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

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Inflammatory Bowel Disease in Older Patients

From gut feeling towards evidence-based medicine

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Design and lay-out: Elisa Calamita, persoonlijkproefschrift.nl
Cover: *Sunflowers in stormy weather* by Elisa Calamita
Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint

ISBN: 978-94-6483-095-8

The printing of this thesis was financially supported by: Nederlandse Vereniging voor Gastroenterologie (NVGE), Dr. Falk Pharma Benelux, Galapagos, Takeda and Chipsoft

Inflammatory Bowel Disease in Older Patients
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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 6 juni 2023
klokke 16:15 uur

door

Vera Elisabeth Rosa Asscher
Geboren te Amsterdam
in 1993

Promotor
Prof. Dr. J.E. van Hooft

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Dr. P.W.J. Maljaars
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General introduction and outline

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease, comprising Crohn's disease (CD), ulcerative colitis (UC) and IBD-Unclassified (IBD-U).[1] Circa 87.000 individuals are diagnosed with IBD in the Netherlands.[2] IBD is characterized by a relapsing and remitting inflammation of the intestines and patients often present with disabling symptoms such as abdominal pain, (bloody) diarrhoea and fatigue, reducing quality of life.[1] Diagnosis is based on the presence of symptoms, physical examination, blood tests and endoscopy or additional imaging.[3]

IBD is incurable and treatment consists of two pillars: remission induction and maintenance therapy. During a relapse of disease, remission induction is necessary and mainly attempted to achieve by prescribing corticosteroids. After remission induction is reached, tapering off corticosteroids is essential due to their unfavourable safety profile. During maintenance therapy which is often started directly after or during induction therapy, preserving remission and preventing recurrent disease activity are aimed for. Treatment goals can be divided into clinical remission, biochemical and endoscopic (macroscopic inflammation) remission and mucosal healing (microscopic inflammation).[4]

The first step of medical therapy consists of mesalamine or budesonide (in UC) and budesonide without maintenance therapy (in CD). Second line treatment involves systemic steroids and immunomodulators such as thiopurines or methotrexate. The third line consists of biologicals: anti-TNF therapy such as infliximab or adalimumab, ustekinumab or vedolizumab and the more recently available small molecule tofacitinib.[4-6] In general, preference towards surgical therapy is only given in case of lack of response to medical therapy.[7 8]

OLDER PATIENTS WITH INFLAMMATORY BOWEL DISEASE

The population of older patients with IBD, often defined as aged 65 years or older, is increasing. It is estimated that in the next decade more than one-third of all IBD patients will be older adults.[9] A rising prevalence due to ageing of the general population and a rising incidence of IBD in older adults has been observed. The latter could be due to increased use of diagnostic tools for example in the context of colorectal cancer screening. It also has been speculated that decreased microbial diversity and pathophysiologic alterations including cellular senescence and chronic inflammation in older adults play a role in the increased incidence.[10-13]

Older patients with IBD experience a higher risk of negative health outcomes. A higher frequency of IBD-related hospitalization and a higher risk of developing serious adverse events during treatment, such as infections or lymphoproliferative disorders, and the need

for surgery, as compared to younger patients has been observed.[14] Although guidelines do not advise different treatment strategies in older patients as compared to younger patients, several studies have shown that older patients are being treated differently in daily clinical practice. Diagnosis at an older age is associated with lower use of corticosteroid sparing therapies such as immunomodulators and biologics compared with a younger age.[15 16] Besides, older patients more often receive longer courses of corticosteroid therapy and in higher doses.[15-17] The above mentioned differences in treatment are not necessarily due to a milder disease course in older patients[15] and could be due to patient-related factors such as comorbidity and frailty, which are more often present in older patients. Up until now, it has not been clear which considerations from professionals and patients underlie these differences in therapy choices and if these considerations are supported by any evidence.

COMORBIDITY, GERIATRIC CONDITIONS AND FRAILTY

Healthcare in older patients is often challenging due to the presence of multimorbidity. In over two-third of adults aged 65 years or older, two or more chronic morbidities are present.[18] IBD patients are exposed to an even higher risk of morbidity as compared to non-IBD patients due to the chronically present inflammation and medication used.[19 20] However, in randomized clinical trials researching new medications, patients with IBD with significant comorbidities fail to meet the strict inclusion criteria. Especially regarding treatment with recently introduced biologicals or small molecules, it is unknown what the impact of comorbidities is on treatment outcomes.

A higher age is also associated with the presence of geriatric conditions. Geriatric conditions, such as cognitive impairment or a history of falls, are not automatically related to a specific disease or (co-)morbidity.[21] A comprehensive geriatric assessment is used to assess these conditions. This assessment is defined as a multidisciplinary evaluation in which problems are uncovered and resources and strengths of the patient are defined.[22] It includes a geriatric assessment which explores four different domains, namely the somatic, functional, mental and social domain. The somatic domain includes assessment of (co-)morbidities, polypharmacy and malnutrition. This domain is usually included as a part of routine care. The functional domain includes functional performance, measured by the level of independence in (instrumental) activities of daily living, and level of physical capacity, for example measured by gait speed or handgrip strength. The mental domain includes cognitive performance and depression, the social domain includes the evaluation of the social support network.[22] During a comprehensive geriatric assessment, the findings of this geriatric assessment are evaluated by a multidisciplinary team often led by a geriatrician and among others a specialist elderly care nurse and a physiotherapist. The process of a comprehensive geriatric assessment, which is often closely linked with interventions, has been proven effective in the field of oncology as it predicts cancer treatment tolerance, mortality and enhances quality of life and leads to a reduction in the number of invasive treatments performed.[23-25]

The above-mentioned assessment can be integrated into an overall level of frailty. Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis following a stress. There are many ways of measuring frailty, however, a geriatric assessment is considered to be the gold standard.[26] Because a geriatric assessment is a time consuming effort, patients are often screened for frailty prior to an assessment. Based on findings of this screening, the more detailed assessment can be undertaken.[22]

Thus, the difference between older and younger patients does not primarily lie in the age itself, but rather in heterogeneities concerning comorbidities, geriatric conditions and level of frailty. Because of the presence of these heterogeneities, treating the population of older patients with IBD can be challenging. In other medical fields, research performed in older patients shows an association between the presence of frailty and adverse health outcomes, thereby presenting the use of frailty screening or a comprehensive geriatric assessment as a valuable tool in clinical decision making.[27,28] However, in IBD this is still an unexplored subject.

This thesis therefore has three aims:

I) To research factors contributing to current therapy choices and treatment goals in older patients with IBD accounting for the perspectives of both professionals and patients, and to quantify the current evidence on geriatric assessment and its relation with health outcomes.

II) To study the association between comorbidity, prior to start of medical therapy, and safety and effectiveness outcomes in patients with IBD.

III) To assess the prevalence of frailty in older patients with IBD and its association with health outcomes over time.

THESIS OUTLINE

This thesis starts by evaluating underlying considerations which can contribute to the disparities in treatment of older patients as compared to adult patients with IBD by using qualitative methods, interviewing both professionals and patients. The results are presented in **Chapter 2**. This chapter also explores the relationship between frailty and therapy goals in IBD treatment in current practice. **Chapter 3** quantifies the current evidence on geriatric assessment and its association with adverse health outcomes in IBD patients by performing a systematic literature review. **Chapter 4** describes the association between comorbidities prior to start of anti-TNF therapy and safety and effectiveness outcomes, **Chapter 5** describes the association between comorbidities prior to start of ustekinumab or vedolizumab therapy and safety and effectiveness outcomes, both by using real world data. **Chapter 6** describes the prevalence of deficits in geriatric assessment in a multicentre cohort of older patients with IBD. In addition, this chapter looks into the association between deficits in a geriatric assessment, disease activity and disease burden. **Chapter 7** studies the longitudinal relation between frailty screening, geriatric assessment and hospitalization after 18 months in the same cohort, thereby researching the value of frailty screening as a clinically applicable risk stratification in the treatment of older patients with IBD. Finally, in **Chapter 8** the overall findings of this thesis are summarized, clinical implications are discussed, and future research ideas proposed.

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2

Perspectives on treatment of inflammatory bowel disease in older patients: applying gut feeling in an evidence-based era?

EMJ Gastroenterology 2022

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ABSTRACT

Background The older inflammatory bowel disease (IBD) population is challenging to treat because of heterogeneity in characteristics related to frailty. We aimed to study factors contributing to the difference in treatment between older and younger patients with IBD and the relation between frailty and therapy goals, from the perspective of both professionals and IBD patients.

Methods Semi-structured interviews in 15 IBD professionals and 15 IBD patients aged ≥65 years.

Results Professionals had 1-20 years of experience, three practiced in an academic hospital. Patients were aged 67-94 and had a disease duration between 2-62 years. We found that professionals aim more often for clinical remission and less often for endoscopic remission in older compared to younger patients. Older patients also aim for clinical remission but valued objective confirmation of remission as a reassurance. Professionals sometimes opt for surgery earlier in treatment course, while older patients aimed to prevent surgery. Professionals' opinion on corticosteroids in older patients differed, while patients preferred to avoid corticosteroids. In professionals and patients, there was a shift towards goals related to frailty in patients with frailty. However, professionals did not assess frailty systematically but judged frailty status by applying a clinical view.

Conclusions Many therapy goals differed between older and younger patients, in both professionals and patients. Professionals did not assess frailty systematically, yet aspects of frailty influenced therapy goals. This underlines the need for clinically applicable evidence on frailty in IBD, which could aid tailored treatment.

INTRODUCTION

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and Ulcerative Colitis (UC), are chronic diseases occurring as a relapsing and remitting inflammation of the intestines. Patients experience disabling symptoms such as abdominal pain, diarrhea and fatigue.[1 2] The prevalence and incidence of IBD is increasing, especially in the older patient population.[3 4] IBD treatment is often challenging in older patients as this population is heterogenous in their functional, mental and social capacities, and sometimes live with frailty.[5 6] Moreover, it has been established that older patients with IBD are often undertreated as compared to younger patients.[7] Corticosteroids are only suitable for remission induction and not for maintenance therapy due to their unfavorable safety profile.[8-12] However, longer courses of corticosteroids are prescribed to older patients and step-up towards maintenance therapy such as immunomodulators or biologicals is less frequently initiated.[7 13] This difference in pharmacologic treatment between older and younger patients is not necessarily because of a milder disease course in older patients.[7]

Guidelines do not differ between older patients aged ≥65 years versus younger patients with IBD. The European Crohn's and Colitis Organization (ECCO) advises treating gastroenterologists to assess an individual's frailty when making treatment decisions in older patients.[14] Meanwhile, evidence on prevalence of frailty and the role of frailty in treatment safety and effectiveness in older patients with IBD is scarce.[15-18] It is unclear which patient characteristics are deemed important by professionals and patients in the management of IBD in older patients and which therapy goals are currently being pursued. Furthermore, it is unclear if and how frailty is accounted for in current clinical practice.

We aimed to study factors contributing to the difference in treatment between older and younger patients with IBD and the relation between frailty and therapy goals, from the perspective of both professionals and IBD patients.

MATERIALS AND METHODS

Study design

This was a semi-structured interview study consisting of 34 face-to-face in-depth interviews with professionals and patients. The study is reported following the checklist of the Consolidated criteria for REporting Qualitative research (COREQ)[19] and was conducted in two parts. First, professionals were interviewed between May and July 2019, next older patients with IBD were interviewed between June and October 2020.

Participants

Professionals

Professionals were defined as either gastroenterologists with a focus on IBD or nurses specialized in the treatment of IBD working in the Netherlands. Professionals were approached for inclusion by e-mail. Purposive sampling was applied to ensure a heterogeneous population,[20] and professionals were included based on differences in age, sex, geographical location of practice, nature of hospital of practice (referral vs. general hospital), and possession of a PhD title. Professionals were included after signing informed consent and agreeing to having the interview audio taped. We aimed to include at least 15 professionals (ten gastroenterologists and five IBD nurses).

Patients

Patients were recruited at the Leiden University Medical Center (LUMC), the Netherlands, and were eligible if they had a confirmed clinical, endoscopic and/or histological diagnosis of CD, UC or IBD-Unclassified. Patients were approached for participation using a letter written on behalf of their treating physician. We aimed to include 15 patients aged 65 years or older. We applied purposive sampling by selecting older patients from our cohort study on geriatric assessment in older patients with IBD to ensure a heterogenous population.[21] In this way we could select patients based on information in the electronical medical record such as age, sex, IBD disease history, disease duration, IBD medication and place of living, and also based on frailty, comorbidity and educational level. All patients were included after signing informed consent and agreeing to having the interview audio taped.

In addition, to explore if new themes were generated, we aimed to interview five younger patients aged 18-65 years with IBD.

Data collection and setting

Interviews were conducted face-to-face and consisted of two parts; in part A we conducted a semi-structured interview and in part B the interviewer presented pre-written cards. The interviews with professionals were conducted at their workplace, the interviews with patients were performed at their location of preference (hospital or at their home). A caregiver or family member was allowed to be present during the patient interviews and to participate in the interview. Interviews were conducted by two female master students in medicine who both had completed their clinical rounds (professionals were interviewed by SW, patients by CV). The interviewers did not know the professionals or patients beforehand and the interviewers introduced themselves by providing the above information prior to the interview. Both interviewers conducted three practice interviews. Field notes were made during and after each interview. During interviews with professionals and patients, we performed interim analyses and consultation was performed with members of the research team. No repeat interviews were carried out.

Part A was conducted according to a predefined interview scheme with open ended questions and a list of potential additional questions to create more in-depth responses. The interview scheme was developed by the research team (VA, AP, SP and PM). At the start of the interview the interviewer introduced herself and collected information about the participant's baseline characteristics.

In Part B we presented two sets of cards to the participants. First, the interviewer presented cards with on each one patient characteristic, such as characteristics regarding disease activity and frailty. Professionals and patients were asked to create a hierarchy from most to least important in making treatment decisions in older patients with IBD. The same approach was applied to cards with on each one therapy goal regarding older patients with IBD, such as measures of disease control and preservation of functional status. For both the characteristics and the goals, participants were allowed to place more than one card in the same hierarchy level. Next, we asked professionals if their hierarchy of patient characteristics and/or therapy goals would be different if applied to younger patients. Finally, we asked both professionals and patients if and how impairments regarding each of the six geriatric characteristics would change the hierarchy of the therapy goals. In each interview, we also presented a couple of empty cards to allow participants to add patient characteristics and/or therapy goals to the list.

Additionally, we asked professionals if they were reticent in prescribing certain IBD medications in older patients. Initially, we asked them only an open-ended question regarding this topic. However, after having performed six interviews, we added questions about specific medications because we noted that opinions on these medications (corticosteroids and methotrexate) differed or because we were specifically interested as medication had recently been approved for IBD care (tofacitinib). Further, after having completed the interviews with professionals, we found that there was a difference in therapy goals and treatment strategies considered to be applied to older patients as compared to younger patients. We therefore decided to add a question to the patient interviews by telling the patients about this finding and asking them for their opinion. Moreover, we asked patients about characteristics of frailty. However, after having performed four interviews, we noted that this question was hard to answer and we made it more personal by asking '*Do you think that you are frail at the moment?*', '*Why do you or do you not think you are frail at the moment?'*, and '*What would make you (more/less) frail?'*. Furthermore, we added some additional cards in the interviews with patients: after three practice interviews we added "*worries about family or loved ones"* to the set of cards on patient characteristics, and *"decrease in inflammation in the blood (CRP)"* to the set of cards on therapy goals. After seven interviews we added *"Inflammation in the stool (FCP)"* to the former set of the cards. When no new ideas or themes emerged in three successive interviews we concluded that data saturation had been reached.

Data analyses

All interviews were transcribed verbatim using Amberscript and transcripts were not returned to participants. The data from Part A were analyzed based on the Grounded Theory approach.[22] Two coders coded each interview independently. VA and SW coded the interviews with professionals, VA and CV coded the patient interviews. The two coders frequently met during the coding process to compare codes until consensus was reached. Open coding was performed and a code list was developed inductively, codes were renamed and re-ordered in Excel whenever the coders agreed this was necessary. The code list was used for all subsequent interviews in the same sample of interviewees. In parallel to open coding axial coding took place, in which the coders performed classification of the codes into categories and themes. This categorization was completed and revised whenever necessary during and after the interview rounds. To apply structure to the themes that were found, selective coding was applied and themes were categorized into disease-related (such as IBD symptoms or IBD complications), treatment-related (such as IBD medication or surgery) and geriatric themes, related to daily functioning (such as functional or cognitive status).

The data from Part B were analyzed by listing the hierarchy of cards provided by each participant in a separate Excel file. During the analysis we focused on each participants' top three; most participants included more than one card per hierarchy level. These were analyzed independently by the same two coders as in part A (VA and SW, and VA and CV respectively). During the analysis both coders read the considerations that the participants mentioned while ordering the cards, and listed them per card. To create order and to enhance the ability to recognize patterns between different participants, we categorized the cards and applied colors to each category. In patients, we looked if the presence of geriatric impairments, found during a geriatric assessment, seemed associated with patterns in hierarchy. Participants did not provide feedback on the findings.

Ethical Considerations

The study protocol was declared not subjective to the medical research involving human subjects act by the Medical Research and Ethics Committee (MREC) at the LUMC (Leiden, the Netherlands, protocol number N19.026) and was approved in all participating centers in which professionals had their practice. Written informed consent was obtained from all participants.

RESULTS

Participants

In total, 34 interviews were conducted in 15 professionals, 15 older patients and four younger patients. For the interviews with professionals, we approached 15 gastroenterologists and 10 IBD nurses of which 10 and five respectively participated. Three gastroenterologists did not want to participate due to lack of time, and two gastroenterologists and three

nurses did not respond. Two nurses wanted to participate, but could not be included for logistical reasons. The interviews with professionals lasted between 27 and 51 minutes. Gastroenterologists had a median age of 45 years, ranging from 39 to 61. IBD nurses had a median age of 41 years, ranging from 34 to 54. The years of experience in IBD care in professionals ranged from one to 20 years (table 1).

For the interviews with patients, 20 older patients with IBD were approached, of whom 15 participated. Two older patients were not willing to participate, one patient did not speak Dutch and two patients could not be reached. Eight patient interviews took place at the LUMC, one interview took place over the telephone due to COVID-19 restrictions and the other interviews took place at the patients' home. During three interviews a spouse or child was present. Interviews took between 37 and 69 minutes. Patients had a median age of 74 years, ranging from 67 to 94. Disease duration ranged between 2 and 62 years and patients used different IBD medications at the time of the interview. Four patients had a high comorbidity level as measured by the Charlson Comorbidity Index, 10 patients had two or more impaired geriatric domains in their geriatric assessment and were therefore classified as frail (table 1). Five younger patients with IBD were approached and included. However, one patient withdrew consent due to disease severity.

Professionals

Therapy goals in treatment of older patients with IBD according to professional

We asked professionals what goals they aim for in the treatment of older patients with IBD and if these goals differ from those for younger patients. Some professionals said they aim for the same goals in older versus younger patients with IBD. However, other professionals stated they aim for different therapy goals in older patients with IBD.

Regarding disease-related goals, a number of professionals stated that clinical remission was often more important, whereas endoscopic remission and mucosal healing were reported to be less important in older patients. The prevention of long-term complications was considered to be less important in older patients and some participants tended to treat older IBD patients less aggressively. This was motivated by some professionals' believe that disease course is more indolent in older patients.

> "Free of symptoms, with the least possible amount of immunosuppression, yes that's it. And the presence of biochemical remission or mucosal healing, that really doesn't matter much to me"
> Professional; gastroenterologist (nr. 6)

Table 1. Professionals' and patients' characteristics

Characteristic (professional)	Gastroenterologist (n=10)	IBD nurse (n=5)	Characteristic (patient)	Older patients with IBD (n=15)	Younger adult patients with IBD (n=4)
Sex, female	4	4	Sex, female	6	2
Age†	45 (39-61)	41 (34-54)	Age†	74 (67-94)	30 (25-45)
Years of experience in IBD†	10 (3-20)	6 (1-10)	Educational level (high)	4	1
Practicing in academic medical center	2	1	CCI≥3	4	-
PhD title	7	0	High frailty level (≥2 impaired geriatric domains	10	2*
Contacts with IBD patients in last 2 weeks †Δ	43 (12-160)	80 (40-500)	IBD type, CD	8	2
Contacts with IBD patients aged ≥65 years in last 2 weeks †Δ	6 (1-53)	10 (2-125)	Disease duration†	34 (2-62)	4 (3-12)
			Current IBD medication		
			-None	4	0
			-5-ASA	7	2
			-Corticosteroid	3	0
			-Immunomodulator	2	0
			-Biological	4	3

IBD; Inflammatory Bowel Diseases, PhD; doctor philosophea, highest university degree. †median (range) Δ at outpatient or inpatient department, during telephone consultation or supervision. CD; Crohn's disease, CCI; Charlson Comorbidity Index; 5-ASA; 5-Aminosalicylates *considers itself frail

Second, other treatment-related goals in older patients with IBD were named, than in younger patients. Professionals reported to aim more towards remission with as little immunosuppression as possible in older patients and to prescribe medication with as little adverse events as possible. When remission is achieved, a couple of professionals declared to stop maintenance therapy sooner in older patients. Sometimes, professionals tended towards surgery earlier in the treatment course in older patients as compared to younger patients. One professional mentioned to aim for as little burden for the older patient as possible by reducing hospital visits.

Third, goals related to daily functioning were identified. Professionals put more focus on functioning in daily life, preventing social isolation and immobilisation, and retaining physical activity in older than in younger patients. An overview of therapy goals is depicted in figure 1.

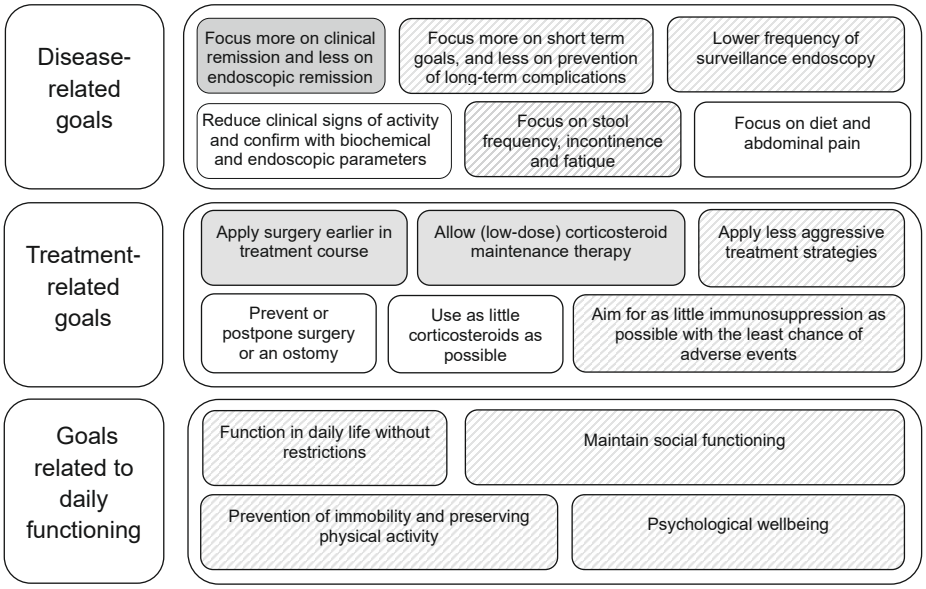

Figure 1. Conceptualisation of therapy goals in the treatment of older patients with inflammatory bowel diseases as compared to younger patients, according to professionals and patients.
Regarding patients' answers; both quality of life goals and therapy goals were incorporated in this figure. Grey: named by professionals; white: named by patients; grey and white shaded: named by both professionals and patients.

