 (2.0-7.0) | .003 |
| Median pMS (IQR) | 0.0 (0.0-1.0) | 1.0 (0.0-2.0) | 1.0 (0.0-2.5) | .010 |
| Current IBD therapy | | | | |
| No current IBD therapy | 38 (17.8) | 40 (25.0) | 8 (25.0) | .216 |
| Mesalamine | 101 (47.4) | 58 (36.3) | 11 (34.4) | .066 |
| Prednisone or budesonide | 14 (6.6) | 19 (11.9) | 6 (18.8) | .036 |
| Immunomodulator | 36 (16.9) | 38 (23.8) | 7 (21.9) | .263 |
| Biological | 50 (23.5) | 51 (31.9) | 6 (18.8) | .113 |
| Prior IBD-related surgery | 77 (36.2) | 63 (39.4) | 16 (50.0) | .317 |

No deficits: 0-1 deficits in geriatric assessment, moderate deficits: 2-3 deficits in geriatric assessment, severe deficits: 4-5 deficits in geriatric assessment. Valid percentages are reported; missing data: educational level, 17; CRP, 81; FCP, 176; biochemical disease activity, 57; endoscopic disease activity, 264; clinical disease activity, 14.

IQR, Interquartile Range; CD, Crohn's disease; UC, Ulcerative Colitis; IBD-U, IBD-Unclassified; CRP, c-reactive protein; FCP, fecal calprotectin; HBI, Harvey-Bradshaw Index; pMS, partial Mayo Score; IBD, inflammatory bowel disease;

High educational level: higher vocational or university.

Only oral IBD therapy was noted.

**Supplementary table 3.** Full list of reasons for hospitalization and their classification

| ID | Reason for hospital admission | All-cause | Acute | IBD-related |
|---|---|---|---|---|
| 97 | Anemia | 1 | 1 | 0 |
| 44 | Anemia due to Crohn's disease activity | 1 | 1 | 1 |
| 55 | Pneumothorax | 1 | 1 | 0 |
| | Persistent pneumothorax | 1 | 1 | 0 |
| 58 | IBD exacerbation | 1 | 1 | 1 |
| | Progressive disease | 1 | 1 | 1 |
| | Progressive disease | 1 | 1 | 1 |
| 74 | Pleural fluid | 1 | 1 | 0 |
| 77 | Dislocation of proximal interphalangeal joint needing surgery | 1 | 1 | 0 |
| 79 | Surgery M. Dupuytren | 1 | 0 | 0 |
| 83 | Phacoemulsification with intraocular lens | 1 | 0 | 0 |
| | Phacoemulsification with intraocular lens | 1 | 0 | 0 |
| 1 | Aneurysm a. femoralis superficialis needing stent | 1 | 1 | 0 |
| 2 | Transient Ischemic Attack | 1 | 1 | 0 |
| 3 | Inguinal herniation needing surgery | 1 | 0 | 0 |
| 6 | Urinary tract infection | 1 | 1 | 0 |
| | Urinary tract infection | 1 | 1 | 0 |
| 8 | Influenza-A | 1 | 1 | 0 |
| | Cataract needing surgery | 1 | 0 | 0 |
| 12 | Subdural hematoma after trauma | 1 | 1 | 0 |
| 13 | Hospital admission abroad; anamnestic ' thick feet needing diuretics' | 1 | 1 | 0 |
| 17 | Fistula needing seton | 1 | 1 | 1 |
| 19 | Cardiology admission for placing constant loop recorder | 1 | 0 | 0 |
| | Placing pacemaker | 1 | 0 | 0 |
| 23 | Hernia cicatricalis needing surgery | 1 | 0 | 0 |
| 34 | Instable angina pectoris | 1 | 1 | 0 |
| | Hernia inguinalis needing surgery | 1 | 0 | 0 |
| 36 | Terminal ileitis due to Crohn's disease needing surgery | 1 | 1 | 1 |
| 38 | Carcinoma of prostate needing surgery | 1 | 0 | 0 |
| 46 | Urothelial carcinoma needing resection | 1 | 1 | 0 |
| 50 | Prothesis of the knee | 1 | 0 | 0 |
| 52 | Prothesis of the knee | 1 | 0 | 0 |
| 103 | Coronary artery bypass graft surgery | 1 | 1 | 0 |
| 104 | Transuretral resection of the prostate | 1 | 0 | 0 |
| 105 | Pulmonary embolism | 1 | 1 | 0 |
| 107 | Cerebrovascular accident | 1 | 1 | 0 |
| 113 | Asthma | 1 | 1 | 0 |
| 116 | Urosepsis | 1 | 1 | 0 |
| 125 | Infection needing antibiotics | 1 | 1 | 0 |
| 128 | Pneumonia | 1 | 1 | 0 |
| 129 | Admission after infliximab infusion with hyponatraemia, hypertension. | 1 | 1 | 1 |
| 131 | Colectomy due to therapy resistant colitis | 1 | 1 | 1 |
| 134 | Diverticulitis | 1 | 1 | 0 |
| 138 | Occlusion of aortic prosthesis | 1 | 1 | 0 |
| 144 | Bypass surgery (femoro-popliteal) | 1 | 0 | 0 |