All professionals included clinical remission or corticosteroid free remission in their top three therapy goals. More than half of the professionals did not put endoscopic remission in their top three. For younger patients, most of the professionals would rank endoscopic remission higher. Some professionals would rank corticosteroid free remission higher in younger patients versus older patients, other professionals would in contrast rank it lower.

> "Corticosteroid free remission, it depends on the case. In younger patients it would be number one priority, in older patients we will sometimes accept low doses."
> Professional; gastroenterologist (nr. 3)

> "Definitely no [corticosteroid] maintenance therapy. I think that is just not right"
> Professional; gastroenterologist (nr. 8)

When looking at therapy goals related to daily functioning; preservation or restoration of independence and mobility was most often chosen for the top three hierarchy. Next, we asked if and how the presence of geriatric impairments in an older patient, such as impaired functioning in daily life, cognition or independence or the presence of multiple comorbidities, would change their ranking of goals. Clinical remission remained the most important therapy goal in most of the professionals, regardless of geriatric impairments. Professionals said that this is the goal they can influence the most. Some professionals chose to strive more towards preservation or restoration of independence and mobility if those were impaired in patients. One professional said that impairments in mobility or functional status could be a reason to choose an ostomy, as incontinence could be more disabling in those patients. A few professionals said corticosteroid free remission was less important to them in an older patient with geriatric impairments. However, other professionals said to aim for corticosteroid free remission, no matter which impairments were present. Some said they put even more emphasis on corticosteroid free remission when there are multiple comorbidities or an impaired cognition.

Preference in IBD medications in professionals

After asking about patient characteristics and therapy goals, we asked professionals if they were reticent in prescribing certain IBD medications in older patients. The results of this question are displayed in table 2.

Table 2. Reticence in prescribing medication in older patients with inflammatory bowel diseases

Reticence	**IBD-medication**	No reticence
	5-ASA	-Not reticent
-No high doses -Only short courses -No maintenance therapy -High risk of infection -Risk of osteoporosis -High risk of adverse events in patients with diabetes or high blood pressure	**Corticosteroids**	-Good short-term solution -Long term adverse events are less important -Accept low dose maintenance when comorbidities are present -Low dose in best solution in some patients -Low dose maintenance budesonide when history of malignancy is present
-Out of fashion -No MTX in older patients -Only when combining with rheumatoid arthritis treatment -Route of administration -Co-administration of folic acid	**Methotrexate**	-Good option or solution for some patients -Milder adverse events compared to thiopurines -First opt for MTX in older-onset instead of biologicals
-More careful in older patients -Stop earlier in older patients -Start with lower dose in older patients -High risk of lymphoma, malignancy, infections -More alert to adverse events in older patients	**Thiopurines**	-We try thiopurines a lot after corticosteroid induction
-High risk of infections in older patients -More alert to adverse events in older patients -Tend to prescribe biologicals more in younger than in older patients -Logistical challenge due to route of administration	**Biologicals**	
-Reticent with infliximab -High risk of adverse events, malignancy -Reticent in patients with cardiovascular problems -Logistical issues when patient is immobile -Afraid for low medication adherence in adalimumab	**Anti-TNF**	-Monotherapy is safe in older patients -I prescribe standard dose
-The fact that it is relatively new	**Ustekinumab**	-A good option -Safe feeling to prescribe -More often prescribe as first choice

Table 2. Continued.

Reticence	**IBD-medication**	No reticence
	Vedolizumab	-A good option -Rather opt for vedo instead of anti-TNFα or thiopurine -Less systemic infections -Safe feeling to prescribe -More often prescribe as first choice -Prefer vedo in case of history of malignancy -Less severe adverse events compared to uste or tofa
-Careful with new medications in older patients -Risk of opportunistic infections -Risk in patients with history cardiovascular or thromboembolic events -High risk of adverse events -Only when you have no other options -Risk of herpes zoster infection	**Tofacitinib**	-Oral route of administering is an advantage -It is an option in older patients
-More reticent to prescribe in older patients -Higher risk of infections	**Combination therapy**	

Table reflects the answers of professionals (gastroenterologists and IBD nurses) to the question: *Are there IBD medications you would prefer not to prescribe in older patients with IBD, and if so, which and why?* After 6/15 interviews we started asking professionals specifically about corticosteroids, methotrexate and tofacitinib. When no comments were made about reticence or preference in older patients columns were left blank in the table.
5-ASA: 5-aminosalicylates.

Aspects of frailty in older patients with IBD according to professionals

First, we asked professionals if they make a distinction between fit and frail patients in daily clinical practice. Thereafter we elaborated on how this distinction was being made and if this influences choice of treatments or therapy goals. A couple of professionals mentioned paying attention to frailty. The way frail patients were identified varied from applying a clinical view, to estimating biological age or life expectancy. None of the professionals reported to assess frailty in older patients with IBD systematically or to apply validated frailty screening tools. Somatic aspects of frailty were most often mentioned, mainly comorbidity, but also polypharmacy and malnutrition. Furthermore, a lot of professionals acknowledged functional status, such as living in an assisted home facility, and not being able to perform activities of daily living, as an important aspect of frailty. A few professionals stated that therapy goals should be based on the presence of frailty, for example preventing surgery in older patients with frailty. However, others said patients with frailty presenting with a flare-up of IBD should be treated the same as other patients.

> "If a patient has dementia and it's all about maintaining quality of life, and we achieve quality of life with clinical remission, then I won't worry about whether this patient does or doesn't use corticosteroids."
> Professional; gastroenterologist (nr. 1)

> "Therapy goals will be different and they depend on how many aspects of, yes, frailty are present. We don't ask specific questionnaires regarding frailty yet, I think actually we should do it in older patients."
> Professional; gastroenterologist (nr. 3)

Patients

Quality of life and therapy goals according to older patients with IBD

First, we asked patients about factors determining quality of life. Aspects of functional status were mentioned most often: patients considered their ability to function in daily life and mobility to determine their quality of life for a large part. Second, we asked patients about their therapy goals in IBD. Therapy goals were again specified into disease-related goals, treatment-related goals and goals related to daily functioning. An overview of therapy goals is depicted in figure 1. Disease related goals were mostly absence of inflammation, in general or as seen during endoscopy, and decrease of IBD symptoms, of which stool-related symptoms (stool frequency, incontinence and diarrhoea) and abdominal pain were named most often.

> "I mean, he didn't dare to go anywhere, not even to a birthday party. He was just too scared he could not make it to the toilet and would be incontinent in front of his friends. So that is what really made him live a very solitary life."
> Daughter of patient (nr. 8)

Themes identified as treatment-related goals were mostly surgery- and medication-related. Surgery-related goals included preventing or postponing surgery, and preventing an ostomy. The patients who already had an ostomy reported to strive towards good functioning of the ostomy. Medication-related goals were finding the most effective medication with the least possible adverse events, aiming for no medication or as little medication as possible and a treatment without corticosteroids. Themes related to functional status, for example being able to function as normally as possible, were mentioned most often when looking at goals related to daily functioning. Younger patients added therapy goals related to the ability to work and the ability to have a successful pregnancy.

When asked to rank the cards with therapy goals, almost all patients ranked clinical remission in their top three. Patients stated that reducing IBD complaints was important because this leads to less disability, more independence and a better quality of life. Almost all patients also ranked decrease in inflammation assessed by blood or stool test or by endoscopy in their top three. Considerations mentioned here were the fact that a decrease in inflammation as seen by objective markers led to an in increase in general health and a decrease in IBD

complaints. Moreover, patients said that having certainty about the severity of inflammation as measured by objective parameters or the presence of polyps was important to them. A large part of the patients strived towards goals related to daily functioning, such as preservation or restoration of independence, good memory, positive mood and social contacts. Patients selecting those goals as most important were of advanced age, frail and had multiple comorbidities, while patients selecting disease related goals as their top priority were often of lower age, less frail and had little comorbidities. Almost half of the patients put striving towards remission without the use of corticosteroids in their top three therapy goals. Their considerations included negative experiences with corticosteroids in the past and the high risk of adverse events. Younger patients mainly prioritized objective markers of disease, only one younger patient selected 'reducing IBD complaints' in their top three hierarchy. Younger patients who considered themselves frail, more often selected goals related to daily functioning.

Aspects of frailty in IBD according to patients

Almost all older patients had a positive experience with the geriatric assessment performed during our cohort study. One patient said she was feeling fooled when undergoing the cognition questionnaire. Many patients thought a geriatric assessment should be part of standard care. Reasons were first, because it could add to an early detection of geriatric impairments. Second, patients thought it would be helpful to optimize therapy goals. Third, it could help tailor individual care, such as by providing written explanations when cognitive impairment is present.

> "Someone who is physically very weak, and tells a story about what he cannot do anymore, for me, it would be a very big decline, but for someone else it could be a very reasonable way of living. I think this can differ a lot per person."
> Patient (nr. 10)

Suggestions for further extension included repeating the assessment every couple of years to monitor functional decline. Younger patients did not undergo a geriatric assessment, however suggestions were given by them to perform a geriatric assessment not only in older but also in younger patients, as younger patients could also be frail. The aspects of frailty that were identified by IBD patients were for a large part related to functioning in daily life; i.e., to be able to do everything yourself, to be able to walk and move without falling. Also, aspects of comorbidity were often mentioned; having other diseases, having pain in general, or having a hearing impairment. Polypharmacy was named as being an aspect of frailty because medications could lead to adverse events. Impaired mental status, namely depression and anxiety, impaired cognition, but also the inability to cope with negative events, was also supposed to influence frailty in a negative way. The presence of social support and informal caretakers was deemed to affect frailty in a positive way. Being of advanced age was mentioned by a couple of patients. Many patients mentioned their IBD as an aspect of frailty, especially in case of a flare-up, incontinence, or diarrhea, or when they have to pay

attention to what they can and cannot eat. Also, feeling fatigued was mentioned as an aspect of frailty. The two patients who had an ostomy at the time of the interview mentioned their ostomy as an aspect of frailty. Patients mentioning functioning in daily life and being able to do everything yourself were all frail, while patients mentioning IBD-related aspects of frailty were mostly less frail. The interviews in younger patients did not yield new aspects of frailty.

DISCUSSION

Current evidence in IBD is pointing towards different treatment regimens being used in older patients, as compared to younger patients.[7 13] Therefore, we aimed to study factors contributing to the difference in treatment between older and younger patients with IBD and the relation between frailty and therapy goals, from the perspective of both professionals and IBD patients. To our knowledge, this is the first study allowing for perspectives of both professionals and patients and thereby creating a comprehensive conceptualization of the treatment of IBD in an older population.

In both professionals and patients, we noted that therapy goals in older patients differed from those in younger patients. A variation of themes was generated on this topic and is presented in figure 1. First, a lot of professionals mentioned to aim more for clinical remission in older patients as compared to younger patients and put lower priority on endoscopic remission. Although older patients themselves were also focussed on clinical remission, a lot of them valued confirmation of remission by objective markers as a reassurance. Second, we noted a discrepancy regarding surgery. Some professionals stated that they opt for surgery earlier in the treatment course of older patients, while older patients themselves strived towards postponing or preventing surgery and an ostomy. A couple of patients explained that they believed to be too old for surgery and were afraid to become dependent of caretakers or nursing aid after surgery. Third, in professionals, we found diverging opinions on the use of corticosteroids in older patients with IBD. Some stated to allow low dose maintenance therapy in older patients, while others were reluctant to even prescribe them short courses of corticosteroids. These views were in contrast with those of patients, who were quite uniform in preferring to avoid corticosteroids. Patients explained that this was mainly based on their earlier, negative, experiences with corticosteroids. This finding is in line with a study by Asl Baakhtari et al., who investigated factors making IBD patients less willing to take corticosteroids.[23]

Furthermore, we found a lot of considerations in professionals regarding reticence or preferences in prescribing IBD medications in older patients, as depicted in Table 2. Interestingly, little to no reticence with regards to prescribing ustekinumab or vedolizumab in older patients was present. This finding is in agreement with the results from a case-based survey which found that vedolizumab was the preferred first-line agent in the treatment of older patients with steroid dependent moderate-to-severe ulcerative colitis.[24]

Both the above mentioned differences in therapy goals, and the experienced reticence in prescribing IBD medications are factors contributing to the use of different treatment regimens in older versus younger patients.

Some professionals said to account for frailty, but none of the professionals assessed frailty systematically. At the same time, professionals reported that presence of aspects of frailty influences therapy goals and treatment modalities. Professionals said to prioritize functional related goals such as maintaining self-dependence and mobility in older patients with a low level of dependence or impaired cognition. In older patients with aspects of frailty, some professionals put higher priority on corticosteroid free remission and others lower priority as compared to older patients without aspects of frailty. Some said to aim more for the prevention of surgery, while others said that in older patients with frailty, they would opt earlier for an ostomy. The fact that frailty status influenced therapy goals and treatment was in line with considerations provided by patients, as patients with frailty more often gave priority to goals related to frailty, which was also found in younger patients who considered themselves frail. This could suggest that frailty status is more important than age in treatment of IBD.

Both professionals and patients emphasized that clinical remission remained important, independent of non-IBD characteristics. Professionals because this is the goal they can influence the most, and patients because a decrease of complaints automatically leads towards an increase in independence, especially regarding decrease of stool incontinence.

Many different aspects of frailty were identified, thereby illustrating that frailty is a heterogenous concept. It was remarkable to see that a lot of patients mentioned disease related aspects, such as the presence of a flare-up or incontinence. This underlines the importance of IBD symptom control in older and frail patients with IBD. Frailty is a concept best measured by performing validated screening questionnaires[25 26] or a complete geriatric assessment.[6] The lack of implementation of frailty measurements in current daily practice is illustrated by the ways frailty is currently measured. Indeed, current studies on frailty in IBD retrospectively assess frailty using ICD codes and not by clinically applicable measurements.[15 27-29] Therefore, the gap between scientific evidence and daily practice is still present. In older patients who are candidates for intensive treatments such as chemotherapy or major surgery, implementation of a routine clinical care pathway provides the opportunity to study associations between characteristics of frailty and treatment outcomes.[30] In older patients with IBD, applying such standardized frailty screening prior to start therapy could also guide decision making and support individualized treatment.

A couple of qualitative studies on perspectives from patients on IBD treatment have been performed,[31-33] and also in other auto-immune diseases.[34 35] This study is however the first to investigate the opinion of both gastroenterologists and older patients on IBD treatment and the concept of frailty. Involving older patients with multiple conditions or frailty in the decision-making process could be challenging because of the potential for competing

outcomes.[36] Nevertheless, Fried et al. found that it was feasible for older patients to prioritize preferences in health outcomes by asking older patients to rank outcomes on a visual analogue scale.[37] The resulting conceptualization of our study therefore delivers important lines of approach for further research and treatment of older patients with IBD. By using semi-structured interviews, open questions allowed in-depth exploration while use of cards yielded additional information and considerations. A couple of studies have been published on the association between frailty and readmissions, infections and mortality.[27-29] In this study, we explored current modalities of frailty measurements and what both professionals and patients consider to be aspects of frailty.

This study also has some weaknesses. All participating patients were under treatment in an academic hospital and could therefore have a more severe IBD history. However, this was minimized by applying purposive sampling and thereby reaching maximum variation. Besides, both professionals and patients could have given socially acceptable answers during interviews. This response bias was minimized by the fact that the interviews were conducted by medical students who had no prior relation with all participants, and participants were not informed on the questionnaires beforehand.

CONCLUSION

Many therapy goals differed between older and younger patients, in both professionals and patients. Professionals did not assess frailty systematically, yet aspects of frailty influenced therapy goals. We believe that the variation in professionals' therapy goals found in this study reflects the lack of evidence on most effective treatment strategies in this heterogenous population. Our results further underline the need for a systematic assessment of frailty of individual patients and collection of evidence on optimal treatment of frail patients.

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3

Systematic review: components of a comprehensive geriatric assessment in inflammatory bowel disease – a potentially promising but often neglected risk stratification

Journal of Crohn's and Colitis 2019

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ABSTRACT

Background The population of older patients with inflammatory bowel disease (IBD) is increasing. Patient age does not fully account for poor outcomes and its clinical utility for risk stratification is limited. Comprehensive Geriatric Assessment (CGA), comprising a somatic, functional, mental and social assessment or frailty, could be a predictor tool.

Aims To systematically review literature on the kind of components of a CGA being used in adult IBD patients and the association of these components with adverse health outcomes.

Methods An electronic literature search was performed on 16th January 2018 using PubMed, Embase, Web of Science, the Cochrane Library, CENTRAL, Emcare and PsycINFO. Longitudinal studies relating somatic, functional, mental and social assessment or frailty to adverse health outcomes during follow-up in IBD patients were included. The Newcastle-Ottawa scale was used to assess individual study quality.

Results Of 4080 identified citations, 27 studies were included reporting 169 associations. Median sample size was 108 patients (IQR 60-704). No studies performed subgroup analyses on older patients and the highest mean age reported was 52.7 years. Somatic and functional assessments were used in three studies; mental in 24 and social in five. No study assessed cognitive status, functional performance or frailty. In 62 associations (36.7%) components of a CGA were significantly associated with adverse health outcome measurements.

Conclusions Components of a CGA were associated with adverse health outcomes in IBD patients, but older patients were underrepresented. More studies among older patients with IBD are warranted to further establish the clinical impact of a CGA.

INTRODUCTION

The number of older patients with inflammatory bowel disease (IBD) is increasing.[1] This increase can be explained by both a rising prevalence due to the aging of the population and a rising incidence of IBD in older patients,[1 2] but also by greater availability of treatment options.[3] A recent population-based epidemiologic study from the Netherlands reported a doubling of the IBD incidence in older patients, from 11.71 per 100,000 persons in 1991 to 23.66 per 100,000 persons in 2010.[1]

Older patients with IBD are at higher risk of IBD-related hospitalization and surgery than younger patients.[4] They are also at higher risk of developing serious adverse events during IBD treatment such as infections or lymphoproliferative disorders.[4] Older patients show a larger heterogeneity in their somatic, functional, mental and social abilities or frailty compared to younger patients.[5 6] A CGA aims to systematically explore these components of a patients' health.[7] In other medical fields such as oncology and nephrology, research performed in older patients shows a relationship between impairments found during a CGA and adverse health outcomes which could be helpful in clinical decision making.[8 9] In IBD, preliminary baseline results from our cohort study in 135 IBD patients aged ≥65 years, indicated a high prevalence of frailty, measured with the Geriatric 8 questionnaire and impaired physical capacity, measured using handgrip strength.[10] However, how impairments in these components of a CGA may be related to (adverse) health outcomes in IBD patients has not been systematically evaluated.

Therefore, the aim of this systematic review is to study the literature on the different components of a CGA used in adult IBD patients and the association of these components with adverse health outcomes, impaired quality of life (QoL) and functional or cognitive decline after follow-up.

MATERIALS AND METHODS

Search strategy

Our literature search aimed to identify original longitudinal studies in IBD patients in which the association between components of a CGA at baseline and IBD-related adverse health outcomes, non-IBD-related adverse health outcomes, (HR)QoL questionnaires and functional or cognitive decline after follow-up was examined. In our search strategy IBD was defined as Crohn's disease (CD) or ulcerative colitis (UC). If a study included patients with IBD-unclassified (IBD-U) or indeterminate colitis (IC), these results were taken into account as well.[11]

Components of a Comprehensive Geriatric Assessment

The purpose of a CGA is to systematically explore four different domains as a reflection of patients' health namely the somatic, functional, mental and social domains.[7] The somatic domain includes malnutrition by using malnutrition screening tools, taking a medical history, medication use and anthropometrics. This domain is usually included as part of routine care. The functional domain includes functional performance, and can be measured with questionnaires such as (instrumental) activities of daily living ((I)ADL)) as well as physical capacity, measured with tests such as handgrip strength, gait speed or balance, or measured with questionnaires. The mental domain includes both cognitive status (measured with tests such as the Six Item Cognitive Impairment Test (6CIT) or the Mini-Mental State Examination (MMSE)) and depression or anxiety (measured with questionnaires such as the Geriatric Depression Scale (GDS)). The social domain assesses social support and is measured by questionnaires assessing living situation or marital status. The above-mentioned domains are integrated into an assessment of the overall level of frailty. Frailty is a state of increased vulnerability to poor resolution of homeostasis following a stress. Its presence, which can be assessed using frailty indices such as the Groningen Frailty Indicator,[12] increases the risk of adverse outcomes.[8 13]

Outcome parameters

Outcome parameters were categorized in IBD-related adverse health outcomes, non-IBD-related adverse health outcomes, (HR)QoL questionnaires and functional or cognitive decline after follow-up.

The following outcomes were considered IBD-related: An exacerbation or flare-up of disease measured with IBD disease activity scores such as (simplified) Crohn's disease activity index ((S)CDAI), simple clinical colitis activity index (SCCAI), Harvey Bradshaw index (HBI), partial Mayo score (PMS) or modified Truelove and Witts activity index (MTWAI), or with biological parameters such as c-reactive protein, faecal calprotectin, haemoglobin, haematocrit, mean corpuscular volume, leucocytes, platelet count or erythrocyte sedimentation rate or established with endoscopic/radiologic examination. The need to step up medication, use of corticosteroids, the need for IBD-related surgery and the occurrence of IBD-related complications such as strictures, fistulas and extra intestinal manifestations were also considered to be relevant IBD-related outcomes. The (Short) Inflammatory Bowel Disease Questionnaire ((S)IBDQ) was considered to be an IBD-related outcome parameter because of the amount of questions considering IBD symptoms.

The following outcomes were considered to be non-IBD-related adverse health outcomes: Emergency department visits, outpatient department visits, all-cause hospitalization, any surgery or any abdominal surgery, length of any hospital stay and mortality.

Outcome parameters reporting on (HR)QoL, functional decline (using questionnaires such as (I)ADL) or cognitive decline (using measurements or questionnaires such as the six item cognitive impairment test (6CIT)) were also considered relevant outcome measures.

Literature search

On January 16th, 2018 seven online databases (PubMed, Embase, Web of Science, the Cochrane Library, CENTRAL, Emcare and PsycINFO) were searched using synonyms of IBD, combined with synonyms of different components of a CGA. As we surmised that the number of studies addressing components of a CGA in an older IBD population would be low, we included all studies that investigated components of a CGA known to influence adverse health outcomes in older patients in adult patients. After the initial search a second search was performed solely regarding anxiety terms. For full details of the search strategy for PubMed, see supplemental material A. The searches were restricted to articles in Dutch and English. Also, conference and meeting abstracts were excluded. There were no restrictions in publication date.

Study selection

The eligibility of all studies identified by the search was independently evaluated by at least two authors (VA, FLK or EK). For any article that seemed potentially relevant based on the title and abstract, the full text was retrieved and screened. Studies were included when containing original data reporting on an association between any component of a CGA at baseline and an outcome of interest after follow-up in IBD patients in a longitudinal study design. In case of disagreement on the eligibility of studies, consensus was reached after discussion with at least one additional author (FvD, SM or PM). Discussion with additional authors because of disagreement on eligibility took place in 24 out of 4080 studies, which represents a 99.4% agreement on the selection of studies during evaluation of eligibility. Cross-referencing was performed using the reference list of the included publications to ensure all relevant studies were identified.

Data extraction and quality assessment

The following items were extracted from each study: Publication data (author, year and journal), study design, setting, duration of follow-up, patient characteristics (sample size, mean age, disease type, inclusion criteria), type of geriatric assessment (somatic, functional, mental and social assessment or frailty), correction for confounding factors, the outcome and conclusion of the study. To assess the methodological quality and risk of bias of the studies included, we adapted the Newcastle-Ottawa scale to the purpose of this review (supplemental material B).[14] Two authors (VA and FLK) performed data extraction and quality assessment, in case of disagreement a third author was consulted (PM). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist, which is a checklist for evidence-based minimum set of items for reporting in systematic reviews, is available upon request.[15]

Data presentation

Study characteristics are presented in tables per included study. Accumulated descriptive statistics of the included studies are presented by calculating the percentage of studies reporting on associations between components of a CGA with outcomes. The overall

sample size of included studies is expressed as median and interquartile range (IQR). In this review, an "association" implies an investigated, but not necessarily a statistically significant relationship between a component of a CGA and an outcome of interest. The main findings of the included studies regarding the associations of components of a CGA with outcomes of interest are presented in tables. When authors performed an adjustment for potential confounders, these confounders are tabulated per included study and when hazard ratio (HR), odds ratio (OR) or relative risk (RR) were adjusted for confounders, this is reported as an adjusted ratio (aHR, aOR or aRR). When possible, the fully adjusted model was reported.

Supplementary analysis

Because of the low median sample size in the included studies a supplementary analysis was performed. The six studies with the largest sample size were analysed and the association of components of a CGA with outcomes of interest was described.

RESULTS

Search results and study selection

The first database search identified 3296 unique citations (figure 1). After initial screening of title and abstract, 246 studies were potentially eligible and full text was screened. After full-text review, 226 were excluded and the remaining 20 studies were included. A second additional database search identified 784 citations and yielded 5 studies (for flowchart see supplementary figure 1). Cross-referencing yielded two additional relevant studies, which resulted in a total of 27 studies included in this review.

Study characteristics

Table 1 shows an overview of the included studies. The median sample size of all included studies was 108 patients (IQR 60-704). Out of the 27 included studies, 22 (81.5%) were performed in the United States or Europe.[16-37] The majority of the included studies had an observational prospective study design (77.8%).[18 20-24 26-31 33-42] The median follow-up time was 12 months (IQR 10-22.9) and follow-up data were extracted from medical records or insurance data in 38.6% of associations,[16 17 19 25 27 32 42] assessed during hospital visits in 33.1%[18 21 23 24 27 29-31 33 34 36-38] and self-reported in 28.6%.[20 22 25 26 28 35 39-41] Twelve (44.4%) studies included both CD and UC,[16 17 19 20 22 28 32-35 40 41] two of these included IBD-U or IC as well.[33 40] Ten studies included only CD patients,[18 23-27 31 36 38 42] five studies only UC.[21 29 30 37 39] None of the studies were specifically designed for older patients or performed subgroup analyses on older patients.

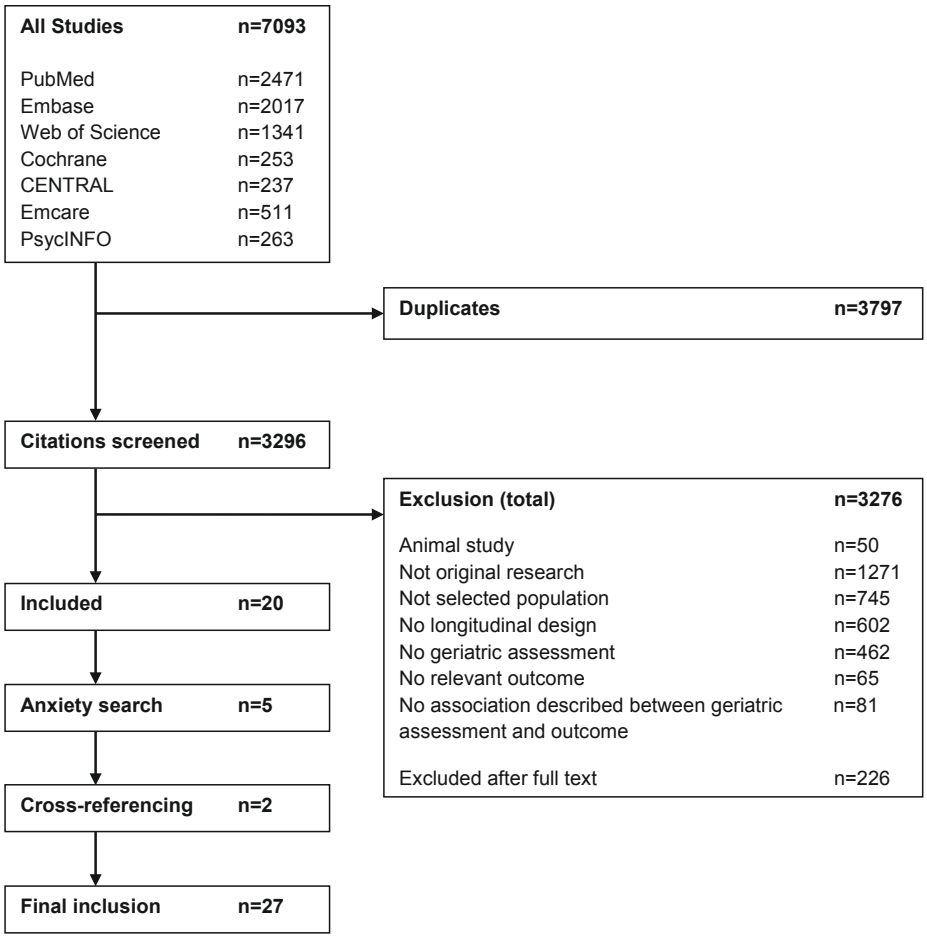

Figure 1. Flowchart

Reported components of a Comprehensive Geriatric Assessment

The included studies reported on a total of 169 associations in which the relationship between a component of a CGA and outcome measurement was investigated. An "association" therefore implies an investigated, but not necessarily a statistically significant relationship. Somatic and functional assessment were measured in 39 associations (23.1%),[27 32 42] mental in 117 associations (69.2%)[16-22 24-26 28-41] and social in 13 associations (7.7%).[16 20 22 23 36] None of the studies used a measurement of functional performance, cognitive status, or frailty (figure 2).

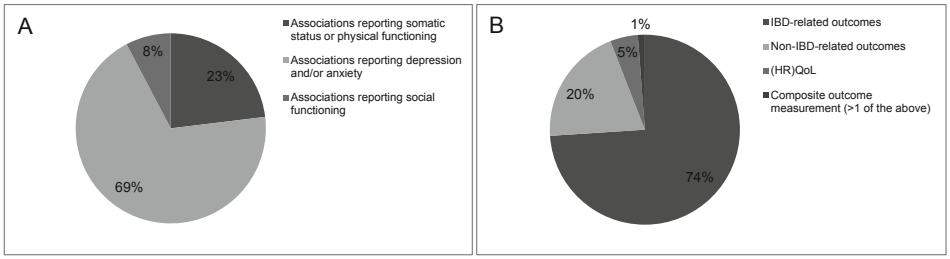

Figure 2. Visual representation of associations described in the included studies. A: percentage of associations described per component of a comprehensive geriatric assessment. No association reported on cognitive impairment, functional decline, or frailty. B: percentage of associations described per adverse health outcome measurement. No association described functional or cognitive decline as an outcome measurement. [HR]QoL, health-related quality of life.

Reported outcomes

IBD-related adverse health outcomes were the main outcome of interest, reported as an outcome measurement in 125 associations (74.0% of all associations)).[17 18 20 21 23-31 33-42] (HR)QoL was used as an outcome measurement in eight associations (4.7%).[18 25] One of the included studies (1.2% of the associations) used a composite outcome measurement comprising (HR)QoL, disease progression and any readmissions or hospitalizations.[25] None of the studies used functional or cognitive decline as an outcome measurement (figure 2).

Association of geriatric impairments and outcomes

Table 2 shows an overview of the investigated associations of components of a CGA with adverse health outcomes. A significant association between a component of a CGA and outcome of interest in which more geriatric impairment leads to worse outcome was presented as '+'. A significant association between a component of a CGA and outcome of interest in which more geriatric impairment leads to better outcome was presented as '-'. A non-significant association was presented as 'ns'. In supplementary table 1 the available association measures are presented. In 62 associations (36.7%) there was a statistically significant association between an impairment in somatic, functional, mental or social assessment and a higher risk of adverse health outcomes (figure 3).[16-19 22-28 31-34 36 42] When the authors performed an adjustment for potential confounders, these confounders are tabulated in supplementary table 2. The detected effect of geriatric impairments on the outcomes of interest is summarized in figure 4.

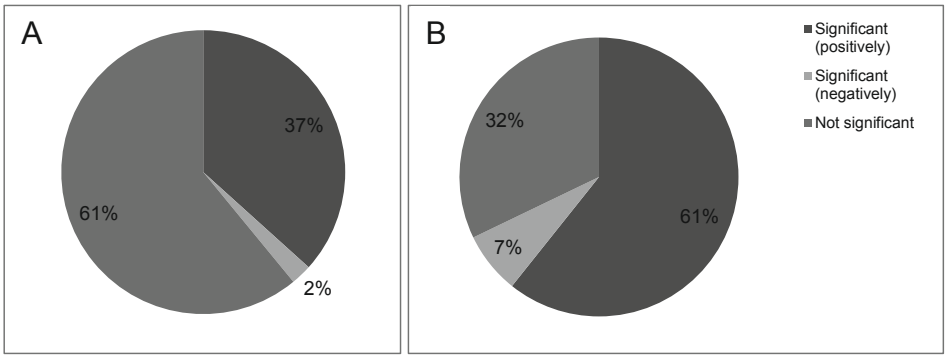

Figure 3. Visual representation of significant associations. Positive significant associations are associations in which more geriatric impairment led to more adverse outcomes, negative significant associations in which more geriatric impairment led to less adverse outcomes. A: percentage of significant associations in associations of all included studies. B: percentage of significant associations in associations of the six largest studies.

Somatic and functional assessment

Somatic and functional assessment was performed in three studies, resulting in 39 associations (23.1% of all associations). Of these, 32 associations reported on malnutrition and seven reported on physical capacity (all handgrip strength). None of the studies reported on functional performance using questionnaires such as ADL or IADL.

The different studies used a variety of screening tools to measure malnutrition. These were the malnutrition universal screening tool,[42] malnutrition inflammation risk tool,[27] subjective global assessment,[27 42] nutrition risk screening 2002,[42] Onodera's prognostic nutritional index,[42] controlling nutritional status,[42] bioelectrical impedance analysis measuring phase angle[27] and malnutrition diagnosis code.[32]

Malnutrition or high risk of malnutrition was highly prevalent in the included studies, with a range between 10.6% and 72.5%. Takaoka et al, using the Onodera's prognostic nutritional index, reported that up to 72.5% of included hospitalized patients were at high risk of malnutrition.[42] Micic et al. analyzed hospital discharges in 55.942 patients and found that, when using ICD-9 malnutrition code, 10.6% of patients were diagnosed with malnutrition.[32] In their study, malnutrition was an independent predictor of 30-day readmission (aOR 1.37, 95% CI 1.22-1.54).[32]

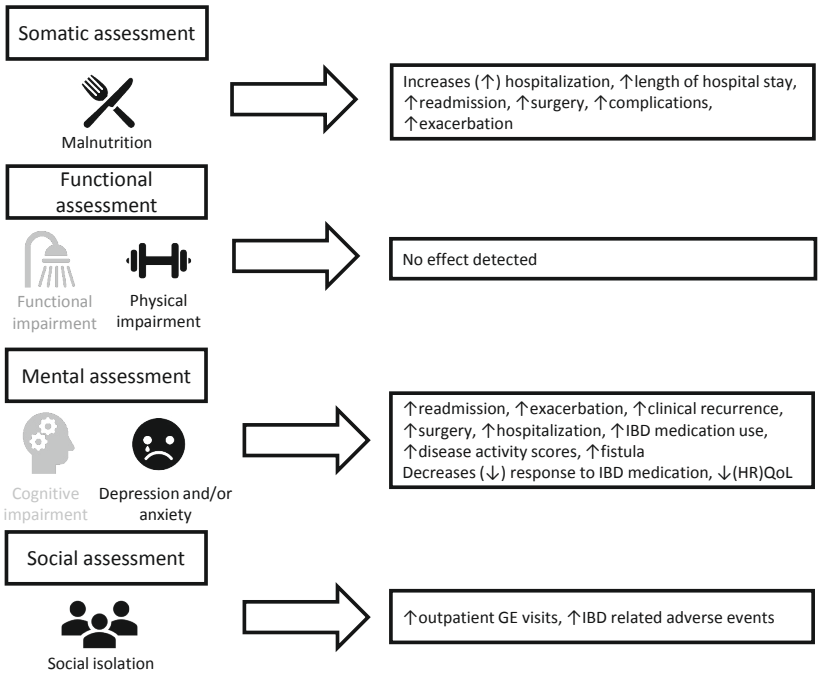

Figure 4. The detected effect of geriatric impairments on adverse health outcomes in inflammatory bowel disease patients. No studies on functional or cognitive impairment were found.

Jansen et al. reported on physical capacity using handgrip strength, resulting in seven associations. A mean handgrip strength at baseline of 38.2 kg (SD 9.9) was reported but no data on the prevalence of impaired handgrip strength were presented.

Handgrip strength did not predict different measures of disease activity, disease-related complications or a composite endpoint in this study.[27] 97.4% of the associations on somatic or physical capacity included only CD patients. Malnutrition or impaired physical capacity was a significant predictor of adverse health outcomes in 10 out of 39 associations (25.6%) (figure 5).

Mental assessment

Mental assessment was evaluated in 24 studies, resulting in 117 associations (69.2% of all associations). Of these, all associations reported on depression and/or anxiety. None of the studies reported on cognitive status.

Depressive and/or anxiety symptoms were mostly measured with the Hospital Anxiety and Depression Scale (HADS), in eight studies (33 associations).[18 24 29 33 36 37 40 41] The presence of a depression diagnosis code, anxiety diagnosis code or a combination of these was used in four studies, resulting in 30 associations.[16 17 19 32]

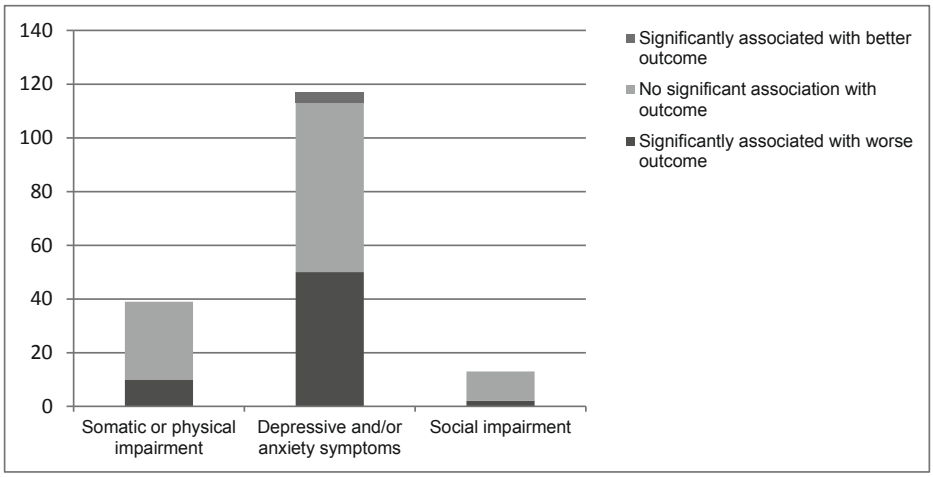

Figure 5. Graphic representation of associations of somatic or physical impairment, depressive and/or anxiety symptoms, and social impairment with adverse health outcomes in inflammatory bowel disease patients. No studies reported on cognitive impairment, functional impairment, or frailty.

Depressive symptoms or a diagnosis of depression were present in between 2.3% and 32.0% of patients.[16 19] Anxiety symptoms or diagnosis were present in between 9.4% and 39.0% of patients.[19 41]

Ananthakrishnan et al. combined a diagnosis of a depressive disorder and/or a generalized anxiety diagnosis into one 'psychiatric comorbidity' factor. In their cohort of 10.834 patients, this factor was associated with the occurrence of several adverse health outcomes. For instance, psychiatric comorbidity was associated with an increased risk of IBD-related surgery in CD (aOR 1.22 (95%CI 1.01-1.47)) and the use of steroids in CD patients (aOR 1.83 (95% CI 1.58-2.13)).[17]

A study by Mikocka-Walus et al. assessing depressive and anxiety symptoms with the HADS found that depression was associated with their composite outcome measure "clinical recurrence" in both CD and UC. Anxiety was associated with clinical recurrence in CD, but not in UC.[33]

Half of all associations on depressive and/or anxiety symptoms (49.5%) described CD patients, the other associations described UC patients (26.4%) or no distinction was made in IBD type (23.9%). Depressive and/or anxiety symptoms were predictive of adverse health outcomes in 50 out of 117 associations (42.7%) (figure 5).[16-19 24-26 28 31-34 36] Of the associations reporting on patients with CD, 57.9% was statistically significant and 42.9% of associations reporting on UC patients was statistically significant.

Social assessment

Social assessment was evaluated in five studies and this resulted in 13 associations (7.7% of all associations). Three associations reported on marital status or living situation (living together versus alone).[16 20 22] The other 10 associations assessed social support or social functioning using the Social Network Index, Social Support Inventories (medical outcomes study (MOS) and enhancing recovery in coronary heart disease (ENRICHD)) or Social Support List.[20 22 23 36]

Allegretti et al. reported the highest percentage of 57.9% patients being single, divorced or widowed.[16] A study by De Boer et al. reported 12% of patients as living alone.[22]

Bernstein et al. assessed the amount of high-contact roles using the Social Network Index.[20] This index calculates the number of different social roles in which the patient participates at least once every two weeks involving contact with a familiar person.[20] The study reported a presence of 19.9% of ≤4 high-contact roles in the 'flare' group compared to 17.4% in the 'non flare' group, this difference was not significant.[20] In a study by Camara et al. mean social support was 24.26, SD 5.50, measured with the ENRICHD Social Support Inventory on a scale from 6 (low social support) to 30 (high social support). Better social support was an independent predictor of less adverse events (aOR 0.666, 95%CI 0.516-0.859, p=0.002).[23]

Four associations (30.8%) described CD patients, in other associations on social functioning no difference was made regarding IBD type. There were no associations on social functioning in UC patients alone. In two out of the 13 associations (15.4%) a significant relationship between lower social functioning and adverse health outcomes was reported (figure 5).[22 23]

Supplementary analysis

The average sample size of the included studies was relatively low, which causes a low power to detect statistical significance. Hence, to enhance statistical power, we selected the six studies with the largest sample size.[17 19 26 28 32 33] These studies accounted for 56 associations (33.1% of total associations) with a minimum sample size of 2289 patients and a maximum of 52.498 patients. The associations described in these studies mostly (98.2%) assessed depressive and/or anxiety symptoms. 62.5% of these associations showed a statistically significant relationship between a component of a CGA and a higher risk for adverse health outcomes (figure 3).

Quality assessment

The overall study quality assessed by the modified Newcastle-Ottawa scale was moderate to low (table 3). There were concerns about the representativeness of the cohorts, the duration of follow-up and the adequacy of follow-up.

None of the studies focused on older patients or performed separate analyses on a subgroup of older patients. Six studies (partly) excluded older patients with the lowest

maximum age of exclusion of 55 years reported in the study by Deter et al.[21 25 27 29 34 38] Ten studies had a questionable duration of follow-up which was partly or not enough for investigated outcomes to occur[18 20-22 26 27 36-38 41] and six studies did not report on patients lost to follow-up.[17 18 25 28 32 42]

DISCUSSION

This systematic review aimed to identify longitudinal studies describing components of a CGA in IBD patients and their associations with adverse health outcomes. There were three main findings. First, components of a CGA were used in 27 studies and none of these studies specifically described older patients with IBD, nor performed subgroup analyses on older patients. Second, cognitive status, functional performance and frailty were not assessed and objectively measured physical capacity was assessed in only one study. Third, a statistically significant association was present between a component of a CGA and a higher risk of adverse health outcomes in more than one-third of the associations.

The purpose of a CGA is to systematically explore different geriatric domains as a reflection of patients' health. However, none of the studies described a complete geriatric assessment at baseline in relation to outcome measures. Therefore, the components of which a CGA is ought to be constructed and which are considered geriatric relevant components, were assessed in this review. In 27 out of all screened citations a component of a CGA was assessed. Besides this, the population of the included studies was young; the highest mean age reported in a study was 52.7 years.[17] Several studies employed an upper age limit for exclusion of patients and most studies had exclusion criteria concerning the presence of comorbidities or IBD-disease history such as bowel resection or stricturing disease as well. Although the increasing incidence and prevalence (between 10-30%) of IBD in older patients is well known,[1 43] our systematic review found that components of a CGA are scarcely used in IBD literature and have not been used in older IBD patients. Therefore, there is currently no evidence for a relationship between any of these components and adverse health outcomes in the older IBD patient population. Unfortunately this underrepresentation of older patients is not only present in the IBD literature. As a result of an upper age limit or exclusion criteria regarding comorbidities, clinical trial evidence on the treatment of older patients in general is still absent.[44] Due to this lack of evidence, guidelines concerning older patients with IBD are falling behind and decision making in this patient group is a challenge for clinicians.

Besides the underrepresentation of older patients with IBD in the included studies, several components of a CGA were also underrepresented, or not assessed at all. Promising geriatric measurements, such as cognitive status and frailty were not assessed in patients with IBD. Only one study reported objectively measured physical capacity using handgrip strength.[27]

Cognitive impairment is prevalent and associated with adverse health outcomes in older patients, as shown in research conducted in oncology and nephrology.[5 6 9 45] Even in community-dwelling older adults cognitive impairment is prevalent. A study by Thein et al. in community-dwelling Chinese older adults with and without diabetes aged ≥55 years found that 12.4% of the overall cohort (2696 patients) was cognitively impaired.[46] Frailty, defined as a state of increased vulnerability,[8 13] is strongly associated with adverse health outcomes in both community-dwelling older adults as in patients as well.[8 47 48] Physical capacity, which can be assessed with gait speed or handgrip strength, is understood as the ability to integrate physiological systems into coordinated, efficient movements to achieve optimum functioning.[49 50] The association between physical capacity and adverse health outcomes has been examined by several studies in other fields of medicine and in community-dwelling older adults.[51 52]

In this systematic review we did not find any study on cognitive status or frailty in IBD patients. This is reason for concern as geriatric problems are prevalent in the older IBD population. For instance, in our multicentre cohort study, over half of all patients had one or more aberrant test results in their geriatric assessment. A weak handgrip strength was present in 22.7% and frailty, measured with the Geriatric 8 questionnaire, was found in 43.7% of older patients with IBD.[10 53] We did find one study by Jansen et al. reporting an objective measurement of physical capacity (handgrip strength). Handgrip strength is often used to diagnose sarcopenia,[54] and there is a growing evidence for the association between sarcopenia and adverse health outcomes.[55] However, the study by Jansen et al. did not find a significant association between reduced handgrip strength and adverse health outcomes. This could be explained by the short follow-up duration (6 months), low mean age (40 years) and small sample size (55 patients).[27] Thus, in older patients with IBD, evidence regarding impairments in psychical capacity, cognitive status or frailty and its associations with adverse health outcomes is lacking.