**Supplementary table 3.** Continued.

| ID | Reason for hospital admission | All-cause | Acute | IBD-related |
|---|---|---|---|---|
| 158 | Cholecystectomy | 1 | 0 | 0 |
| 159 | Hypertensive crisis | 1 | 1 | 0 |
| 163 | Bleeding ostomy | 1 | 1 | 1 |
| 169 | Dehydration due to gastroenteritis | 1 | 1 | 0 |
| 178 | Urosepsis | 1 | 1 | 0 |
| 182 | Suspicion of sigmoid volvulus | 1 | 1 | 0 |
| 183 | Incision and drainage of fistula | 1 | 1 | 1 |
| 192 | Ileus | 1 | 1 | 1 |
| | Ileus | 1 | 1 | 1 |
| 194 | Exacerbation IBD | 1 | 1 | 1 |
| 195 | Ileocecal resection | 1 | 1 | 1 |
| 203 | Surgery for polyposis nasi | 1 | 0 | 0 |
| 207 | Exacerbation IBD | 1 | 1 | 1 |
| | Exacerbation IBD | 1 | 1 | 1 |
| | Exacerbation IBD | 1 | 1 | 1 |
| | Resection jejunum due to stenosis | 1 | 1 | 1 |
| 224 | Pneumonia | 1 | 1 | 0 |
| | Exacerbation IBD | 1 | 1 | 1 |
| 225 | Exacerbation COPD with fever needing antibiotics | 1 | 1 | 0 |
| | Acute kidney failure | 1 | 1 | 0 |
| 228 | Viral infection (not specified) | 1 | 1 | 0 |
| 231 | Ileocecal resection | 1 | 1 | 1 |
| 232 | Cholangitis | 1 | 1 | 0 |
| | Cholangitis | 1 | 1 | 0 |
| | Cholangitis | 1 | 1 | 0 |
| | Cholangitis | 1 | 1 | 0 |
| 235 | Attempted suicide | 1 | 1 | 0 |
| | Abscess near appendix needing drainage and antibiotic treatment | 1 | 1 | 1 |
| 250 | Colectomy with ileo-rectal anastomosis due to colorectal carcinoma | 1 | 1 | 1 |
| 257 | Exacerbation IBD needing ileum resection | 1 | 1 | 1 |
| | Exacerbation | 1 | 1 | 1 |
| 261 | Pneumonia | 1 | 1 | 0 |
| 263 | Collapse | 1 | 1 | 0 |
| 264 | Admission due to psychiatric cause | 1 | 1 | 0 |
| 270 | Acute hearing loss | 1 | 1 | 0 |
| 272 | Rectal blood loss due to rectal ulcers | 1 | 1 | 1 |
| 273 | Cardioversion | 1 | 0 | 0 |
| | Cardioversion | 1 | 0 | 0 |
| | Cardioversion | 1 | 0 | 0 |
| 275 | Nephrolithiasis | 1 | 1 | 0 |
| 277 | Ileocecal resection | 1 | 1 | 1 |
| | Suspected anastomotic leakage needing resection | 1 | 1 | 1 |
| 292 | Palpitations | 1 | 1 | 0 |
| 306 | Laparoscopic removal adnex | 1 | 0 | 0 |
| 309 | Ileus | 1 | 1 | 1 |