Despite the relatively young population included and the lack of a CGA, we found impairments in the components of a CGA to be prevalent and, in more than one-third of the associations, significantly associated with adverse health outcomes. Older patients are more susceptible to geriatric impairments such as depression, low physical capacity and malnutrition compared to younger patients[56-58]. It is very likely that prevalence of geriatric impairment and its association with adverse health outcomes have been underestimated in this review when applied to older patients. Evidence on the underlying pathophysiological relationship between components of a CGA and adverse health outcomes is still scarce, especially in IBD. In figure 6 we present a summary of the potential pathophysiological interactions between these components and IBD disease outcomes. In IBD patients, depression contributes to lower pain thresholds, more reported symptoms and a poorer well-being.[59 60] This could contribute to the relationship between depressive symptoms and adverse health outcomes found in this systematic review. In the Health Aging and Body Composition (Health ABC) study on 3075 individuals aged 70-79 years a significant and independent association between physical capacity, measured with both low quadriceps

muscle strength and low handgrip strength, and serum levels of the inflammatory markers tumor necrosis factor (TNF) and interleukin (IL)-6 was found.[61 62] High levels of inflammatory markers are associated with increased morbidity and mortality in older persons.[63] In IBD patients, these proinflammatory markers correlate with disease activity and it has been shown that patients with IL-6 serum levels >20 picograms per millilitre have a 17-fold increased risk of relapse over a 1-year period compared with patients with a lower level.[64 65] The latter could also contribute to the relationship between low physical capacity and (IBD-related) adverse health outcomes. Malnutrition, besides being one of the principal mechanisms involved in the genesis of sarcopenia,[66] is also a well-known risk factor for poor prognosis in IBD, especially postoperative complications.[67]

The disease course of IBD could also influence several components of a CGA, in this way causing a bidirectional relationship between geriatric impairment and adverse health outcomes. For example, IBD patients experiencing an exacerbation of disease express a higher risk of malnutrition, due to the decrease of oral food intake or increased gastrointestinal nutrient loss.[66] While studying the predictive role of a CGA in IBD, relationships should therefore be interpreted with caution and associations should be corrected for disease activity to take into account this possible bi-directional relationship. The multimodal effects of IBD and its treatment may very well be an important cause of geriatric impairments or frailty.

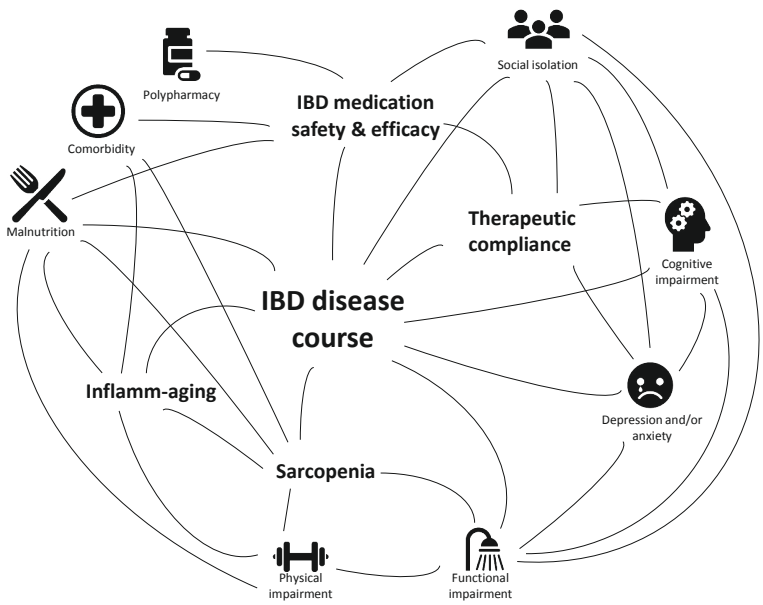

Figure 6. Potential pathophysiological interactions between components of a comprehensive geriatric assessment and inflammatory bowel disease [IBD] -related disease outcomes.

To enhance statistical power, as sample sizes in the included studies were small, a sensitivity analysis was performed by selecting six studies with the largest patient population. The percentage of statistically significant associations increased from 36.7% to 62.5%. This suggests that most included studies lacked statistical power to detect significant differences. However, 98.2% of the associations described by the six largest studies reported on depression and/or anxiety and therefore are not representative of a full CGA. We were unable to perform sensitivity analyses separately for each component of a CGA due to the few studies included per factor: three quarters of the associations included in our systematic review described depressive and/or anxiety symptoms. Alexakis et al. performed a systematic review and meta-analysis on the relationship between depressive state and disease course in adults with IBD but due to a lack of randomised controlled studies, small study populations and a large variety in depression symptom scores it was inconclusive.[68] Therefore, even though the majority of associations found in our systematic review concerned depression and/or anxiety, no firm conclusion can be drawn regarding the influence of depression and/or anxiety on adverse health outcomes.

A limitation of this review is the fact that, because of the heterogeneity of the components of a CGA, outcome measures and reported measures of association, we could not perform a formal meta-analysis. Furthermore, interpretation of the results regarding the number of significant associations has to be interpreted with caution due to a possibility of publication bias, as negative or non-significant associations may not have been reported in included studies. Besides this, the amount of older patients in the included studies is low, therefore it is not guaranteed that results of these studies can be extrapolated to the population of older patients with IBD.

The strengths of our review include the extended systematic search performed in seven online databases without a restriction on publication date. In this way all potential relevant studies concerning associations on components of a CGA and adverse health outcomes in IBD patients were assessed. In addition, a quality assessment using the adapted Newcastle Ottowa Scale was performed. One of the greatest strengths of this review is the important addition to existing literature regarding IBD in the older patient, because little research has been performed on this subject so far.

The findings of this study imply that more research regarding geriatric assessment in older IBD patients is needed. With more evidence available on the association between components of a CGA and adverse health outcomes, a risk stratification could be made regarding geriatric impairment. In this way, older patients at high risk for adverse health outcomes could be selected on time and monitored closely or even opt for an alternative treatment regimen according to their risk profile.

Table 1. Characteristics of the included studies

Publication characteristics			**Study population**				**Study characteristics**
Author	*Year*	*Country*	*Number of patients at baseline*	*Age, year (mean)*	*Disease type*	*Inclusion criteria*	*Follow-up duration*
Allegretti [16]	2015	USA	324	41.7	CD/UC	≥18 years, hospital admission for non-elective IBD-related reason	90 days
Ananthakrishnan [17]	2013	USA	10834	CD: 49.5 & 44.7; UC: 52.7 & 47.9†	CD/UC	Exclusion of patients with anxiety or depression date of diagnosis code prior to surgery	CD 11.5 years & 7.7 years; UC 12.5 years & 9.1 years†
Banovic [18]	2010	France	57	41.2	CD	Outpatients complaining of fatigue, no steroid dependence, no rheumatoid or peripheral arthritis	1 year
Barnes [19]	2017	USA	52498	CD: 20.2% ≥60 UC: 31.2% ≥60‡	CD/UC	≥18 years, excluding patients with discharge codes for both CD and UC	90 days
Bernstein [20]	2010	USA	704	52.1	CD/UC	>18 years	1 year
Bitton [21]	2003	USA	60	39	UC	>18 years and ≤80 years, clinical remission for ≥1 month, endoscopic remission at baseline, p.o. or rectal mesalamine dose stable for 1 month or 6-mercaptopurine and azathioprine dose stable for 3 months, no use of p.o. or rectal corticosteroids within the past 30 days	1 year
Bitton [38]	2008	Canada	101	33.6	CD	18-65 years, clinical remission for ≥1 month, p.o. or rectal mesalamine dose stable for 1 month or 6-mercaptopurine and azathioprine dose stable for 3 months, no use of p.o. or rectal corticosteroids within the past 30 days, no current complications, no previous extensive small bowel resection, no presence of ileostomy or colostomy, no antibiotic use at baseline	1 year

Table 1. Continued.

Publication characteristics			**Study population**				**Study characteristics**
Author	*Year*	*Country*	*Number of patients at baseline*	*Age, year (mean)*	*Disease type*	*Inclusion criteria*	*Follow-up duration*
Boer, de [22]	1998	The Netherlands	271	42	CD/UC	Attending IBD outpatient clinic in year prior to study, completion of follow-up	1 year
Cámara [23]	2011	Switzerland	467	41.6	CD	Complete/returned questionnaires at follow-up	1.5 year
Cámara [24]	2011	Switzerland	476	41.8	CD	Adult patients with recurrence of CD symptoms, no missing or invalid information on important control variables, returning baseline questionnaires within 6 months of inclusion	1.5 year
Deter [25]	2008	Germany	108	52.9% <30, 47.1% >30	CD	18-55 years, at least one active disease episode (defined as requiring drug treatment) in last 2 years, no psychotherapy, no resection for CD within last 2 years and no further relapse thereafter, no ongoing immunosuppressive therapy or resection in the near future, no colostomy or ileostomy	2 years
Gaines [26]	2016	USA	5707	43§	CD	≥18 years, internet access	1 year

Table 1. Continued.

Publication characteristics			**Study population**				**Study characteristics**
Author	*Year*	*Country*	*Number of patients at baseline*	*Age, year (mean)*	*Disease type*	*Inclusion criteria*	*Follow-up duration*
Jansen [27]	2016	Germany	55	40	CD	18–75 years, CDAI <200, occurrence of relapse/flare-ups, intestinal complication or hospitalization within the last 2 years, known disease location and behaviour within the last 2 years, absence of cancer or other severe disease, no pregnancy or lactation, no high-dose systemic corticosteroid treatment within 3 months before study entry, absence of stoma or short bowel syndrome and no BMI <17.5 or severe weight loss	6 months
Kochar [28]	2018	USA	2798	41	CD/UC	≥18 years, excluding patients without follow-up	Mean 22 months
Langhorst [29]	2013	Germany	80	45.1 & 48.7¶	UC	18-75 years, self-reported clinical remission for ≥1 week and <12 months, an interval of 4 weeks in remission for 4 weeks at the beginning of the 12-months interval, absence of clinically active disease, no infectious or chronic active colitis, no current use of antibiotics or corticosteroids, no treatment within the last 3 months with immunosuppressive drugs, no complete colectomy, no relevant somatic comorbidities, no pregnancy	1 year

Table 1. Continued.

Publication characteristics			**Study population**				**Study characteristics**
Author	*Year*	*Country*	*Number of patients at baseline*	*Age, year (mean)*	*Disease type*	*Inclusion criteria*	*Follow-up duration*
Levenstein [30]	2000	Italy	63	38.8	UC	Clinical remission, for at least 2 months off systemic or local steroids, using oral and rectal 5-aminosalicylate or oral azulfidine in maintenance doses as sole therapy, completion of follow-up	68 months
Mardini [31]	2004	USA	18	31§	CD	No history of psychosis and/or clinical depression that required hospitalization, no stricturing disease and/or history of ileostomy, total colectomy or short gut syndrome	2 years
Maunder [39]	2005	Canada	146	42.7	UC	≥18 years, no colectomy or indications of cardiovascular illness	7-37 months (median 686 days)
McCombie [40]	2015	New Zealand	54	33.5§	CD/UC/IBD-U	≥18 years, return of questionnaires <1 month of administration	6 months
Micic [32]	2017	USA	43680	47.8	CD/UC	≥18 years, primary discharge diagnosis of CD or UC, or primary diagnosis of an IBD-related complication and a secondary diagnosis of CD or UC, no death during index admission, exclusion of elective admissions	30 days
Mikocka-Walus [41]	2008	Australia	139	50∞	IBD/IBS/HCV	Sufficient knowledge of English	1 year

Table 1. Continued.

Publication characteristics			**Study population**				**Study characteristics**
Author	*Year*	*Country*	*Number of patients at baseline*	*Age, year (mean)*	*Disease type*	*Inclusion criteria*	*Follow-up duration*
Mikocka-Walus [33]	2016	Switzerland	2289	40.5§	CD/UC/IC	Diagnosis established ≥4 months before inclusion or at least 1 recurrence of symptoms, completion of baseline and follow-up visit, no pregnancy, no missing data on depression and anxiety scores	8 years
Mittermaier [34]	2004	Austria	60	31§	CD/UC	18-65 years, in remission 8 to 12 weeks after a flare defined as CDAI/CAI and in remission at baseline for at least 4 weeks (CDAI<150 or CAI <5), sufficient knowledge of German, no known or evident psychiatric diseases, no psychopharmacotherapy use, absence of stoma	1.5 year
North [35]	1991	USA	33Δ	39.8	CD/UC	At least one gastrointestinal exacerbation during study period, occurring no earlier than 4 months after date of enrolment	2 years
Persoons [36]	2005	Belgium	100	34	CD	≥18 years, refractory, active (CDAI>150) luminal disease treated with infliximab (5 or 10 mg/kg), no short bowel syndrome, absence of stoma, no participation in clinical trial	10 months

Table 1. Continued.

Publication characteristics			**Study population**				**Study characteristics**
Author	*Year*	*Country*	*Number of patients at baseline*	*Age, year (mean)*	*Disease type*	*Inclusion criteria*	*Follow-up duration*
Riley [37]	1990	UK	100	Range 20-78	UC	≥18 years, maintenance sulphasalazine (2-4 g daily) or delayed release mesalazine (800-1600 mg daily). Clinical remission (absence of blood in stool and macroscopic appearance of normal mucosa or erythema only on sigmoidoscopy), absence of oral or rectal steroids within one month of study entry	48 weeks
Takaoka [42]	2017	Japan	40	32.4§	CD	Hospitalized at gastroenterology unit during inclusion	A median of 25.5 days (IQR 13.5-45.0)

Abbreviations: USA, United States of America; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; p.o., per os; CDAI, Crohn's disease activity index; BMI, body mass index; IBD-U, inflammatory bowel disease-unclassified; IBS, inflammatory bowel syndrome; HCV, hepatitis c virus; IC, indeterminate colitis; CAI, clinical activity index; mg, milligram; kg, kilogram; UK, United Kingdom; g, gram; IQR, interquartile range.

†Age and follow-up duration only mentioned separately for patients with CD or UC and with or without psychiatric comorbidity ‡Age only mentioned separately for CD and UC §Median, ¶Mean age only mentioned separately for relapse group and continued remission group, ∞Number of patients stated in table is number of IBD patients and only associations regarding IBD patients from this study are included, Δ33 patients out of 85 patients developed the endpoint (a flare) in the 2 year study period and were included in analyses.

Table 2. Associations of components of a comprehensive geriatric assessment with adverse health outcome measurements

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Allegretti [16]	324	Mental assessment by depression diagnosis Mental assessment by anxiety diagnosis Social assessment by marital status	90-days readmission	Depression: readmission + Anxiety: readmission ns Marital status: readmission ns
Ananthakrishnan [17]	10834	Mental assessment by psychiatric comorbidity (depressive disorder diagnosis and/or generalized anxiety diagnosis)	IBD-related surgery, IBD-related hospitalization, all-cause hospitalization, anti-TNF use, immunomodulator use, steroid use, outpatient visits, GE visits, abdominal CT/MRI scan, lower GI endoscopies	IBD-related surgery: CD+ (anxiety+, depression ns) UC ns, IBD-related hospitalization: CD ns UC –, all-cause hospitalizations: CD + UC +, anti-TNF use: CD ns UC ns, immunomodulator use: CD + UC ns, steroid use: CD + UC +, outpatient visits: CD + UC ns, GE visits: CD ns UC ns, abdominal CT/MRI scan: CD ns UC -, GI endoscopies: CD- UC **-**
Banovic [18]	52	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	QoL (SF36 Vitality, mental health and general health), CDAI score	Depression: vitality +, mental health +, general health +, CDAI ns. Anxiety: vitality ns, mental health +, general health +, CDAI ns
Barnes [19]	52498	Mental assessment by depression diagnosis Mental assessment by anxiety diagnosis	90-days readmission	Depression: readmission CD + UC + Anxiety: readmission CD + UC +
Bernstein [20]	704	Mental assessment by Positive and Negative Affect Schedule Social assessment by Social Network Index Social assessment by married/not married	Exacerbation	Low positive mood: ns High negative mood: ns Social functioning: ns Marital status: ns
Bitton [21]	60	Mental assessment by depression (SCL-90-R) Mental assessment by anxiety (SCL-90-R)	Exacerbation	Depression: ns Anxiety: ns
Bitton [38]	101	Mental assessment by depression (SCL-90-R) Mental assessment by anxiety (SCL-90-R)	Exacerbation	Depression: ns Anxiety: ns

Table 2. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Boer, de [22]	222	Mental assessment by depression (CES-D) Mental assessment by emotional functioning (IBDQ) Social assessment by IBDQ Social assessment by living alone yes/no Social assessment by MOS Social Support Survey	GE and GP visits	Depression: GE ns GP ns Emotional functioning: GE ns GP ns Social functioning (IBDQ): GE + GP ns Social functioning (living alone): GE ns GP ns Social functioning (social support): GE ns GP ns
Cámara [23]	458	Social assessment by ENRICHD Social Support Inventory	IBD-related adverse event	Social functioning: +
Cámara [24]	461	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Exacerbation	Depression: +, anxiety: +
Deter [25]	87	Mental assessment by depression (BDI) Mental assessment by anxiety (STAI)	Combined measurement of health care utilization, HRQoL, and the somatic course of disease	Depression: combined outcome ns, health care utilization ns, HRQoL ns, somatic course ns Anxiety: combined outcome ns, health care utilization ns, HRQoL +; somatic course ns
Gaines [26]	2144	Mental assessment by PROMIS depression questionnaire	SCDAI >150, any abdominal surgeries, any hospitalizations, use of anti-TNF therapy	Depression: SCDAI +, any abdominal surgeries ns, any hospitalizations +, use of anti-TNF ns
Jansen [27]	55	Somatic assessment by malnutrition (SGA) Somatic assessment by malnutrition (MIRT) Somatic assessment by malnutrition (BIA Phase angle) Functional assessment by handgrip strength	CDAI, HBI, CD-related hospitalizations, flares, complications, CD-related surgeries, composite assessment of CD-related doctor visits, complications, CD-associated hospitalization, exacerbation, CD-related surgery and changes in CD medication	Malnutrition (SGA): all seven outcome parameters ns Malnutrition (MIRT): hospitalizations +, surgeries +, complications +, exacerbation +, composite assessment +, CDAI: ns, HBI ns Malnutrition (BIA phase angle) and handgrip strength: for both all seven outcome parameters ns

Table 2. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Kochar [28]	2798	Mental assessment by depression (PHQ-8)	Exacerbation, new biologic prescription, new steroid prescription, any hospitalization, IBD-related surgery	Depression: exacerbation CD + UC ns, new biologic prescription CD + UC +, new steroid prescription CD + UC ns, hospitalization CD + UC +, IBD-related surgery CD + UC +
Langhorst [29]	75	Mental assessment by depression (HADS-D)	Exacerbation	Depression: exacerbation ns
Levenstein [30]	62	Mental assessment by depression (CES-D)	Exacerbation	Depression: exacerbation ns; short term (<8 months) exacerbation ns
Mardini [31]	18	Mental assessment by depression (BDI) Mental assessment by anxiety (BAI)	CDAI score	Depression: CDAI +, anxiety CDAI +
Maunder [39]	99	Mental assessment by depression (CES-D)	Disease activity	Depression: disease activity ns
McCombie [40]	54	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	SIBDQ score	Depression: SIBDQ ns, anxiety: SIBDQ ns
Micic [32]	43680	Somatic assessment by Malnutrition diagnosis Mental assessment by Depression diagnosis Mental assessment by Anxiety diagnosis	All-cause hospital readmission within 30 days	Malnutrition: readmission +, depression: readmission ns, anxiety: readmission +
Mikocka-Walus [41]	59†	Mental assessment by depression (HADS-D) Mental assessment by depression (SCL-90-R) Mental assessment by anxiety (HADS-A) Mental assessment by anxiety (SCL-90-R)	Exacerbation	Depression (HADS-D): exacerbation ns, depression (SCL90): exacerbation ns, anxiety (HADS-A): exacerbation ns, anxiety (SCL90): exacerbation ns

Table 2. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Mikocka-Walus [33]	2007	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Clinical recurrence, fistulas, exacerbation, IBD surgery, biologic use, steroid use	Depression: clinical recurrence CD + UC +, fistula CD +, exacerbation UC +, IBD surgery CD+, biologic use CD +, steroid use CD + Anxiety: clinical recurrence CD + UC -, exacerbation CD – UC +, biologic use UC +, steroid use UC +
Mittermaier [34]	60	Mental assessment by depression (BDI) Mental assessment by anxiety (STAI1)	Exacerbation	Depression: exacerbation at 12 months +, exacerbation at 18 months +. Anxiety: exacerbation at 12 months ns, exacerbation at 18 months +
North [35]	32	Mental assessment by depression (BDI) Mental assessment by visual analog depression scale	Change in disease activity and exacerbation	Depression (BDI): gastrointestinal scale score 1-month lag ns, gastrointestinal scale score 2-month lag ns, 1 month before exacerbation ns, 2 months before exacerbation ns. Depression (visual analog depression scale): gastrointestinal scale score 1-month lag ns, gastrointestinal scale score 2-month lag ns, 1 month before exacerbation ns, 2 months before exacerbation ns.
Persoons [36]	100	Mental assessment by MDD presence (PHQ-9) Mental assessment by anxiety (HADS-A) Social assessment by SSL-I	Response to infliximab, achievement of remission, time to retreatment	Depression: response to infliximab ns, failure to achieve remission +, time to retreatment + Anxiety: response to infliximab ns, failure to achieve remission ns, time to retreatment ns. Social support: response to infliximab ns, failure to achieve remission ns, time to retreatment ns

Table 2. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Riley [37]	92	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Exacerbation	Depression: exacerbation ns Anxiety: exacerbation ns
Takaoka [42]	40	Somatic assessment by malnutrition (SGA) Somatic assessment by malnutrition (MUST) Somatic assessment by malnutrition (NRS 2002) Somatic assessment by malnutrition (O-PNI) Somatic assessment by malnutrition (CONUT)	Intestinal resection, LOS	Malnutrition (SGA): intestinal resection ns, LOS + Malnutrition (MUST score): intestinal resection ns, LOS ns Nutritional risk (NRS 2002): intestinal resection ns, LOS + Malnutrition (O-PNI): intestinal resection ns, LOS + Malnutrition (CONUT): intestinal resection ns, LOS +

NB: +: a significant association between a component of a geriatric assessment and outcome of interest in which more geriatric impairment leads to worse outcome; -: a significant association between a component of a geriatric assessment and outcome of interest in which more geriatric impairment leads to better outcome. When both univariate and multivariate analyses were performed, only results from multivariate analyses (most corrected model) are tabulated. For an extended version of table 2 including association measures see supplementary table 1. For corrected confounders see supplementary table 2

Abbreviations: ns, non-significant; HR(QoL), (health related) quality of life; IBD, inflammatory bowel disease; anti-TNF, anti-tumor necrosis factor; GE, gastroenterologist; CT, computerized tomography; MRI, magnetic resonance imaging; GI, gastrointestinal; CD, Crohn's disease; UC, ulcerative colitis; HADS-D, hospital anxiety and depression scale-depression component; HADS-A, hospital anxiety and depression scale-anxiety component; SF36, short form 36; (S)CDAI, (short) Crohn's disease activity index; SCL-90-R, symptom checklist 90 revised; CES-D, center for epidemiologic studies depression scale; IBDQ, inflammatory bowel disease questionnaire; MOS, medical outcomes study; GP, general practitioner; ENRICHD, enhancing recovery in coronary heart disease; BDI, Beck depression inventory; STAI, stait trait anxiety index; PROMIS, patient reported outcomes measurement information system; SGA, subjective global assessment; MIRT, malnutrition inflammation risk tool; BIA, bioelectrical impedance analysis; HBI, Harvey Bradshaw index; PHQ, patient health questionnaire; BAI, Beck anxiety inventory; MDD, major depressive disorder; SSL-I, social support list-interactions; MUST, malnutrition universal screening tool; NRS, nutrition risk screening; O-PNI, Onodera's prognostic nutritional index; CONUT, controlling nutritional status; LOS, length of hospital stay. †Total of 124 patients, 59 IBD patients.

Table 3. Quality assessment of the included studies

Publication characteristics		**Selection**		**Outcome**		
Author	*Year*	*Representativeness of the exposed cohort*	*Ascertainment of exposure (geriatric measure)*	*Assessment of outcome*	*Sufficient duration of follow-up*	*Adequacy of follow-up*
Allegretti [11]	2015	+/-	+	+	+	+
Ananthakrishnan [12]	2013	+	+	+	+	?
Banovic [13]	2010	-	+	+	+/-	?
Barnes [14]	2017	+	+	+	+	+
Bernstein [15]	2010	+	+	+	+/-	+/-
Bitton [16]	2003	-	+	+	+/-	+
Bitton [35]	2008	--	+	+	+/-	-
Boer, de [17]	1998	+	+	+	+/-	+/-
Cámara [18]	2011	+/-	+	+	+	+
Cámara [19]	2011	+/-	+	+	+	+
Deter [20]	2008	--	+	+/-	+	?
Gaines [21]	2016	+	+	+	+/-	+/-
Jansen [22]	2016	-	+	+	-	+
Kochar [23]	2018	+/-	+	+	+	?
Langhorst [24]	2013	-	+	+	+	-
Levenstein [25]	2000	+/-	+	+	+	+
Mardini [26]	2004	-	+	+	+	+
Maunder [37]	2005	-	+	+	+	+/-
McCombie [33]	2015	+/-	+	+	+	+/-
Micic [27]	2017	+	+	+	+	?
Mikocka-Walus [34]	2008	+	+	+	+/-	+
Mikocka-Walus [28]	2016	+	+	+	+	-
Mittermaier [29]	2004	-	+	+	+	+
North [30]	1991	+/-	+	+	+	+
Persoons [31]	2005	-	+	+	+/-	+
Riley [32]	1990	+	+	+	+/-	+
Takaoka [36]	2017	-	+	+	+	?

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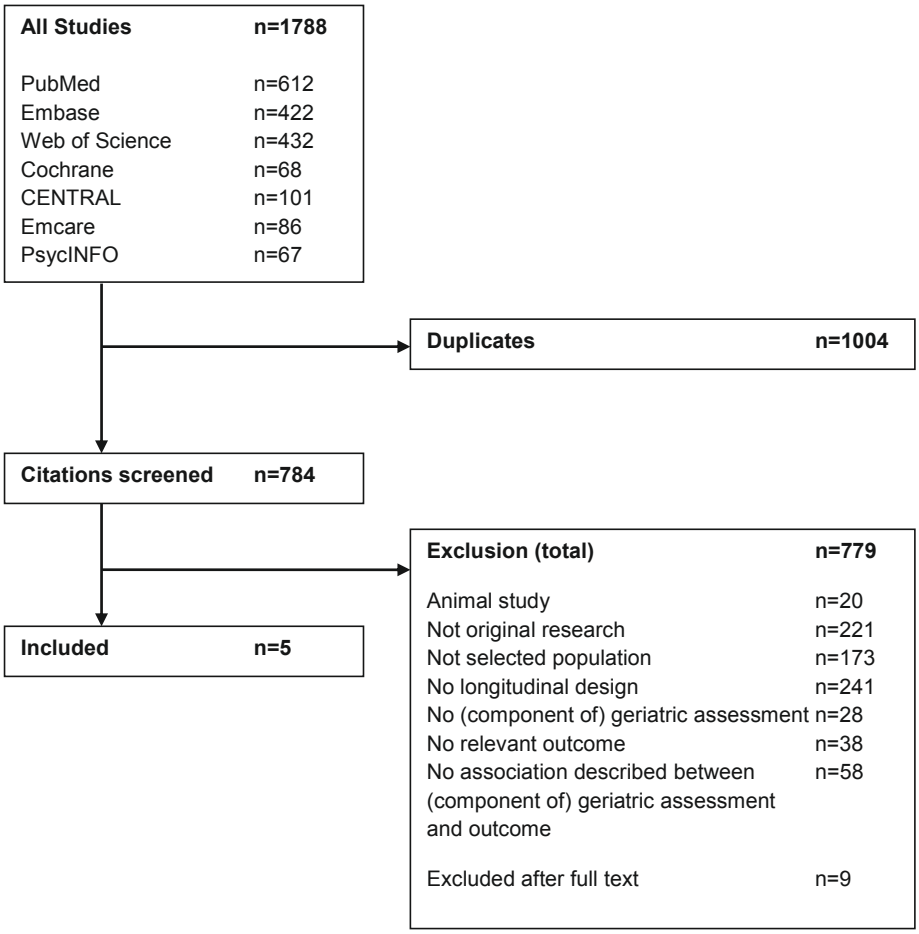

Supplementary figure 1. Additional flowchart

Supplementary table 1. Detailed table of associations of components of a comprehensive geriatric assessment with adverse health outcome measurements

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Allegretti [16]	324	Mental assessment by depression diagnosis Mental assessment by anxiety diagnosis Social assessment by marital status	90-days readmission	Depression: readmission + (aHR 1.99, 95% CI 1.33-3.00) Anxiety: ns¶ Marital status: ns¶
Ananthakrishnan [17]	10834	Mental assessment by psychiatric comorbidity (depressive disorder diagnosis and/or generalized anxiety diagnosis)	IBD-related surgery, IBD-related hospitalization, all-cause hospitalization, anti-TNF use, immunomodulator use, steroid use, outpatient visits, GE visits, abdominal CT/MRI scan, lower GI endoscopies	IBD-related surgery: CD+ (a[1]OR 1.22, 95% CI 1.01-1.47) (anxiety + (OR 1.36, 95% CI 1.05-1.75), depression ns (OR 1.20, 95% CI 0.95-1.53)) UC ns (aOR 1.01, 95% CI 0.80-1.28), IBD-related hospitalization: CD ns (aOR 1.05, 95% CI 0.88-1.26) UC – (aOR 0.77, 95%CI 0.63-0.93), all-cause hospitalizations: CD + (aOR 1.48, 95% CI 1.19-1.83) UC + (aOR 1.28, 95% CI 1.07-1.52), anti-TNF use: CD ns (aOR 1.17, 95% CI 0.96 – 1.43) UC ns (aOR 1.15, 95% CI 0.86 – 1.53), immunomodulator use: CD + (aOR 1.43, 95% CI 1.21 – 1.67) UC ns (aOR 1.16, 95% CI 0.97 – 1.39), steroid use: CD + (aOR 1.83, 95% CI 1.57 – 2.13) UC + (aOR 1.42, 95% CI 1.22-1.64), outpatient visits: CD + (aOR 2.80, 95% CI 1.54-4.06) UC ns (aOR 1.43, 95% CI 0.73-2.14), GE visits: CD ns (aOR 1.54, 95% CI 0.84-2.25) UC ns (aOR 0.72, 95% CI 0.24-1.20), abdominal CT/MRI scan: CD ns (aOR 1.06, 95% CI 0.77-1.34) UC - (aOR 0.69, 95% CI 0.40-0.90), GI endoscopies: CD- (aOR 0.56, 95% CI 0.33-0.79) UC - (aOR 0.50, 95% CI 0.24-0.75)
Banovic [18]	52	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	QoL (SF36 Vitality, mental health and general health), CDAI score	Depression: vitality + (r=-0.50, P<*0.005*), mental health + (r=-0.54, P<*0.005*), general health + (r=-0.38, P<*0.005*), CDAI ns (r=0.2). Anxiety: vitality ns (r=-0.37), mental health + (r=-0.66, P<*0.005*), general health + (r=-0.50, P<*0.005*), CDAI ns (r=0.03)
Barnes [19]	52498	Mental assessment by depression diagnosis Mental assessment by anxiety diagnosis	90-days readmission	Depression: CD + (aOR 1.18, 95% CI 1.11-1.26) UC + (aOR 1.28, 95% CI 1.14–1.45) Anxiety: CD + (aOR 1.27, 95% CI 1.07-1.50) UC + (aOR 1.35, 95% CI 1.07–1.70)

Supplementary table 1. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Bernstein [20]	704	Mental assessment by Positive and Negative Affect Schedule Social assessment by Social Network Index Social assessment by married/not married	Exacerbation defined as MIBDI	Low positive mood: ns (aOR 1.16, 95% CI 0.70-1.93) High negative mood: ns (aOR 1.04, 95% CI 0.58-1.88) Social functioning: ns (aOR 1.21, 95% CI 0.61-2.38) Marital status: ns (aOR 1.59, 95% CI 0.85-2.95)
Bitton [21]	60	Mental assessment by depression (SCL-90-R) Mental assessment by anxiety (SCL-90-R)	Exacerbation defined as symptoms and endoscopy	Depression: ns (HR 1.011, 95% CI, 0.95-1.08) Anxiety: ns (HR 1.000, 95% CI 1.00-1.00)
Bitton [38]	101	Mental assessment by depression (SCL-90-R) Mental assessment by anxiety (SCL-90-R)	Exacerbation defined as CDAI >150 with an increase of ≥70 points from baseline	Depression: ns (HR 1.6, 95% CI 0.9-2.7) Anxiety: ns (HR 1.4, 95% CI 0.77-2.6)
Boer, de [22]	222	Mental assessment by depression (CES-D) Mental assessment by emotional functioning (IBDQ) Social assessment by IBDQ Social assessment by living alone yes/no Social assessment by MOS Social Support Survey	GE and GP visits	Depression: GE ns¶ GP ns¶ Emotional functioning: GE ns¶ GP ns¶ Social functioning (IBDQ): GE +¶ GP ns¶ Social functioning (living alone): GE ns¶ GP ns¶ Social functioning (social support): GE ns¶ GP ns¶
Cámara [23]	458	Social assessment by ENRICHD Social Support Inventory	IBD-related adverse events comprising: progression of disease as measured by occurrence of flare, non response to medication, extraintestinal manifestations or complications	Social functioning: + (aOR 0.666, 95% CI 0.516-0.859)
Cámara [24]	461	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Exacerbation defined as ≥100 increase in CDAI, medication step-up, extraintestinal manifestations or complications	Depression: + (aOR 1.42, 95% CI 1.05-1.90) Anxiety: + (aOR 1.46, 95% CI 1.08-1.97)
Deter [25]	87	Mental assessment by depression (BDI) Mental assessment by anxiety (STAI)	Combined measurement of health care utilization (defined as data on hospital days and sick leave days), the HRQoL (no definition given), and the somatic course of disease (CDAI)	Depression: combined outcome ns¶, health care utilization ns¶, HRQoL ns¶, somatic course ns¶ Anxiety: combined outcome ns¶, health care utilization ns¶, HRQoL + (aβ-0.45, P=*.0003*); somatic course ns¶

Supplementary table 1. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Gaines [26]	2144	Mental assessment by PROMIS depression questionnaire	SCDAI >150, any abdominal surgeries, any hospitalizations, use of anti-TNF therapy	Depression: SCDAI + (aOR 1.21, 95% CI 1.07-1.36), any abdominal surgeries ns (aOR 0.94, 95% CI 0.72-1.22), any hospitalizations + (aOR 1.26, 95% CI 1.06-1.49), use of anti-TNF ns (aOR 0.91, 95% CI 0.78-1.08)
Jansen [27]	55	Somatic assessment by malnutrition (SGA) Somatic assessment by malnutrition (MIRT) Somatic assessment by malnutrition (BIA Phase angle) Functional assessment by handgrip strength	Disease activity (CDAI and HBI), CD-related hospitalizations, flares, complications (new stenosis, fistula or abscess), CD-related surgeries. The authors made a composite assessment of the parameters CD-related doctor visits, complications, CD-associated hospitalization, flare-up, CD-related surgery and changes in CD medication	Malnutrition (SGA): all seven outcome parameters ns¶ Malnutrition (MIRT): hospitalizations + (ρ 0.398, *P=.003*), surgeries + (ρ 0.371, *P=.006*), complications + (ρ 0.333, *P=.015*), flares + (ρ 0.299, *P=.030*), composite assessment + (ρ 0.528, *P<.001*), CDAI: ns (ρ 0.260, *P=.077*); HBI ns (ρ 0.188, *P=.195*) Malnutrition (BIA phase angle) and handgrip strength: for both all seven outcome parameters ns¶
Kochar [28]	2798	Mental assessment by depression (PHQ-8)	Exacerbation by disease activity index (modified HBI ≥5 or SCCAI >2), new biologic prescription, new steroid prescription, any hospitalization, IBD-related surgery	Depression: exacerbation CD + (aRR 2.3, 95% CI 1.9-2.8) UC ns (aRR 1.3, 95% CI 0.9-1.8), new biologic prescription CD + (aRR 1.8, 95% CI 1.4-2.3) UC + (aRR 1.6, 95% CI 1.1-2.3), new steroid prescription CD + (aRR 1.8, 95% CI 1.1-3.2) UC ns (aRR 1.8, 95% CI 0.9-3.8), hospitalization CD + (aRR 1.3, 95% CI 1.2-1.5) UC + (aRR 1.3, 95% CI 1.1-1.5); IBD-related surgery CD + (aRR 1.3, 95% CI 1.1-1.6) UC + (aRR 1.8, 95% CI 1.2-2.6)
Langhorst [29]	75	Mental assessment by depression (HADS-D)	Exacerbation defined as CAI>4 or an increase of CAI >3 from baseline, endoscopic activity index and histological evaluation	Depression: exacerbation ns (aHR 1.08, 95% CI 0.95–1.22)
Levenstein [30]	62	Mental assessment by depression (CES-D)	Exacerbation defined as symptoms rated ≥1 on a symptom scale of 0–8 that lasted ≥10 days and that were associated with at least one of two confirmation criteria: intensified therapy prescribed by a physician and/or rectal inflammation seen by study endoscopists.	Depression: exacerbation ns (middle/high tertile CES-D score vs low tertile: HR 0.83/HR 0.99, 95% CI 0.30-2.3/95% CI 0.36-2.7); short term (<8 months) exacerbation ns (middle/high tertile CES-D score vs low tertile: 22.2%/10.8% vs 20.5%, *P=.93*)

Supplementary table 1. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Mardini [31]	18	Mental assessment by depression (BDI) Mental assessment by anxiety (BAI)	CDAI score	Depression: CDAI + (aβ 5.92, *P=.0004*), anxiety CDAI + (aβ 2.42, *P=.02*)
Maunder [39]	99	Mental assessment by depression (CES-D)	Disease activity by St. Mark's index	Depression: disease activity ns (r=0.19, *P>.05*)
McCombie [40]	54	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	SIBDQ score	Depression: SIBDQ ns (*P=.61*)¶, anxiety: SIBDQ ns (*P=.20*)¶
Micic [32]	43680	Somatic assessment by Malnutrition diagnosis Mental assessment by Depression diagnosis Mental assessment by Anxiety diagnosis	All-cause hospital readmission within 30 days	Malnutrition: readmission + (aOR 1.37, 95% CI 1.22-1.54), depression: readmission ns¶, anxiety: readmission + (aOR 1.17, 95% CI 1.01-1.36)
Mikocka-Walus [41]	59†	Mental assessment by depression (HADS-D) Mental assessment by depression (SCL-90-R) Mental assessment by anxiety (HADS-A) Mental assessment by anxiety (SCL-90-R)	Exacerbation measured by CDAI or SCCAI	Depression (HADS-D): exacerbation ns (aOR 1.057, 95% CI 0.919-1.215), depression (SCL90): exacerbation ns (aOR 1.003, 95% CI 0.928-1.085), anxiety (HADS-A): exacerbation ns (aOR 0.967, 95% CI 0.841-1.111), anxiety (SCL90): exacerbation ns (aOR 1.040, 95% CI 0.989-1.092)
Mikocka-Walus [33]	2007	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Clinical recurrence (defined as CDAI/MTWAI, exacerbation or worsening of the disease as established by physicians, fistulas and stenosis, anal fissure, abscess, IBD surgery, biologic use, steroid use), fistulas, exacerbation, IBD surgery, biologic use, steroid use	Depression: clinical recurrence CD + (*P=.001*)¶ UC + (*P=.005*)¶, fistula CD + (*P=.009*)¶, exacerbation UC + (*P=.013*)¶, IBD surgery CD + (*P=.007*)¶, biologic use CD + (*P=.016*)¶, steroid use CD + (*P=.035*)¶ Anxiety: clinical recurrence CD + (*P=.031*)¶ UC - (*P=.066*)¶, exacerbation CD – (*P=.070*)¶ UC + (*P=.044*)¶, biologic use UC + (*P<.001*)¶, steroid use UC + (*P=.013*)¶
Mittermaier [34]	60	Mental assessment by depression (BDI) Mental assessment by anxiety (STAI)	Exacerbation (defined as clinical criteria, CDAI≥150 or an increase of 70 points, or by a CAI of ≥6 for UC plus assessment of laboratory parameters)	Depression: exacerbation at 12 months + (*P<.01*)¶, exacerbation at 18 months + (*P<.01*)¶. Anxiety: exacerbation at 12 months ns (Kendall τ 0.1949), exacerbation at 18 months + (Kendall τ=0.1844 *P<.05*)

Supplementary table 1. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
North [35]	32	Mental assessment by depression (BDI) Mental assessment by visual analog depression scale	A change in disease activity using gastrointestinal scale score Exacerbation using gastrointestinal scale score	Depression (BDI): gastrointestinal scale score 1-month lag ns (regression slope 0.19 (95% CI -0.15-0.52)), gastrointestinal scale score 2-month lag ns (regression slope -0.16 (95% CI -0.65-0.34)), 1 month before exacerbation ns (regression slope -0.46 (95% CI -1.58-0.67)), 2 months before exacerbation ns (regression slope -0.02 (95% CI -1.36-1.32)). Depression (visual analog depression scale): gastrointestinal scale score 1-month lag ns (regression slope 0.03 (95% CI -0.09-0.15)), gastrointestinal scale score 2-month lag ns (regression slope 0.06 (95% CI -0.05-0.18)), 1 month before exacerbation ns (regression slope 0.25 (95% CI -0.23-0.72)), 2 months before exacerbation ns (regression slope -0.21 (95% CI -0.70-0.28)).
Persoons [36]	100	Mental assessment by MDD presence (PHQ-9) Mental assessment by anxiety (HADS-A) Social assessment by SSL-I	Response to infliximab, achievement of remission (CDAI<150), time to retreatment	Depression: response to infliximab ns¶, failure to achieve remission + (aOR=0.166, 95% CI=0.049-0.567, *P=.004*), time to retreatment + (aHR=2.271, 95% CI=1.36-3.79, *P=.002*) Anxiety: response to infliximab ns¶, failure to achieve remission ns¶, time to retreatment ns¶. Social support: response to infliximab ns¶, failure to achieve remission ns¶, time to retreatment ns¶
Riley [37]	92	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Exacerbation defined as symptomatic deterioration and sigmoidoscopy	Depression: exacerbation ns¶ Anxiety: exacerbation ns¶

Supplementary table 1. Continued.

Author	Number of patients	Component of comprehensive geriatric assessment and measured method	Outcome	Association
Takaoka [42]	40	Somatic assessment by malnutrition (SGA) Somatic assessment by malnutrition (MUST) Somatic assessment by malnutrition (NRS 2002) Somatic assessment by malnutrition (O-PNI) Somatic assessment by malnutrition (CONUT)	Intestinal resection, LOS (defined as <28 days vs ≥28 days)	Malnutrition (SGA): intestinal resection ns (operation 53.8%, non-operation 29.6% *P=.071*), LOS + (LOS≥28: 52.6% vs LOS<28: 23.8%, *P=.008*) Malnutrition (MUST score): intestinal resection ns (operation 76.9%, non-operation 51.9%, *P=.314*), LOS ns (LOS≥28: 79.0% vs LOS<28: 42.9%, *P=.058*) Nutritional risk (NRS 2002): intestinal resection ns (operation 76.9%, non-operation 51.9%, *P=.109*), LOS + (LOS≥28: 84.2% vs LOS<28: 52.4%, *P=.032*) Malnutrition (O-PNI): intestinal resection ns (operation median 32.8, non-operation median 37.2, *P=.078*), LOS + (LOS≥28: 33.9 vs LOS<28: 38.2, *P=.006*) Malnutrition (CONUT): intestinal resection ns (operation median 8.0, non-operation median 5.0, *P=.078*), LOS + (LOS≥28: 7.0 vs LOS<28: 5.0, *P=.019*)

NB: +: a significant association between a component of a geriatric assessment and outcome of interest in which more geriatric impairment leads to worse outcome; -: a significant association between a component of a geriatric assessment and outcome of interest in which more geriatric impairment leads to better outcome. When both univariate and multivariate analyses were performed, only results from multivariate analyses (most corrected model) are tabulated. For corrected confounders see supplementary table 2. When a study used more than one model for confounder corrections this is presented as [1] and displayed in supplementary table 2.

Abbreviations: (a)HR, (adjusted) hazard ratio; ns, non-significant; CI, confidence interval; IBD, inflammatory bowel disease; anti-TNF, anti-tumor necrosis factor; CT, computerized tomography; MRI, magnetic resonance imaging; GI, gastrointestinal; GE, gastroenterologist; (a)OR, (adjusted) odds ratio; CD, Crohn's disease; UC, ulcerative colitis; HADS-D, hospital anxiety and depression scale-depression component; HADS-A, hospital anxiety and depression scale-anxiety component; SF36, short form 36; (S)CDAI, (short) Crohn's disease activity index; r, Pearson's correlation coefficient; MIBDI, Manitoba IBD index; SCL90R, symptom checklist 90 revised; CES-D, center for epidemiologic studies depression scale; IBDQ, inflammatory bowel disease questionnaire; MOS, medical outcomes study; GP, general practitioner; (a)β, (adjusted) standardized regression coefficient; ENRICHD, enhancing recovery in coronary heart disease; BDI, Beck depression inventory; STAI, stait trait anxiety index; PROMIS, patient reported outcomes measurement information system; SGA, subjective global assessment; MIRT, malnutrition inflammation risk tool; BIA, bioelectrical impedance analysis; HBI, Harvey Bradshaw index; ρ, Spearman's correlation coefficient; PHQ, patient health questionnaire; (a)RR, (adjusted) relative risk; CAI, colitis activity index; BAI, Beck anxiety inventory SCCAI, simple clinical colitis activity index; MTWAI, modified Truelove Witts activity index; MDD, major depressive disorder; SSL-I, social support list-interactions; MUST, malnutrition universal screening tool; NRS, nutrition risk screening; O-PNI, Onodera's prognostic nutritional index; CONUT, controlling nutritional status; LOS, length of hospital stay. †Total of 124 patients, 59 IBD patients.