**Supplementary table 3.** Continued.

| ID | Reason for hospital admission | All-cause | Acute | IBD-related |
|---|---|---|---|---|
| | Exacerbation COPD | 1 | 1 | 0 |
| 310 | Exacerbation colitis | 1 | 1 | 1 |
| | Guillain-Barre possibly due to azathioprine | 1 | 1 | 1 |
| 312 | Benign prostate hypertrophy needing surgery | 1 | 0 | 0 |
| 315 | Atrioventricular block | 1 | 1 | 0 |
| 316 | Infected endovascular aortic prothesis due to fistula | 1 | 1 | 1 |
| 325 | Lumbar stenosis needing surgery | 1 | 0 | 0 |
| 329 | Bleeding ulcer | 1 | 1 | 0 |
| | Cardiac ablation | 1 | 1 | 0 |
| | Lower gastrointestinal tract bleeding | 1 | 1 | 0 |
| 340 | Stenosis needing ileocecal resection | 1 | 1 | 1 |
| 342 | Cerebrovascular accident | 1 | 1 | 0 |
| | Decline in general condition | 1 | 1 | 0 |
| 344 | Cerebrovascular accident | 1 | 1 | 0 |
| 346 | Exacerbation IBD | 1 | 1 | 1 |
| 353 | Nissen fundoplication | 1 | 0 | 0 |
| | Pericarditis | 1 | 1 | 0 |
| | Chest pain | 1 | 1 | 0 |
| 355 | Palpitations | 1 | 1 | 0 |
| | Coronary angiogram | 1 | 0 | 0 |
| 358 | Inguinal hernia needing surgery | 1 | 0 | 0 |
| 359 | Cholangitis | 1 | 1 | 0 |
| | Cataract needing surgery | 1 | 0 | 0 |
| 361 | Fascia dehiscence after surgery | 1 | 1 | 1 |
| | Abscess near hepatic flexure | 1 | 1 | 1 |
| | Symptomatic cholecystolithiasis | 1 | 1 | 0 |
| | Exacerbation IBD | 1 | 1 | 1 |
| | Enterocutaneous fistula | 1 | 1 | 1 |
| 363 | Resection of rectum and placing ileostomy | 1 | 1 | 1 |
| 365 | Exacerbation IBD | 1 | 1 | 1 |
| | Exacerbation IBD | 1 | 1 | 1 |
| 367 | Cataract needing surgery | 1 | 0 | 0 |
| 368 | Varicose vein surgery | 1 | 0 | 0 |
| | Knee prothesis | 1 | 0 | 0 |
| 371 | Rectal blood loss ( ulcerations due to platelet inhibitor use) | 1 | 1 | 0 |
| 375 | Cerebrovascular accident | 1 | 1 | 0 |
| | Atrium fibrillation | 1 | 1 | 0 |
| 376 | Cerebrovascular accident | 1 | 1 | 0 |
| 381 | Inguinal hernia | 1 | 0 | 0 |
| | Prostate carcinoma needing surgery | 1 | 0 | 0 |
| 383 | Kidney stone removal | 1 | 0 | 0 |
| 388 | Progressive anemia | 1 | 1 | 0 |
| 391 | Drainage of fistula | 1 | 1 | 1 |
| 394 | Coronary angiogram | 1 | 0 | 0 |
| 405 | Adrenal crisis | 1 | 1 | 0 |
| | Urinary tract infection | 1 | 1 | 0 |