Supplementary table 2. Adjustment for confounders per included study

Author	Component of comprehensive geriatric assessment	Corrected for confounders
Allegretti [16]	Mental assessment by depression diagnosis Mental assessment by anxiety diagnosis Social assessment by marital status	Age, LOS, sex, race, chronic pain, IBD type, previous abdominal operation, tobacco use, ethanol abuse, opiate use, steroids in the previous 6 months, infliximab use at index admission, pain clinic follow-up scheduled after discharge, gastrointestinal follow-up scheduled after discharge, and psychiatric follow-up scheduled after discharge. Employment, insurance, education.
Ananthakrishnan [17]	Mental assessment by psychiatric comorbidity (depressive disorder diagnosis and/or generalized anxiety diagnosis)	Age, age at first diagnosis, gender, modified Charlson co-morbidity score, duration of follow-up, and propensity score (to address confounding by disease activity). [1]: adjusted as well for use of anti-TNF or immunomodulator therapy prior to surgery.
Banovic [18]	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Not mentioned
Barnes [19]	Mental assessment by depression diagnosis Mental assessment by anxiety diagnosis	Age, female sex, tobacco abuse, chronic pain, comorbidity score, location and teaching status of hospital, payer/insurance, CDI, need for IBD-related surgery, LOS for index hospitalization, fistula presence.
Bernstein [20]	Mental assessment by Positive and Negative Affect Schedule Social assessment by Social Network Index Social assessment by married/not married	Sex, IBD type, age at diagnosis ≤25 years, smoker, any use of NSAIDs, any infection, use of antibiotics, low childhood SES, fewer high-contact roles ≤4, any major life stress event, high perceived stress, low positive mood, high negative mood.
Bitton [21]	Mental assessment by depression (SCL-90R) Mental assessment by anxiety (SCL-90R)	ns in univariate analyses
Bitton [38]	Mental assessment by depression (SCL-90R) Mental assessment by anxiety (SCL-90R)	ns in univariate analyses
Boer, de [22]	Mental assessment by depression (CES-D) Mental assessment by emotional functioning (IBDQ) Social assessment by IBDQ Social assessment by living alone yes/no Social assessment by MOS Social Support Survey	Age, sex, insurance, education, living alone, co-morbidity, disease activity, disease duration, disease type, IBDQ subscores, experienced burden of disease, social support, depression score (CES-D).

Supplementary table 2. Continued.

Author	Component of comprehensive geriatric assessment	Corrected for confounders
Cámara [23]	Social assessment by ENRICHD Social Support Inventory	Baseline disease activity, female sex, age, disease duration, days in hospital, 5-Aminosalycilates, Sulfasalazine, Steroids, Immunosuppressors, anti-TNF agents, antibiotics, smoking, BMI, positive family history, adherence, time difference, social diversion, social inhibition.
Cámara [24]	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Stress, baseline disease activity, days in hospital, type of therapy (5-Aminosalycilates, sulfasalazine, steroids, immunosuppressors, anti-TNF agents, antibiotics), BMI, smoking, gender, age, disease duration.
Deter [25]	Mental assessment by depression (BDI) Mental assessment by anxiety (STAI)	CDAI at baseline, steroid intake, disease duration, sick leave at randomization, behaviour control.
Gaines [26]	Mental assessment by PROMIS depression questionnaire	Age, gender, race, baseline SCDAI, disease duration, baseline anti-TNF use, BMI, current smoking, level of educational attainment, and sleep, baseline history of hospitalization or surgery, use of steroids and adherence to oral medications.
Jansen [27]	Somatic assessment by malnutrition (SGA) Somatic assessment by malnutrition (MIRT) Somatic assessment by malnutrition (BIA Phase angle) Functional assessment by handgrip strength	Not mentioned
Kochar [28]	Mental assessment by depression (PHQ-8)	Sex, remission status, disease activity.
Langhorst [29]	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Sex, baseline mucosal healing, baseline histology healing, baseline long-term stress, short term stress at last visit before relapse.
Levenstein [30]	Mental assessment by depression (CES-D)	ns in univariate analyses
Mardini [31]	Mental assessment by depression (BDI) Mental assessment by anxiety (BAI)	Age, smoking history, alcohol consumption, employment status, current use of psychotropic medications.
Maunder [39]	Mental assessment by depression (CES-D)	Not mentioned

Supplementary table 2. Continued.

Author	Component of comprehensive geriatric assessment	Corrected for confounders
McCombie [40]	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Baseline SIBDQ
Micic [32]	Somatic assessment by Malnutrition diagnosis Mental assessment by Depression diagnosis Mental assessment by Anxiety diagnosis	Disease type, age, sex, smoking, opioid dependence, cannabis dependence, primary payer, median income, teaching status of hospital, intraabdominal fistula or abscess, bowel obstruction, Clostridium difficile colitis, hypovolemia, electrolyte disturbance, anemia, blood transfusion during hospitalization, any surgery performed, elective surgery.
Mikocka-Walus [41]	Mental assessment by depression (HADS-D) Mental assessment by depression (Symptom Checklist-90R) Mental assessment by anxiety (HADS-A) Mental assessment by anxiety (Symptom Checklist-90R)	Disease activity at baseline, IBD subtype, sex, years since diagnosis and age.
Mikocka-Walus [33]	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Sex (only adjusted in clinical recurrence (composite outcome measurement) analyses)
Mittermaier [34]	Mental assessment by depression (BDI) Mental assessment by anxiety (STAI1)	Depression analyses corrected for: number of flares within the previous year, medication and smoking at baseline, baseline CDAI scores. STAI1 analysis was not corrected.
North [35]	Mental assessment by depression (BDI) Mental assessment by visual analog depression scale	IBD type, BDI was adapted because of overlap with gastrointestinal scale (appetite, weight loss (two questions), general fatigue, and worries about health were removed).

Supplementary table 2. Continued.

Author	Component of comprehensive geriatric assessment	Corrected for confounders
Persoons [36]	Mental assessment by MDD presence (PHQ-9) Mental assessment by anxiety (HADS-A) Social assessment measured with SSL-I	Response to infliximab: all ns in univariate analyses Achievement of remission analysis: baseline CDAI, 'significant biological variables', previous surgery, female gender. Time to retreatment analysis: MDD, use of antidepressant, HADS-A, age, age of diagnosis, member of patient association, any treatment for flare within the previous year, colonic localization, number of days since previous treatment, CDAI, CDAI at re-evaluation, response at re-evaluation.
Riley [37]	Mental assessment by depression (HADS-D) Mental assessment by anxiety (HADS-A)	Not mentioned
Takaoka [42]	Somatic assessment by malnutrition (SGA) Somatic assessment by malnutrition (MUST) Somatic assessment by malnutrition (NRS 2002) Somatic assessment by malnutrition (O-PNI) Somatic assessment by malnutrition (CONUT)	Not mentioned

Abbreviations: LOS, length of hospital stay, IBD, inflammatory bowel disease; HADS-D, hospital anxiety and depression scale-depression component; HADS-A, hospital anxiety and depression scale-anxiety component; CDI, Clostridium difficile infection; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; SCL90R, symptom checklist 90 revised; ns, non significant; CES-D, center for epidemiological studies depression scale;
IBDQ, inflammatory bowel disease questionnaire; MOS, medical outcomes study; ENRICHD, enhancing recovery in coronary heart disease; TNF, tumor necrosis factor; BMI, body mass index; BDI, Beck depression inventory; STAI, Stait trait anxiety index; (S)CDAI, (short) Crohn's disease activity index; PROMIS, patient reported outcomes measurement information system; SGA, subjective global assessment; MIRT, malnutrition inflammation risk tool; BIA, bioelectrical impedance analysis; PHQ, patient health questionnaire; BAI, Beck anxiety inventory; MDD, major depressive disorder; SSL-I=Social Support List-Interactions; MUST, malnutrition universal screening tool; NRS, nutrition risk screening; O-PNI, Onodera's prognostic nutritional index; CONUT, controlling nutritional status;

SUPPLEMENTAL MATERIAL A – PUBMED SEARCH DETAILS

("Inflammatory Bowel Diseases"[Mesh] OR "Inflammatory Bowel Diseases"[tw] OR "Inflammatory Bowel Disease"[tw] OR "IBD"[tw] OR "crohn"[tw] OR "crohns"[tw] OR "crohn's"[tw] OR "ulcerative colitis"[tw] OR "colitis ulcerosa"[tw] OR "Inflammatory Bowel"[tw])

AND

("Geriatric Assessment"[Mesh] OR "Geriatric Assessment"[tw] OR "Geriatric Assessments"[tw] OR "Frail Elderly"[mesh] OR "Frailty"[tw] OR "frail"[tw] OR "Groningen Frailty Indicator"[tw] OR "Geriatric 8"[tw] OR "tilburg frailty indicator"[tw] OR "frailty indicator"[tw] OR "Fried criteria"[tw] OR "frailty index"[tw] OR "frail scale"[tw] OR "Edmonton Frail Scale"[tw] OR "Vulnerable Elders Survey-13"[tw] OR "VES-13"[tw] OR "Groningen Activity Restriction Scale"[tw] OR "Montreal Cognitive Assessment"[tw] OR "Comprehensive Geriatric Assessment"[tw] OR "multidimensional geriatric assessment"[tw] OR "Geriatric Depression Scale"[tw] OR "functional status"[tw] OR "Cognition"[mesh:noexp] OR "cognition"[tiab] OR "cognitive"[tiab] OR "social"[ti] OR "Comorbidity"[Mesh] OR "comorbidity"[tw] OR "co morbidity"[tw] OR "co-morbidities"[tw] OR "comorbidities"[tw] OR "multi morbidity"[tw] OR "multimorbidity"[tw] OR "polypharmacy"[tw] OR "Polypharmacy"[Mesh] OR "Katz Index"[tw] OR "Lawton IADL"[tw] OR "Physical Performance Test"[tw] OR "health-related quality of life"[tw] OR "health related quality of life"[tw] OR "Mini-Nutritional Assessment"[tw] OR "Mini-Nutritional Assessment short form"[tw] OR "Mini-Mental State Examination"[tw] OR "Six Item Cognitive Impairment Test"[tw] OR "6CIT"[tw] OR "6 CIT"[tw] OR "clock drawing test"[tw] OR "Mini-cog"[tw] OR "frax tool"[tw] OR "short physical performance battery"[tw] OR "handgrip strenght"[tw] OR "Charlson Comorbidity Index"[tw] OR "Adult Comorbidity Evaluation-27"[tw] OR "Timed Up and Go"[tw] OR "Timed Up Go"[tw] OR "Timed Up & Go"[tw] OR "tugt"[tw] OR "Nutritional Risk Screening"[tw] OR "Malnutrition Screening Tool"[tw] OR "neuropsychological assessment"[tw] OR "Neuropsychological Tests"[Mesh] OR "Neuropsychological Tests"[tw] OR "Neuropsychological Test"[tw] OR "activities of daily living"[tw] OR "Activities of Daily Living"[Mesh] OR "gait speed"[tw] OR "loss of independence"[tw] OR "muscle strenght"[tw] OR "Mobility Limitation"[Mesh] OR "Risk Assessment"[Majr] OR "risk stratification"[tw] OR ("MNA"[tw] AND nutrition*[tw]) OR "SNAQ"[tw] OR "simplified nutritional appetite"[tw] OR "simplified nutritional assessment"[tw] OR "malnutrition universal screening"[tw] OR ("must"[tw] AND nutrition*[tw]) OR ("Health Reported"[tw] AND "Quality of Life"[tw]) OR "HRQOL"[tw] OR "HR QOL"[tw] OR "Depression"[Mesh] OR "Depressive disorder"[Mesh] OR "mental depression"[tw] OR "depressive disorder"[tw] OR "depressive disorders"[tw] OR "mood"[tw] OR "GDS"[tw] OR "geriatric depression scale"[tw] OR "CES-D"[tw] OR "HADS"[tw] OR "Beck Depression Inventory"[tw] OR "BDI"[tw])

Additional anxiety PubMed search:

("Inflammatory Bowel Diseases"[Mesh] OR "Inflammatory Bowel Diseases"[tw] OR "Inflammatory Bowel Disease"[tw] OR "IBD"[tw] OR "crohn"[tw] OR "crohns"[tw] OR "crohn's"[tw] OR "ulcerative colitis"[tw] OR "colitis ulcerosa"[tw] OR "Inflammatory Bowel"[tw])

AND

("Anxiety"[Mesh] OR "Anxiety"[tw] OR "Anxiety Disorders"[Mesh:NoExp] OR "Beck Anxiety Inventory"[tw] OR "Stait Trait Anxiety Inventory"[tw])

SUPPLEMENTAL MATERIAL B - QUALITY ASSESSMENT OF STUDIES, BASED ON THE NEWCASTLE-OTTAWA SCALE[9]

1. Selection

Representativeness of the exposed cohort

++ Study focusses on older patients (≥60 years) or makes a clear statement about the group of older patients included and population is representative of the average IBD patient and beholds a heterogeneous population

+ Some older patients (≥60 years old) included and representative of the average IBD patient

+/- almost no older patients included (≥60 years old), somewhat representative of the average IBD patient

- No older patients and somewhat representative of the average IBD patient

-- No older patients and not representative of the average IBD patient

? No clear description of abundance of older patients or IBD characteristics

Ascertainment of exposure (geriatric assessment)

+ Clearly described and validated geriatric assessment tool/questionnaire, or validated diagnosis /diagnosis code.

+/- Partly described or validated geriatric measurement, or a partly described code / diagnosis is used with vague statement on how diagnosis was obtained

- A Geriatric assessment tool/questionnaire is used but not validated nor described, or a code / diagnosis is used without statement on the obtainment of diagnosis.

2. Outcome

Assessment of outcome

+ Clear description of method measuring outcome (validated GA or validated diagnosis)

+/- Partly described outcome or only status description of a diagnosis

- Unclear description of method measuring outcome

? No description

Sufficient duration of follow-up

+ Yes, follow-up was long enough for outcomes to occur

+/- Partly enough

- No

? No description of follow up period

Adequacy of follow up of cohorts

+ Complete follow up (all subjects accounted for), or subjects lost to follow up unlikely to introduce bias (loss to follow up < 10%),

+/- loss to follow up more than 10% but clear description of those lost

- Follow up rate < 90% and no description of those lost

? No statement

4

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

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ABSTRACT

Aim To assess safety and effectiveness of anti-tumor necrosis factor (anti-TNF) therapy in IBD patients ≥60 years.

Methods Ninety IBD patients ≥60 years at initiation of anti-TNF therapy, 145 IBD patients ≥60 years without anti-TNF therapy and 257 IBD patients <60 years at initiation of anti-TNF therapy were retrospectively included in this multicentre study. Primary outcome was the occurrence of severe adverse events (SAE's), serious infections and malignancies. Secondary outcome was effectiveness of therapy. Cox regression analyses were used to assess differences in safety and effectiveness. In safety analyses, first older patients with and without anti-TNF therapy and then older and younger patients with anti-TNF therapy were assessed.

Results In older IBD patients, the use of anti-TNF therapy was associated with serious infections (aHR 3.920, 95% CI 1.185-12.973, p=.025). In anti-TNF exposed patients, cardiovascular disease associated with serious infections (aHR 3.279, 95% CI1.098-9.790, p=.033), and the presence of multiple comorbidities (HR 9.138 (1.248-66.935), p=.029) with malignancies, while patient age did not associate with safety outcomes. Effectiveness of therapy was not affected by age or comorbidity.

Conclusions Older patients receiving anti-TNF therapy have a higher risk of serious infections compared to older IBD patients without anti-TNF therapy, but not compared to younger patients receiving anti-TNF therapy. However, in anti-TNF exposed patients, comorbidity was found to be an indicator with regards to SAE's. Effectiveness was comparable between older and younger patients.

INTRODUCTION

As a consequence of the aging population and the rising prevalence of inflammatory bowel diseases (IBD), the group of older patients with Crohn's disease (CD) or ulcerative colitis (UC) is enlarging. [1] Currently, approximately 10-30% of IBD patients is >60 years old and about 10-15% of new IBD cases is diagnosed in patients >60 years of age. [2-4]

Safety and effectiveness of medication may differ between older and younger patients, as a consequence of comorbidity, polypharmacy, senescence of the immune system or altered clearance of drugs. [5 6] Results from clinical trials cannot be extrapolated to the older patient population with IBD because these patients are generally excluded from trial participation and available data from observational studies on the occurrence of severe adverse events (SAE's) in older IBD patients exposed to anti-TNF therapy are inconsistent. [7-10] Besides this, previous literature has been focussing on patient age, rather than comorbidity as a predictor of safety and effectiveness in patients with IBD receiving anti-tumor necrosis factor (TNF) therapy.

The aim of the present study is therefore to assess safety and effectiveness of anti-TNF therapy in patients with IBD aged 60 years and older while accounting for the presence of comorbidities.

METHODS

Patients

This is a retrospective multicentre cohort study combining data from five hospitals in the Netherlands (University Medical Centre Utrecht (UMCU), St. Antonius Hospital Nieuwegein, Diakonessenhuis Utrecht, Leiden University Medical Centre (LUMC) and Maastricht University Medical Centre (MUMC)) on the effect of patient age on safety and effectiveness of anti-TNF therapy (infliximab (IFX), adalimumab (ADA) or certolizumab pegol (CZP)). Ethical approval has been granted by the medical research ethics committee Leiden The Hague Delft, MREC registration number G20.057 and research was conducted in accordance with the ethical standards as laid down in the declaration of Helsinki. Patients with an established IBD diagnosis were assigned to one of three groups.[11] First, patients exposed to anti-TNF therapy for the first time at ≥60 years, second, patients without any exposure to anti-TNF therapy aged ≥60 years and third, patients <60 years exposed to anti-TNF therapy.

The following data were collected: age, sex, diagnosis, date of diagnosis, duration of follow-up, number of IBD-related hospitalizations and data on anti-TNF therapy and immunosuppressive medication. Oral prednisone treatment was documented if prescribed for a period of at least six months at daily doses of ≥7.5 milligrams. Hepatic comorbidities (steatosis, drug induced liver disease, chronic hepatitis B, chronic hepatitis C and alcoholic

liver disease), gastro-intestinal comorbidities (celiac disease, diverticular disease, ischemic colitis, drug induced colitis and radiation enteropathy), cardiovascular comorbidities (acute mesenteric ischemia, ischemic heart disease, cerebrovascular disease and hypertension), pulmonary comorbidities (asthmatic bronchitis and chronic obstructive pulmonary disease) and the presence of diabetes were recorded.

Outcomes

Primary outcome was safety, defined as the occurrence of any SAE, serious infection or malignancy. Any SAE was defined as any event that resulted in (prolonging) hospitalization, was fatal or life-threatening or led to significant disability. Serious infections were defined similarly. A malignancy was considered a SAE. In addition, serious infections and malignancies were analysed separately as safety outcomes. Hospitalization at start of anti-TNF therapy was not considered a SAE.

Secondary outcome was effectiveness of therapy, defined by treatment response, which was categorized as total sustained clinical benefit (primary clinical benefit or secondary clinical benefit, see below) or no sustained clinical benefit. Patients still receiving anti-TNF therapy at the last day of follow-up or in whom therapy had been discontinued because of remission were assigned to the total sustained clinical benefit group. If anti-TNF therapy had never been switched to another type of TNF-inhibitor, total sustained clinical benefit was scored as primary clinical benefit. Total sustained clinical benefit after one or more switches of anti-TNF therapy was labelled secondary clinical benefit. If anti-TNF therapy was discontinued because of primary non-response, loss of response, occurrence of an adverse event or any other reason, patients were classified as having 'no sustained clinical benefit'. Primary non-response was defined as lack of improvement of clinical signs and symptoms after induction therapy. Loss of response was defined as recurrence of disease activity during maintenance therapy after achieving an appropriate induction response. [12]

Statistical analysis

All analyses were performed using IBM SPSS Statistics version 23.0 (SPSS, Inc, Chicago, IL). For continuous data, descriptive statistics were calculated as means with standard deviations (SD) when data were normally distributed and medians with interquartile ranges (IQR) when not normally distributed. Comparisons between groups were performed using Independent-Samples-T Test or Mann-Whitney U test. Categorical variables were reported using absolute numbers and percentages, comparisons were performed using the $\chi 2$ test or Fisher's exact test. Cox proportional hazards model was used to assess the effect of patient age and comorbidity on primary and secondary outcomes and to assess the effect of therapy as a time dependent variable on primary outcome. To assess whether comorbidity or patient age at start of first anti-TNF therapy affected effectiveness outcomes, Cox proportional hazards model was used. Safety was defined in three different outcomes: any SAE, serious infection and malignancy. For any SAE and malignancy analyses, events occurring until end of follow-up were used. For serious infections, events occurring up until three months

after last administration of medication were used. Effectiveness was defined as duration of anti-TNF therapy.

To assess the influence of anti-TNF therapy on the occurrence of infections and malignancies as a time dependent variable, exposure to anti-TNF therapy was tested as a time-dependent covariate in a Cox proportional hazards model. Exposure time was defined as time from the first anti-TNF infusion until the occurrence of a SAE or end of follow-up. We selected older IBD patients with and without anti-TNF therapy and used duration of follow up since date of diagnosis until end of follow-up as 'time' in the malignancy analysis and follow-up since date of diagnosis until 3 months after the last date of first anti-TNF therapy or end of follow-up in the infection analysis. Hospitalization of any infection or the diagnosis of any malignancy was used as 'status'. In the analyses regarding malignancies, covariates age, comorbidity (categorized in no comorbidity, one comorbidity and two or more comorbidities, or specified in cardiovascular disease and diabetes), use of immunosuppressive therapy (oral prednisone and MTX/thiopurine use), use of budesonide and use of anti-TNF therapy were used. In the analysis regarding serious infections, immunosuppressive therapy was not used as a covariate because a cut off follow-up duration was applied and start and stop dates of immunosuppressive therapy had not been consistently documented. A p-value of <.05 was considered statistically significant.

RESULTS

Study population characteristics

We identified 347 IBD patients currently using anti-TNF therapy, of whom 90 were 60 years or older at initiation of anti-TNF therapy and of whom 257 patients were younger than 60 years at the start of anti-TNF therapy. An additional 145 anti-TNF naive IBD patients of 60 years or older served as controls. The first group of patients was included in the hospitals UMCU (24.4%), St. Antonius Hospital Nieuwegein (16.7%), Diakonessenhuis Utrecht (5.6%), LUMC (17.8%) and MUMC (35.7%). Patients from group 2 were included in the hospitals UMCU (81.7%), Sint Antonius Hospital Nieuwegein (1.9%), Diakonessenhuis Utrecht (4.7%), LUMC (4.3%) and MUMC (7.4%). Patients in group 3 were included in UMCU (99.3%) and LUMC (0.7%). Characteristics of these patients are shown in table 1.

Older patients receiving anti-TNF therapy less often had CD compared to patients receiving anti-TNF therapy at a younger age. The older patients more often had diabetes, gastro-intestinal, cardiovascular and other comorbidities and less often used MTX or thiopurine therapy compared to younger patients with anti-TNF therapy (87.8% versus 96.1%, p<.010). Patients in the anti-TNF naive group were diagnosed at a younger age when compared to the older patients on anti-TNF therapy. Anti-TNF naive patients differed from the older patients on anti-TNF therapy with respect to diagnosis (less CD, more UC) and the use

of immunosuppressive therapy (less thiopurines or MTX). Comorbidity rates were similar between older IBD patients with and without anti-TNF therapy.

Does anti-TNF therapy influence the occurrence of safety outcomes in older patients?

To assess the effect of anti-TNF therapy on safety outcomes in older patients, all older patients were analysed using date of diagnosis as start of follow up, with the use of anti-TNF therapy as a time-dependent covariate.

Twenty-eight serious infections occurred during follow-up. Use of anti-TNF therapy was found to increase risk of serious infections (aHR 3.920, 95% CI 1.185-12.973, p=.025) in multivariable Cox regression. Age at diagnosis, number of comorbidities (table 2) and the presence of cardiovascular disease or diabetes (data not shown) present did not affect the risk of serious infections (table 2).

Twenty-six malignancies occurred during follow-up. Univariable and multivariable Cox regression analysis did not show an association between the use of anti-TNF therapy and the development of malignancies during follow-up (table 3). The presence of the comorbidities diabetes and/or cardiovascular disease was also not associated with occurrence of malignancies (data not shown). Infections and malignancies are presented in supplementary table 1 and 2.

Do patient age or comorbidity affect the safety of anti-TNF therapy?

To assess the effect of patient age and comorbidity on safety outcomes in anti-TNF therapy, all anti-TNF exposed patients were analysed. One hundred and eighteen SAE's (any SAE) occurred after start of first anti-TNF therapy, the majority (46, 40.0%) because of exacerbation of disease and 26 (22.3%) because of IBD-related surgery. Age at start of anti-TNF therapy and comorbidity were not associated with the occurrence of any SAE (supplementary table 3a). The incidence of IBD-related surgery did not differ between older and younger anti-TNF users (5 out of 90 patients (5.6%) versus 21 out of 257 (8.2%), p=0.417).

Twenty serious infections occurred after start of anti-TNF therapy, but age did not affect the risk of occurrence. The presence of cardiovascular disease was independently associated with the occurrence of serious infections (aHR 3.279, 95% CI 1.098-9.790, p=.033), whereas presence of diabetes or the presence of any comorbidity was not (supplementary table 3b).

Eight malignancies were diagnosed after start of anti-TNF therapy, age was not a risk factor (supplementary table 3c).The presence of two or more comorbidities was independently associated with the risk of developing a malignancy (aHR 9.138, 95% CI 1.248-66.935, p=.029, supplementary table 3c). A list of all SAE's occurring after start of first anti-TNF therapy is presented in supplementary tables 4, 5 and 6.

Do patient age or comorbidity affect the effectiveness of anti-TNF therapy?
The clinical effectiveness of anti-TNF therapy did not differ between older and younger anti-TNF users (table 4) or between patients with and without comorbidity. Follow up, defined as the time from first anti-TNF administration until discontinuation of therapy was significantly shorter in the group of older patients compared to younger patients (median duration 70.5 weeks (34.0-155.3) versus 110.0 weeks (41.5-217.0), p=.017, table 4). Follow up did not differ between patients with and without comorbidity (median duration 114.0 weeks (47.0-221.0) versus 92.0 weeks (35.0-200.5), p=.161). When using Cox regression analysis, age at start of anti-TNF therapy, comorbidity and type of anti-TNF therapy did not affect duration of treatment (table 5). The presence of diabetes or cardiovascular disease during follow-up did not significantly affect the duration of treatment as well (data not shown).

The number of older patients discontinuing anti-TNF therapy because of adverse events was significantly higher compared to younger patients (55.9% versus 28.1%, p=.004, table 4) while the number of older patients stopping because of loss of response was significantly lower (26.5% versus 59.5%, p=.001, table 4). The number of patients with comorbidity discontinuing anti-TNF therapy because of adverse events was significantly higher compared to patients without comorbidity (47.1% versus 27.9%, p=.018). The number of patients with comorbidity stopping because of loss of response was lower as compared to patients without comorbidity, although this did not differ significantly (43.1% versus 56.7%, p=.111). Reasons for stopping are presented in supplementary table 7.

Table 1. Characteristics of study population

	Older patients with anti-TNF therapy (n=90)	**Older patients without anti-TNF therapy (n=145)**	**Younger patients with anti-TNF therapy (n=257)**
Age at inclusion in years, median [IQR]	68.72 [66.74-73.00]	69.44 [65.01-75.02]	37.43 [27.72-20.24]***
Male, n (%)	49 (54.4)	84 (57.9)	121 (47.1)
Age at diagnosis, mean (±SD)	52.15 (16.10)	46.39 (15.75)**	26.16 (11.27)***
Age at start anti-TNF therapy, mean (±SD)	67.56 (6.00)	n.a.	34.18 (12.94)***
Disease duration in years, median [IQR]	16.67 [5.73-29.48]	21.31 [12.04-34.14]**	10.14 [5.58-18.23]*
Duration of FU in weeks (start first anti-TNF till end FU or stop therapy) median [IQR]	70.50 [34.00-155.25]	n.a.	110.00 [41.50-217.00]*

Table 1. Continued.

	Older patients with anti-TNF therapy (n=90)	**Older patients without anti-TNF therapy (n=145)**	**Younger patients with anti-TNF therapy (n=257)**
Duration of FU in months (date diagnosis till malignancy or end FU), median [IQR]	194.00 [66.00-322.50]	249.00 [144.00-396.00]	n.a.
Duration of total anti-TNF therapy in years, median [IQR]	1.72 [0.81-4.04]	n.a.	3.34 [1.44-5.41]***
Type of IBD, n (%)			
CD	56 (62.2)	67 (46.2)**	206 (80.2)**
UC	30 (33.3)	71 (49.0)**	44 (17.1)**
IBD-U/IC	4 (4.4)	7 (4.8)	7 (2.7)
Montreal Classification, n(%)			
CD Location L1/L2/ L3/L4	11 (19.6)/ 18 (32.1)/ 26 (46.2)/ 1 (1.8)	14 (21.2)/ 25 (37.9)/ 27 (40.9)/ 0 (0.0)	30 (14.6)/ 61 (29.6)/ 112 (54.4)/ 3 (1.5)
CD Behaviour B1/ B2/B3	19 (34.5)/ 26 (47.3)/ 10 (18.2)	36 (53.7)/ 17 (25.4)/14 (20.9)*	81 (39.5)/ 68 (33.2)/ 56 (27.3)
Perianal disease	21 (41.1)	10 (15.2)**	85 (43.4)
UC extension E1/ E2/E3	0 (0.0)/ 14 (45.2)/ 17 (54.8)	2 (2.9)/29 (42.6)/ 37(54.4)	1 (2.2)/ 12 (26.7)/ 32 (71.1)
Comorbidity, n (%)			
Hepatic	6 (6.7)	14 (9.7)	8 (3.1)
Gastrointestinal	19 (21.1)	28 (19.3)	6 (2.3)***
Cardiovascular	35 (38.9)	74 (51.0)	34 (13.2)***
Pulmonary	10 (11.1)	18 (12.4)	18 (7.0)
Diabetes Mellitus	14 (15.7)	18 (12.4)	12 (4.7)**
Comorbidity, n (%)			
No comorbidity	35 (38.9)	47 (32.4)	191 (74.3)***
One comorbidity	33 (36.7)	55 (37.9)	54 (21.0)
Two or more comorbidities	22 (24.4)	43 (29.7)	12 (4.7)
Type of TNF-inhibitor, n (%)			
IFX	67	n.a.	220*
ADA	44		129
CZP	0 (0.0)		5

Table 1. Continued.

	Older patients with anti-TNF therapy (n=90)	**Older patients without anti-TNF therapy (n=145)**	**Younger patients with anti-TNF therapy (n=257)**
Immunosuppressant, n (%)			
Thiopurines/MTX	79 (87.8)	51 (35.4)***	247 (96.1)**

Older Inflammatory Bowel Disease (IBD) patients (≥60 years) at initiation of anti-tumor necrosis factor (anti-TNF) therapy were compared to older IBD patients (≥60 years) without any anti-TNF therapy and with younger IBD patients aged <60 years at initiation of anti-TNF therapy. Significant differences are shown. *** p<.001, **p<.01, *p<.05.

IQR=interquartile range, SD=standard deviation, FU=follow-up, CD=Crohn's disease, UC=ulcerative colitis, IBD-U=IBD Unclassified, IC=Indeterminate Colitis, IFX=Infliximab, ADA=Adalimumab, CZP=Certoluzimab pegol, MTX=Methotrexate.

L4 was reported when only upper Gastrointestinal (GI) disease was present, CD Location was missing in N=1 (group 3), CD Behaviour was missing in N=1 (group 1) and N=1 (group 2), Perianal disease was missing in N=5 (group 1), N=10 (group 2) and N=1 (group 3), UC Extension was missing in N=3 (group 1), N=6 (group 2) and N=10 (group 3). The use of MTX was missing in N=1 in the group with older IBD patients without anti-TNF therapy.

Table 2. Univariable and multivariable analysis on the occurrence of serious infections in older anti-TNF users and older non-users, using follow-up time from date of diagnosis until 3 months after last administration of anti-TNF therapy or end of follow-up

	Univariable Analysis			**Multivariable analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
anti-TNF therapy	5.131	1.679-15.684	0.004	3.920	1.185-12.973	0.025
Age at diagnosis	1.026	0.997-1.057	0.078	1.018	0.987-1.049	0.264
Comorbidity*						
1	1.308	0.550-3.112	0.544	1.164	0.487-2.785	0.733
2 or more	1.202	0.445-3.247	0.717	0.999	0.363-2.751	0.998

HR=Hazard Ratio, CI=Confidence Interval, TNF=Tumor Necrosis Factor *reference is zero comorbidities.

Table 3. Univariable and multivariable analysis on the occurrence of malignancies in older anti-TNF users and older non-users, using follow-up time from date of diagnosis until end of follow-up

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Anti-TNF therapy	2.617	0.770-8.894	0.123	1.422	0.284-7.128	0.668
Age at diagnosis	1.046	1.010-1.082	0.011	1.025	0.989-1.063	0.178
Comorbidity*						
1	3.248	1.058-9.971	0.040	2.706	0.844-8.683	0.094
2 or more	4.036	1.238-13.156	0.021	2.869	0.809-10.183	0.103
Budesonide	1.681	0.771-3.663	0.191	1.746	0.758-4.018	0.190
Oral prednisone	0.721	0.287-1.815	0.488	1.012	0.365-2.802	0.982
MTX and/or thiopurine use	0.700	0.321-1.527	0.270	0.630	0.245-1.621	0.338

HR=Hazard Ratio, CI=Confidence Interval, TNF=Tumor Necrosis Factor, MTX= Methotrexate *reference is zero comorbidities

Table 4. Treatment response in older and younger anti-TNF users

	Older anti-TNF patients (n=90)	**Younger anti-TNF patients (n=257)**	**P-value**
First anti-TNF therapy, n (%)			
IFX	59 (65.6)	199 (77.4)	0.035
ADA	31 (34.4)	58 (22.6)	
First anti-TNF treatment duration in weeks, median [IQR]	70.50 [34.00-155.25]	110.00 [41.50-217.00]	0.017
Stop date of first anti-TNF therapy n (%)*			0.004
year <2005	0 (0,0)	14 (11.0)	
year 2005-2009	6 (17.1)	46 (36.2)	
year ≥2010	29 (82.9)	67 (52.8)	
Total sustained clinical benefit,	73 (81.1)	201 (78.2)	0.653
n (%)	55 (61.1)	133 (51.8)	0.141
Primary clinical benefit, n (%)	18 (20.0)	68 (26.5)	0.257
Secondary clinical benefit, n (%)			
Stop reasons for first anti-TNF treatment , n (%)			
Primary non-responder	1 (2.9)	5 (4.7)	1.000
Secondary loss of response	9 (26.5)	72 (59.5)	0.001
Adverse event	19 (55.9)	34 (28.1)	0.004
Other	5 (14.7)	10 (8.3)	0.323

Treatment response compared between patients on anti-TNF therapy aged ≥60 years and aged <60 years. Stop date of first anti-TNF therapy: the year in which the first anti-TNF therapy was stopped. Total sustained clinical benefit: still receiving anti-TNF therapy at last day of FU or anti-TNF therapy discontinuation because of remission. Primary clinical benefit: no switch to other anti-TNF therapy during FU and still receiving anti-TNF therapy at last day of FU or discontinuation of remission of disease. Secondary clinical benefit: clinical benefit after one or more switches of anti-TNF therapy. Primary non-responder: lack of improvement of clinical signs and symptoms after induction therapy. Secondary loss of response: recurrence of disease activity during maintenance therapy after achieving an appropriate induction response. Percentages per stop reason were calculated as percentage of all stop reasons per group. TNF= Tumor Necrosis Factor, IQR=Interquartile Range, IFX=Infliximab, ADA=Adalimumab, FU=Follow-Up

Table 5. Univariable and multivariable analysis on duration of first anti-TNF treatment

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	0.999	0.991-1.008	0.906	1.000	0.990-1.010	0.966
Comorbidity*						
1	0.739	0.501-1.088	0.126	0.731	0.484-1.104	0.137
2 or more	1.130	0.676-1.887	0.642	1.130	0.635-2.012	0.678
Type of anti-TNF therapy±	1.087	0.753-1.568	0.657	1.114	0.767-1.620	0.570

HR=Hazard Ratio, CI=Confidence Interval, TNF=Tumor Necrosis Factor *reference is zero comorbidities, ±reference is infliximab therapy (certolizumab pegol was not used as first anti-TNF therapy)

DISCUSSION

In this multicentre study we found that the presence of comorbidity was a better indicator of serious infections and malignancies in anti-TNF exposed patients than patient age. Effectiveness of anti-TNF therapy was comparable between older and younger patients. Reasons for cessation of therapy did differ, being more often due to adverse events in older patients and patients with comorbidity.

In our study, exposure to anti-TNF treatment increased the risk of serious infections in older patients with IBD. In the Treat registry an increase in serious infections was observed in anti-TNF treated IBD patients. [13] Lobaton et al. found a higher incidence of serious infections in patients aged ≥65 years on anti-TNF therapy as compared to older patients using immunosuppressive medication and/or corticosteroids. [8]

More recently, two meta-analyses were published assessing safety risks of biologics in older patients with IBD. Both Piovani et al. (RR 2.70, 95% CI 1.56-4.66, serious infections) and Borren and Ananthakrishnan (OR 11.22; 95% CI 3.60-34.99, any infection) found that the risk of infections was substantially increased when comparing older anti-TNF users to older non-users.[14 15]

When comparing younger to older patients, we used age at start of follow-up as a factor in multivariate analysis instead of using an arbitrary cut-off at 60 or 65 years of age. As ageing is a gradual process with a steady reduction of physiologic reserves, this strategy may be a better way to evaluate the role of ageing on occurrence of serious infections and malignancies. In our study, patient age did not affect the occurrence of SAE's, serious infections and malignancies. However, presence of cardiovascular disease did increase the risk of serious infections, and the presence of multiple comorbidities increased the risk of developing a malignancy.

These findings are in contrast to those of the Borren and Ananthakrishnan meta-analysis, in which older patients had a higher risk of malignancy (OR, 3.47; 95% CI, 1.71–7.03) and

infection (OR, 3.48; 95% CI, 1.98–6.14). This may be due to the fact that the patients in a number of these studies were older [16 17] and may have had more comorbidities.

Especially this latter factor may be important as studies on toxicity of chemotherapy found that comorbidity increases the risk for toxicity and is a better indicator for toxicity risk than patient age.[16 17] Previous studies found that presence of comorbidities increased the risk for adverse events in response to immunosuppressive treatments. [18 19]

Desai et al. concluded that older IBD patients were less likely to respond to anti-TNF therapy and had a shorter drug survival as compared to younger patients. Among both patient groups, comorbidity (Charlson Comorbidity Index (CCI) >0) was associated with anti-TNF therapy discontinuation. This could be due to polypharmacy combined with altered drug absorption, distribution and elimination [20] or due to an increased opportunity for drug interactions because of polypharmacy for multiple morbidities. [21]

In line with a recent study on persistence of anti-TNF therapy in older patients with IBD by Porcari et al. [22] we observed a shorter treatment duration in older patients compared to younger patients. However, when analysing both patient groups together using Cox regression analysis and correcting for confounders, age at start of therapy did not affect treatment duration. Older patients did discontinue therapy more frequently due to adverse events, and less often due to loss of response, as compared with younger patients. This has also been described by Desai et al.[7] Both our results and the study by Porcari et al. did not find comorbidity to affect time to cessation of anti-TNF therapy while Desai et al. found increasing comorbidity to be associated with treatment cessation.[7] Regarding effectiveness, Lobaton et al. only found a reduced short-term response to anti-TNF therapy in older patients, but this difference disappeared after six months. [8]

Our study has some limitations, in addition to those inherent to any study with a retrospective design. Clinical activity scores were not available, as a result of which data on clinical treatment response were based on comments in medical reports instead of disease activity scores. Comorbidity scores were based on the sum of comorbidities because information to calculate a comorbidity score such as the CCI was not fully available. However, because data in all patients were obtained from medical reports, reporting bias would have affected all patients equally. Furthermore, younger patients exposed to anti-TNF therapy were mostly (93.4%) included in referral centres and the older non anti-TNF users were included in referral hospitals only. One could argue this could have affected comparability of patients, although we assume that in all hospitals international guidelines considering anti-TNF therapy are maintained, especially concerning reasons to stop therapy. The older non anti-TNF users, although included in a referral centre, had a milder disease compared to older anti-TNF users, as expressed by the infrequent use of immunomodulatory medication in this group during follow-up.

The strength of our study lies in the large number of patients included and the multicentre aspect; patients were included from three referral hospitals and two general hospitals. We believe that our study therefore provides reliable and generalizable data on the effect of anti-TNF compounds in older patients with IBD.

In conclusion, this study shows that the presence of comorbidities, and not an increasing age, is a risk factor for SAE's in IBD patients on anti-TNF therapy. Older patients receiving anti-TNF therapy have a higher risk of serious infections compared to older IBD patients without anti-TNF therapy, but not compared to younger IBD patients receiving anti-TNF therapy. Effectiveness of therapy was comparable between older and younger patients but older patients tend to stop therapy more often because of adverse events and less often due to loss of response compared to younger patients. Careful monitoring of the older IBD patient with multiple comorbidities receiving anti-TNF therapy is recommended.

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Supplementary table 1. List of malignancies occurring during follow-up from date of diagnosis in older anti-TNF users and older non-users

Patient ID	Age at start follow-up	Time after diagnosis in months	Event type
441	16,13	404	Colorectal carcinoma
363	16,96	486	Colorectal cancer
347	20,26	433	Breast cancer
16	23,81	156	Pleomorphic adenoma of the parotid gland
442	24,18	502	Prostate cancer
416	28,96	345	Urothelial carcinoma
448	29,28	285	Colorectal carcinoma
17	30,33	324	Prostate cancer
48	31,81	322	Prostate cancer
444	32,64	244	Endometrial cancer
428	37,19	434	Non-Hodgkin lymphoma
326	37,75	233	Prostate cancer
440	38,41	300	Colorectal carcinoma
325	42,33	248	Pancreatic carcinoma
360	43,04	288	Colorectal cancer
382	43,49	208	Prostate cancer
402	44,42	271	Oesophageal carcinoma
61	46,8	254	Breast cancer
438	51,63	313	Colorectal carcinoma
6	52,29	162	Pancreatic carcinoma
394	52,65	176	Prostate cancer
310	56,22	24	Lung cancer
348	61,89	0	Colorectal cancer
72	62,71	32	Prostate cancer
322	67,85	96	Breast cancer
53	70,82	97	Renal cell cancer

Supplementary table 2. List of infections occurring after date of IBD diagnosis until 3 months after last administration of anti-TNF therapy or until end of follow up in older users and older non-users

Patient ID	Age at start follow-up	Time after diagnosis in months	Event type
1	25,80	156	Perianal abscess
17	30,33	235	Fever
26	59,93	3	Perianal abscess
28	46,58	153	Drainage of abscess
29	18,34	577	Fever due to bacterial translocation
32	24,75	114	Incision abdominal abscess
42	37,19	292	Drainage abdominal abscess
43	30,70	455	Cholangitis (suspect)
44	42,75	229	Perianal abscess next to pouch
47	46,60	6	Drainage perianal abscesses
52	31,13	317	CMV pouchitis and ileitis
58	29,63	264	Drainage of abscess
70	29,99	124	Incision and drainage perianal abscess
71	71,35	0	Fever and cold shivers
323	20,47	264	Abdominal abscess
341	53,15	82	Abscess right lower abdomen
365	43,38	335	Septic abdomen
375	66,38	14	Abscess
381	54,11	138	Abscess
382	43,49	35	Abscess
388	43,03	124	Incision and drainage perianal abscess
395	56,54	230	Intraabdominal abscess
402	44,42	119	Abdominal pain and fever
410	50,48	13	Gastroenteritis
412	53,87	13	Abscess
451	42,00	110	Douglas abscess
480	70,24	50	Abscess
491	64,68	2	Herpes zoster infection

Supplementary table 3a. Univariable and multivariable analysis on the occurrence of any SAE in older and younger IBD patients on anti-TNF therapy

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	0.988	0.988-1.008	0.629	0.992	0.980-1.003	0.154
Diabetes	1.740	0.977-3.098	0.060	1.783	0.990-3.211	0.054
Cardiovascular Disease	1.311	0.853-2.016	0.217	1.503	0.912-2.477	0.110

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	0.988	0.988-1.008	0.629	0.994	0.983-1.006	0.313
Comorbidity*						
1	0.961	0.620-1.491	0.860	1.042	0.655-1.658	0.862
2 or more	1.435	0.811-2.541	0.215	1.678	0.879-3.206	0.117

HR=Hazard Ratio, CI=Confidence Interval *reference is zero comorbidities

Supplementary table 3b. Univariable and multivariable analysis on the occurrence of serious infections in older and younger IBD patients on anti-TNF therapy

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.008	0.984-1.033	0.513	0.992	0.964-1.020	0.559
Diabetes	1.992	0.572-6.938	0.279	1.684	0.473-6.000	0.421
Cardiovascular disease	2.882	1.1727.085	0.021	3.279	1.098-9.790	0.033

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.008	0.984-1.033	0.513	1.002	0.975-1.029	0.907
Comorbidity*						
1	2.004	0.790-5.087	0.144	1.962	0.724-5.318	0.185
2 or more	1.552	0.336-7.166	0.573	1.492	0.282-7.893	0.638

HR=Hazard Ratio, CI=Confidence Interval *reference is zero comorbidities

Supplementary table 3c. Univariable and multivariable analysis on the occurrence of malignancies in older and younger IBD patients on anti-TNF therapy

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.061	1.015-1.109	0.009	1.050	0.995-1.107	0.076
Diabetes	6.506	1.535-27.571	0.011	3.970	0.929-16.961	0.063
Cardiovascular disease	4.250	1.059-17.049	0.041	1.593	0.338-7.519	0.556