**Supplementary table 4.** Full list of infections (any infection and infection needing hospital admission

| ID | Infection type | Any infection | Infection needing hospital admission |
|---|---|---|---|
| 90 | Pneumonia | 1 | 0 |
| 93 | COVID-19 | 1 | 0 |
| 46 | Pneumonia | 1 | 0 |
| 53 | Pneumonia | 1 | 0 |
| 59 | Undefined infection needing antibiotics | 1 | 0 |
| 64 | Urinary tract infection | 1 | 0 |
| 65 | COVID-19 | 1 | 0 |
| 4 | Gastritis, H. Pylori | 1 | 0 |
| 6 | Urinary tract infection | 1 | 1 |
| | Urinary tract infection | 1 | 1 |
| | Gastritis, H. Pylori | 1 | 0 |
| 7 | COVID-19 | 1 | 0 |
| 8 | Influenza-A | 1 | 1 |
| 11 | COVID-19 | 1 | 0 |
| 100 | Mandibular infection | 1 | 0 |
| 108 | Herpes zoster | 1 | 0 |
| 111 | Urinary tract infection | 1 | 0 |
| | Bronchitis | 1 | 0 |
| 114 | Pneumonia | 1 | 0 |
| 116 | Urosepsis | 1 | 1 |
| 119 | Pneumonia | 1 | 0 |
| 125 | Infection needing antibiotics | 1 | 1 |
| 127 | Pneumonia | 1 | 0 |
| 128 | Pneumonia | 1 | 1 |
| 133 | Urinary tract infection | 1 | 0 |
| 134 | Urinary tract infection | 1 | 0 |
| 139 | Pneumonia | 1 | 0 |
| | Pneumonia | 1 | 0 |
| 140 | Clostridium difficile | 1 | 0 |
| 143 | Pneumonia | 1 | 0 |
| 146 | Urinary tract infection | 1 | 0 |
| 147 | Bilateral pneumonia | 1 | 0 |
| 148 | Lower respiratory tract infection | 1 | 0 |
| | Lower respiratory tract infection | 1 | 0 |
| 152 | Campylobacter enteritis | 1 | 0 |
| 156 | Urinary tract infection | 1 | 0 |
| | Pneumonia | 1 | 0 |
| 159 | H. Pylori infection | 1 | 0 |
| 160 | Viral infection (not specified) | 1 | 0 |
| 163 | Candida infection | 1 | 0 |
| 164 | Pneumonia | 1 | 0 |
| 165 | Viral infection (not specified) | 1 | 0 |
| 169 | Dehydration due to gastroenteritis | 1 | 1 |
| 171 | Herpes simplex | 1 | 0 |
| 178 | Urosepsis | 1 | 1 |
| 179 | Epididymitis | 1 | 0 |

**Supplementary table 4.** Continued.

| ID | Infection type | Any infection | Infection needing hospital admission |
|---|---|---|---|
| | Pneumonia | 1 | 0 |
| | Mandibular infection | 1 | 0 |
| 188 | Erysipelas | 1 | 0 |
| 195 | Infection of the skin | 1 | 0 |
| | Infection of the skin | 1 | 0 |
| 197 | Viral infection (not specified) | 1 | 0 |
| 199 | Pneumonia | 1 | 0 |
| 200 | Herpes zoster | 1 | 0 |
| | Erythema migrans | 1 | 0 |
| 206 | Viral infection (not specified) | 1 | 0 |
| 208 | Viral infection (not specified) | 1 | 0 |
| 209 | Conjunctivitis | 1 | 0 |
| 210 | Bacterial infection (not specified) | 1 | 0 |
| 211 | Viral infection (not specified) | 1 | 0 |
| 213 | Herpes zoster | 1 | 0 |
| 219 | Blepharitis | 1 | 0 |
| 224 | Pneumonia | 1 | 1 |
| | Campylobacter infection | 1 | 0 |
| 225 | Urinary tract infection | 1 | 0 |
| | Exacerbation COPD with fever needing antibiotics | 1 | 1 |
| 226 | Upper respiratory tract infection | 1 | 0 |
| 227 | Upper respiratory tract infection | 1 | 0 |
| 228 | Viral infection (not specified) | 1 | 1 |
| 234 | Viral infection (not specified) | 1 | 0 |
| 236 | Viral infection (not specified) | 1 | 0 |
| | Viral infection (not specified) | 1 | 0 |
| 238 | Viral infection (not specified) | 1 | 0 |
| 256 | Mandibular infection | 1 | 0 |
| 257 | Bacterial infection | 1 | 0 |
| 261 | Pneumonia | 1 | 1 |
| 280 | Urinary tract infection | 1 | 0 |
| 292 | Campylobacter infection | 1 | 0 |
| 294 | Urinary tract infection | 1 | 0 |
| | Pneumonia | 1 | 0 |
| 304 | Pneumonia | 1 | 0 |
| 312 | Upper respiratory tract infection | 1 | 0 |
| 327 | Pneumonia | 1 | 0 |
| 329 | Wound infection | 1 | 0 |
| 331 | Bacterial infection | 1 | 0 |
| 340 | Viral infection | 1 | 0 |
| 342 | Viral infection | 1 | 0 |
| 353 | Pericarditis | 1 | 1 |
| | Rotavirus | 1 | 0 |
| 362 | Gastroenteritis | 1 | 0 |
| | Upper respiratory tract infection | 1 | 0 |
| | Pneumonia | 1 | 0 |

**Supplementary table 4.** Continued.

| ID | Infection type | Any infection | Infection needing hospital admission |
|---|---|---|---|
| 364 | Skin infection | 1 | 0 |
| | Infection | 1 | 0 |
| | Skin infection | 1 | 0 |
| 366 | Viral infection (not specified) | 1 | 0 |
| 372 | Pneumonia | 1 | 0 |
| 373 | Respiratory tract infection | 1 | 0 |
| 374 | Respiratory tract infection | 1 | 0 |
| 375 | Urinary tract infection | 1 | 0 |
| 376 | Pneumonia | 1 | 0 |
| 377 | Urinary tract infection | 1 | 0 |
| | Urinary tract infection | 1 | 0 |
| 388 | Influenza | 1 | 0 |
| 395 | Urinary tract infection | 1 | 0 |
| 405 | Urinary tract infection | 1 | 1 |

**Supplementary table 5.** Full list of malignancies

| ID | Malignancy type |
|---|---|
| 71 | Lung carcinoma |
| 74 | Lung carcinoma with malignant pleural effusion |
| 20 | Oesophageal carcinoma |
| 104 | Adenocarcinoma of the prostate |
| 46 | Urothelial cell carcinoma |
| 147 | Neuroendocrine tumor |
| 174 | Pancreas carcinoma with liver metastasis |
| 177 | Melanoma |
| 195 | Non-melanoma skin cancer |
| 213 | Colorectal carcinoma |
| 311 | Multiple myeloma |
| 250 | Colorectal carcinoma |
| 350 | Lung carcinoma |
| 381 | Adenocarcinoma of the prostate |
| 386 | Lung carcinoma |

**Supplementary table 6.** Mortality causes

| ID | Mortality cause |
|---|---|
| 74 | Lung carcinoma, with malignant pleural effusion |
| 113 | Pulmonary comorbidity |
| 23 | Unknown |
| 20 | Oesophageal carcinoma |
| 106 | Extensive arterial vascular disease |
| 145 | Unknown |
| 190 | Infection, not specified |
| 348 | End stage renal disease |
| 370 | Cholangiocarcinoma |
| 386 | Lung carcinoma |
| 398 | Unknown |

**Supplementary table 7.** Deficits in geriatric domains and its association with hospitalizations during follow-up, univariable and multivariable analyses.

| | HR | 95%CI | p-value | aHR | 95%CI | p-value |
|---|---|---|---|---|---|---|
| **All-cause hospitalization** | | | | | | |
| Deficits in geriatric domains | | | | | | |
| Moderate | 1.177 | .759-1.827 | .467 | 0.977 | 0.603-1.583 | .926 |
| Severe | 3.023 | 1.653-5.529 | <.001 | 3.273 | 1.636-6.550 | .001 |
| Age at baseline | 1.006 | .966-1.047 | .784 | 0.961 | .916-1.008 | .099 |
| Biochemical disease activity | 2.482 | 1.616-3.812 | <.001 | 2.651 | 1.695-4.146 | <.001 |
| **Acute hospitalization** | | | | | | |
| Deficits in geriatric domains | | | | | | |
| Moderate | 1.263 | .761-2.096 | .366 | 1.034 | .596-1.794 | .906 |
| Severe | 3.629 | 1.898-6.939 | <.001 | 3.372 | 1.614-7.047 | .001 |
| Age at baseline | 1.020 | .976-1.066 | .386 | .984 | .936-1.034 | .521 |
| Biochemical disease activity | 2.765 | 1.710-4.471 | <.001 | 2.835 | 1.712-4.694 | <.001 |
| **IBD-related hospitalization** | | | | | | |
| Deficits in geriatric domains | | | | | | |
| Moderate | 2.569 | 1.089-6.060 | .031 | | | |
| Severe | 4.639 | 1.517-14.182 | .007 | | | |
| Age at baseline | 1.040 | .972-1.113 | .253 | | | |
| Biochemical disease activity | 3.0379 | 1.608-7.102 | .001 | | | |

Logistic regression analyses. Analyses were performed as complete case analyses; 346 patients were included in multivariable analyses all-cause hospitalizations (n=138 moderate deficits, n=28 severe deficits, n=85 all-cause hospitalizations), 347 patients in acute hospitalization multivariable analyses (n=138 moderate deficits, n=29 severe deficits, n=67 acute hospitalization). No multivariable analyses were performed for IBD-related hospitalization due to small number of outcomes. Moderate deficits in geriatric domains: 2-3 deficits, severe: 4-5 deficits (reference is no deficits: 0-1 deficits). Biochemical disease activity: C-reactive protein ≥10 mg/L and/or fecal calprotectin ≥250 µg/g.