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.061	1.015-1.109	0.009	1.035	0.979-1.095	0.223
Comorbidity*						
1	1.406	0.127-15.534	0.781	0.837	0.065-10.734	0.892
2 or more	19.545	3.741-102.101	0.000	9.138	1.248-66.935	0.029

HR=Hazard Ratio, CI=Confidence Interval *reference is zero comorbidities

Supplementary table 4. List of any serious adverse events after start of anti-TNF therapy up until end of follow-up

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
281	11,4	14	Exacerbation	Exacerbation
306	12,31	382	Exacerbation	Exacerbation
243	14,23	3	Exacerbation	Exacerbation
222	15,27	49	IBD Surgery	Ileocecal resection
187	15,73	15	Exacerbation	Exacerbation
213	16,11	215	Exacerbation	Exacerbation
97	17,37	6	Exacerbation	Exacerbation
221	17,73	23	IBD related complication or symptom	Hematoma, abscess right lower abdomen and perihepatic abscess
207	18,13	80	Exacerbation	Exacerbation
147	18,62	28	IBD Surgery	Ileocecal resection
287	18,66	23	IBD related complication or symptom	Abdominal pain
194	18,71	316	Exacerbation	Exacerbation
120	18,86	144	Exacerbation	Exacerbation
226	19,09	132	Exacerbation	Exacerbation
98	20,11	89	IBD Surgery	Subtotal colectomy
85	20,56	169	Exacerbation/ Infection	Exacerbation or urinary tract infection
160	20,91	399	IBD Surgery	Subtotal colectomy
138	21,1	213	Medication complication	Sensibility loss of the lower legs
181	22,35	180	IBD related complication	Ileocecal abscess
174	22,38	329	Exacerbation	Exacerbation
252	22,6	38	IBD Surgery	Ileocecal resection
275	22,86	41	IBD related complication or symptom	Perianal abscess
141	22,9	135	IBD related complication or symptom	Ileitis
122	23,02	38	IBD related complication or symptom	Therapy refractory disease
105	23,29	34	Exacerbation	Exacerbation
121	23,56	113	IBD related complication or symptom	Extended perianal fistulae
90	23,88	107	Exacerbation	Exacerbation
305	24,04	36	IBD related complication or symptom	Pyoderma gangrenosum

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
268	24,09	66	IBD Surgery	Proctocolectomy
175	24,36	24	Exacerbation	Exacerbation
303	24,58	46	Exacerbation	Exacerbation
162	25,22	4	Exacerbation	Exacerbation
215	25,61	223	IBD related complication or symptom	Rectal blood loss
307	26,26	37	IBD Surgery	Ileocecal resection
135	26,86	208	IBD Surgery	Proctocolectomy
134	26,89	8	Exacerbation	Exacerbation
152	27	177	IBD Surgery	Subtotal colectomy
113	27,71	51	IBD related complication or symptom	Protein losing enteropathy
273	27,77	147	IBD related complication or symptom	Abdominal pain
262	28,34	250	IBD related complication or symptom	Electrolyte disorder
237	28,71	152	Exacerbation	Exacerbation
115	28,9	375	IBD related complication or symptom	Diarrhoea and vomiting
286	29,13	45	Exacerbation	Exacerbation
283	29,4	14	Exacerbation	Exacerbation
119	29,46	290	Exacerbation	Exacerbation
225	29,68	19	Exacerbation	Exacerbation
255	30,1	79	IBD related complication or symptom	Stenosis lineal flexure
117	30,18	45	IBD Surgery	Ileocecal resection
278	31,16	140	IBD related complication or symptom	Ileus
267	31,45	34	Exacerbation	Exacerbation
302	33,51	121	Exacerbation	Exacerbation
233	33,67	64	Infection	Viral enteritis
288	34,18	19	Exacerbation	Exacerbation
197	34,97	72	Exacerbation	Exacerbation
201	36,13	5	IBD related complication or symptom	Stenosis ileum
171	36,38	1	IBD Surgery	Right hemicolectomy
92	36,4	64	IBD Surgery	Ileocecal resection

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
308	37,25	321	Other	Clinical evaluation of Crohn's disease after six weeks treatment with oral prednisone
304	37,86	106	IBD Surgery	Part of jejunum resection
294	38,15	105	Infection	Bacterial meningitis
139	38,31	19	IBD Surgery	Part of jejunum resection
195	39,55	184	Exacerbation	Exacerbation
188	39,94	22	Exacerbation	Exacerbation
227	39,98	43	Other	Clinical injection adalimumab because of previous allergic reaction
190	40,12	208	Exacerbation	Exacerbation
251	40,22	148	Exacerbation	Exacerbation
154	40,54	39	IBD Surgery	Ileocecal resection
186	40,82	270	IBD related complication or symptom	Clinical colonoscopy because of dysplasia and crohn's disease
108	41,56	108	IBD Surgery	Subtotal colectomy
127	42,7	12	Exacerbation	Exacerbation
89	43,48	69	IBD related complication or symptom	Pancreatitis and primary sclerosing cholangitis
191	43,99	42	IBD Surgery	Right hemicolectomy
232	44,17	368	Exacerbation	Exacerbation
78	44,66	328	Malignancy	Urothelial cell carcinoma
218	44,69	28	Exacerbation	Exacerbation
246	44,81	3	IBD related complication or symptom	Constipation
256	47,08	153	Malignancy	Breast cancer
295	47,48	82	Infection	CMV infection
276	47,7	193	IBD Surgery	Ileocecal resection
236	48,02	144	IBD related complication or symptom	Abdominal pain
462	49,83	4	IBD related complication or symptom	Stenosis
457	51,26	544	IBD related complication or symptom/ Infection	Fever and perianal abscess
456	51,55	1	IBD Surgery	Incision and drainage of perianal abscess
196	52,39	60	Exacerbation	Exacerbation

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
142	53,69	176	Exacerbation	Exacerbation
467	54,11	205	IBD related complication or symptom	Perianal abscess
470	54,22	9	Medication complication	Nausea and vomiting during azathiopurine treatment
460	54,75	6	IBD related complication or symptom	Anemia
466	56,6	213	IBD related complication or symptom	Ileus
472	56,77	28	IBD Surgery	Colectomy
478	57,46	177	Infection	Fever
82	58,43	4	IBD Surgery	Subtotal colectomy
487	59,46	6	Exacerbation	Exacerbation
54	60,76	11	IBD Surgery	Subtotal colectomy
6	61,63	43	IBD Surgery	Subtotal colectomy
70	61,74	10	Exacerbation	Exacerbation
44	61,77	6	IBD related complication or symptom	Perianal abscess
29	62,13	207	IBD related complication or symptom	Stenosis ileum
19	62,93	176	Exacerbation	Exacerbation
41	64,12	50	IBD related complication or symptom	Ileus
38	64,16	41	Exacerbation	Exacerbation
15	64,57	6	IBD Surgery	Subtotal colectomy
7	64,64	80	IBD Surgery	Subtotal colectomy
32	64,83	15	Infection	Cryptosporidium infection
40	65,14	77	IBD related complication or symptom	Ileus
11	65,66	41	Exacerbation	Exacerbation
64	65,71	68	IBD related complication or symptom	Constipation
476	65,77	24	IBD Surgery	Sigmoid resection
33	66,21	254	IBD related complication or symptom	Rectal blood loss and anemia

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
43	67,18	10	IBD related complication or symptom	Stenosis
51	67,59	42	Exacerbation	Exacerbation
26	68,4	65	Infection	Pneumonia
62	69,52	77	Infection	Listeria bacteraemia
14	71,73	46	Exacerbation	Exacerbation
28	72,58	10	Exacerbation	Exacerbation
12	73,94	262	Exacerbation	Exacerbation
10	74,09	1	Exacerbation	Exacerbation
53	76,85	108	Malignancy	Renal cell tumor

Supplementary table 5. List of serious infections after start of anti-TNF therapy until 12 weeks after last administration of anti-TNF medication

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	Infection
221	17,73	23	Perihepatic and right lower abdomen abscess
85	20,56	169	Exacerbation or urinary tract infection
252	22,6	19	Cecal abscess
275	22,86	41	Perianal abscess
159	24,2	15	Drainage of abscess
303	24,58	250	Drainage of abscess
233	33,67	64	Viral enteritis
92	36,4	11	Drainage of abscess
294	38,15	105	Bacterial meningitis
251	40,22	519	Perianal abscess
295	47,48	82	CMV infection
457	51,26	544	Perianal abscess
456	51,55	1	Incision and drainage perianal abscess
467	54,11	205	Perianal abscess
472	56,77	196	Gastro-enteritis
478	57,46	181	Fever
487	59,46	457	Pneumonia
44	61,77	6	Perianal abscess
32	64,83	15	Cryptosporidium infection
43	67,18	78	Cholangitis

Supplementary table 6. List of malignancies after start of anti-TNF therapy until end of follow-up

Patient ID	Age at start anti-TNF therapy	Time after start therapy in weeks	Malignancy
89	43,48	298	Biliary adenocarcinoma
78	44,66	328	Urothelial carcinoma
218	44,69	582	Renal cell carcinoma
256	47,08	153	Breast cancer
487	59,46	0	Renal cell carcinoma
6	61,63	221	Pancreatic cancer
61	65,83	113	Breast cancer
53	76,85	108	Renal cell carcinoma

Supplementary table 7. List of stop reasons for first anti-TNF therapy

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
281	11,40	150	Adverse event	Allergic reaction
238	11,55	285	Loss of response	
123	15,12	219	Loss of response	
222	15,27	87	Loss of response	
187	15,73	17	Loss of response	
86	16,31	8	Adverse event	None specified
207	18,13	9	Loss of response	
110	18,32	36	Loss of response	
179	18,51	32	Loss of response	
194	18,71	260	Loss of response	
120	18,86	97	Loss of response	
266	18,97	8	Non response at first admission	
226	19,09	202	Loss of response	
98	20,11	8	Adverse event	Allergic reaction with antibodies
160	20,91	133	Adverse event	None specified
138	21,1	160	Loss of response	
203	21,35	297	Adverse event	None specified
249	21,64	69	Adverse event	Alopecia
177	21,73	17	Loss of response	
157	21,86	25	Loss of response	
100	22,15	53	Other	Patients wish; tiredness after admissions
181	22,35	26	Loss of response	
174	22,38	331	Loss of response	Loss of response
275	22,86	43	Loss of response	
141	22,9	164	Other	Pregnancy wish

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
296	22,91	8	Non response at first admission	
122	23,02	43	Loss of response	
137	23,02	2	Non response at first admission	
81	23,09	104	Adverse event	None specified
105	23,29	70	Other	Painful injection sites
121	23,56	492	Loss of response	
136	23,58	104	Other	Logistic reasons
90	23,88	47	Loss of response	
305	24,04	14	Loss of response	
268	24,09	13	Adverse event	Allergic reaction
159	24,2	56	Loss of response	
175	24,36	25	Adverse event	None specified
303	24,58	243	Loss of response	
146	25,01	16	Adverse reaction	Allergic reaction with antibodies
162	25,22	305	Other	None specified
104	25,43	69	Loss of response	
215	25,61	192	Other	Discontinuation at patients own initiative
106	25,87	39	Loss of response	
214	26,23	340	Loss of response	
307	26,26	200	Adverse event	Back pain
135	26,86	76	Loss of response	
134	26,89	13	Loss of response	
152	27	10	Adverse event	Non specified
113	27,71	306	Loss of response	
273	27,77	15	Adverse event	Itching injection site
242	28,73	2	Loss of response	
115	28,9	180	Loss of response	
291	29,08	50	Loss of response	
286	29,13	0,57	Adverse event	Infiltrate at site of injection
165	29,35	690	Adverse event	None specified
283	29,4	47	Loss of response	
119	29,46	70	Other	Discontinuation at patients own initiative
220	29,6	5	Other	Surgical intervention

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
225	29,68	4	Other	No reason for treatment discontinuation found
247	29,79	40	Loss of response	
255	30,1	133	Loss of response	
117	30,18	12	Loss of response	
184	30,41	2	Adverse event	None specified
130	31,05	14	Loss of response	
300	31,11	1	Adverse event	Delayed hypersensitivity reaction
278	31,16	39	Adverse event	Allergic reaction
267	31,45	26	Loss of response	
211	32,61	156	Loss of response	
166	32,76	140	Loss of response	
302	33,51	4	Non response at first admission	
87	33,71	63	Loss of response	
197	34,97	131	Adverse event	None specified
308	37,25	6	Non response at first admission	
253	37,47	26	Loss of response	
99	37,48	115	Loss of response	
167	37,68	189	Loss of response	
304	37,86	49	Adverse event	Hyperpigmentation
299	38,01	184	Loss of response	
173	38,24	20	Loss of response	
176	39,05	6	Loss of response	
114	39,48	52	Loss of response	
188	39,94	86	Loss of response	
227	39,98	1	Adverse event	Allergic reaction
190	40,12	95	Adverse event	None specified
251	40,22	513	Loss of response	
124	40,31	52	Loss of response	
154	40,54	39	Loss of response	
186	40,82	52	Loss of response	
289	41,16	6	Adverse event	Skin reaction
108	41,56	57	Loss of response	
208	42,33	24	Loss of response	
127	42,7	49	Adverse event	None specified
89	43,48	61	Loss of response	
189	43,56	297	Loss of response	
191	43,99	26	Loss of response	

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
78	44,66	115	Adverse event	Herpes simplex virus keratitis and patients wish to stop medication
218	44,69	71	Loss of response	
246	44,81	74	Loss of response	
206	45,88	53	Loss of response	
490	46,47	387	Loss of response	
297	47,07	40	Loss of response	
133	48,5	8	Adverse event	Allergic reaction
204	49,38	37	Loss of response	
280	49,4	253	Loss of response	
205	49,74	35	Loss of response	
462	49,83	115	Adverse event	Hypersensitivity reaction
301	49,95	52	Loss of response	
309	50,89	199	Loss of response	
240	52,15	1	Adverse event	Delayed hypersensitivity reaction
185	53,04	15	Adverse event	None specified
142	53,69	26	Other	Arthralgia
470	54,22	0	Adverse event	Fainting
465	54,29	32	Adverse event	Flue-like symptoms
469	56,06	160	Loss of response	
455	57,17	50	Adverse event	Herpes zoster infection
144	57,39	47	Adverse event	Hypersensitivity reaction
478	57,46	365	Loss of response	
475	58,62	95	Loss of response	
461	58,92	2	Adverse event	Allergic reaction
463	58,99	59	Loss of response	
16	60,46	1	Adverse event	Allergic reaction (skin reaction and itching)
489	61,12	21	Adverse event	Itching
6	61,63	43	Loss of response	
70	61,74	11	Other	Subtotal colectomy
1	61,8	6	Adverse event	None specified
29	62,13	213	Loss of response	
17	62,61	100	Adverse event	Pericarditis and kidney failure

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
19	62,93	8	Adverse event	Skin reaction, muscle and joint complaints
18	63,2	12	Adverse event	Itching
56	63,55	123	Loss of response	
41	64,12	65	Adverse event	Antibodies
38	64,16	47	Loss of response	
7	64,64	81	Loss of response	
40	65,14	63	Adverse event	None specified
11	65,66	21	Loss of response	
64	65,71	72	Other	No venous access
50	65,79	104	Adverse event	Other
61	65,83	46	Loss of response	
58	66,92	156	Other	Stop reason not specified
51	67,59	51	Adverse event	Hypertension, dyspnoea, nausea
31	67,89	35	Adverse event	Muscle complaints
26	68,4	43	Adverse event	Skin reaction
474	68,91	26	Other	Wait gain, night sweating
59	69,42	26	Adverse event	Pneumonia
62	69,52	0,14	Adverse event	Listeria meningitis
72	69,8	120	Adverse event	Fever, cold shivers, hypotension
12	73,94	52	Adverse event	None specified
10	74,09	1	No response at first admission	
65	76,75	126	Loss of response	
53	76,85	14	Adverse event	Fever, cold shivers
68	80,65	42	Loss of response	
34	81,6	367	Adverse event	None specified
73	81,92	87	Adverse event	Allergic reaction (dyspnoea)
25	83,82	143	Adverse event	Fever

5

Comorbidity, not patient age, is associated with impaired safety outcomes in vedolizumab- and ustekinumab-treated patients with inflammatory bowel disease

Alimentary Pharmacology and Therapeutics 2020

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ABSTRACT

Background Few data are available on the effects of age and comorbidity on treatment outcomes of vedolizumab and ustekinumab therapy in inflammatory bowel disease (IBD) patients.

Aims To evaluate the association between age and comorbidity with safety and effectiveness outcomes of vedolizumab and ustekinumab in IBD patients.

Methods IBD patients initiating vedolizumab or ustekinumab in regular care were enrolled prospectively. Comorbidity prevalence was assessed using the Charlson Comorbidity Index (CCI). Association between age and CCI, both continuously assessed, with safety outcomes (any infection, hospitalization, adverse events) during treatment and effectiveness outcomes (clinical response and remission, corticosteroid-free remission, clinical remission combined with biochemical remission) after 52 weeks of treatment was evaluated. Multivariable logistic regression was used to adjust for confounders.

Results We included 203 vedolizumab and 207 ustekinumab treated IBD patients, mean age 42.2 (SD 16.0) and 41.6 (SD 14.4). Median treatment duration 54.0 (IQR 19.9-104.0) and 48.4 (IQR 24.4-55.1) weeks, median follow-up time 104.0 (IQR 103.1-104.0) and 52.0 weeks (IQR 49.3-100.4). In vedolizumab, CCI associated independently with any infection (OR 1.387, 95% CI 1.022-1.883, p=.036) and hospitalization (OR 1.586, 95% CI 1.127-2.231, p=.008). In ustekinumab, CCI associated independently with hospitalization (OR 1.621, 95% CI 1.034-2.541, p=.035). CCI did not associate with effectiveness, age did not associate with any of the outcomes.

Conclusions Comorbidities, not age, associate with an increased risk of hospitalizations both treatments, and with any infection in vedolizumab treated IBD patients. This study underlines the importance of comorbidity assessment and safety monitoring of IBD patients with multiple comorbidities.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated disease predominantly affecting the gastrointestinal tract that is characterized by a relapsing and remitting disease course.[1] The presence of IBD associates with an increased risk of comorbidities, such as cardiovascular diseases and diabetes mellitus.[2,3,4] Furthermore, the increase in both incidence and prevalence of IBD and the aging of the general population leads to an increasingly aging IBD patient population with a higher prevalence of comorbidities.[5,6]

In recent years, patient age has been focused on as a potential risk factor for adverse treatment outcomes in immunomodulator or biological therapy.[7-9] A number of these studies have found an increased risk of infections in older patients, especially those treated with biological agents.[7] However, a patients chronological age is an imperfect marker of the reduced physiologic reserve capacity that predisposes patients to an increased risk of adverse treatment outcomes.[10]

The presence of comorbidities could function as a more solid predictor of therapy outcomes as compared to age itself as its presence increases the risk of medication interactions, reduced adherence to treatment and poorer response to treatment.[11] In immunomodulator and anti-TNF treated IBD patients, an increased risk for infections in patients with comorbidities has been detected.[12,13] For thiopurine treatment, an independent association between cardiovascular risk factors and adverse events was observed.[14]

Vedolizumab, an α4β7 antibody,[15,16] and ustekinumab, a human IgG antibody targeting the p40 subunit of IL-12 and IL-23,[17] were introduced for the treatment of IBD offering an alternative treatment option with a different mechanism of action than for example anti-TNF therapy.[18] Both vedolizumab and ustekinumab have displayed a favourable safety profile in the registration trials and observational cohorts.[15-17,19,20] However, in registration trials, both patients of advanced age and those with significant comorbidities failed to meet the strict in- and exclusion criteria, whereas observational cohorts did not evaluate patients with comorbidities. Therefore, it is currently unknown what the impact of the presence of comorbidities is on treatment outcomes of vedolizumab and ustekinumab treated IBD patients.

Using data from the Dutch Initiative on Crohn and Colitis (ICC) Registry,[19,20] a nationwide prospective registry for IBD patients starting novel therapies in standard care, this study aims to assess the impact of patient age and comorbidities on safety and effectiveness outcomes in vedolizumab and ustekinumab treated IBD patients.

MATERIALS AND METHODS

Study design

This is a prospective multicentre cohort study using the Dutch ICC registry, which is a nationwide, observational registry with prospective and systematic follow-up of IBD patients starting IBD treatment in the Netherlands, as previously described in detail.[19 20] Briefly, the ICC registry is used to document the usage, safety and effectiveness of vedolizumab and ustekinumab therapy in IBD patients. Enrolled patients follow a pre-defined schedule of outpatient visits and closely follow regular care. Visits are scheduled at baseline (initiation of therapy), and at week 12, 24, 52, 104 or until discontinuation of medication. An electronic case report form (eCRF) is used to collect data.

Patients

Patients aged 16 years or older with a confirmed clinical, endoscopic and/or histological diagnosis of CD, UC or IBD-Unclassified (IBD-U) and initiating vedolizumab or ustekinumab in regular care were enrolled at 10 participating centres. Data was collected between August 2014 and June 2019. This study included only CD patients on ustekinumab therapy as ustekinumab has only recently been approved for UC patients in the Netherlands. The decision to start therapy was at the discretion of the treating physician and there were no exclusion criteria other than mentioned in the summary of product characteristics. All eligible patients in the participating centres were approached for participation. When patients changed hospital to continue treatment, the information of subsequent visits would be collected through contact with the respective patient and their new treatment facility. Patients who stopped going to their scheduled hospital visits or their infusions were recorded as discontinued at request of patient, were considered treatment failures and imputed as non-responders in the subsequent visits.

Baseline characteristics

Baseline characteristics included age, sex, weight, height, disease duration, behaviour and location according to the Montreal classification (maximum extent at inclusion), previous medication and prior intestinal resections. Disease severity was measured by the Harvey Bradshaw Index (HBI) for CD patients and the Simple Clinical Colitis Activity Index (SCCAI) for UC and IBD-U patients. The use of concomitant immunosuppressive medication was also registered.

The Charlson Comorbidity Index (CCI) was used to identify the prevalence of comorbidities prior to initiation of vedolizumab or ustekinumab therapy. The CCI is a weighted index taking into account the number and severity of 16 predefined comorbidities and is validated for stratifying risk of comorbid conditions in longitudinal studies.[21] For example, the presence of uncomplicated diabetes generates a CCI of 1 point, the presence of a local solid tumor generates 2 points. Age is not included in this index. Theoretically, the CCI could range from a minimum of zero to a maximum of 33 points. In all included patients, the presence

of comorbidities was assessed prior to starting therapy and verified using the electronical medical record.

Outcomes

All outcomes were systematically assessed by following a pre-defined schedule of outpatient visits. To determine safety outcomes, all enrolled patients were analysed. Safety outcomes included: any infection, hospitalizations, treatment related adverse events, and adverse events resulting in discontinuation of IBD treatment. Infections were classified as mild (no use of antibiotics or antiviral mediation necessary), moderate (oral antibiotic or antiviral medication) or severe (hospitalization or intravenously administrated antibiotics/antiviral medication). Hospitalizations included all-cause hospitalizations and were further specified in IBD-related, infection or malignancy related, or other. Medication-related adverse events were classified as not related, possibly or probably related. Only adverse events that were possibly or probably related are reported in this study. Adverse events requiring discontinuation of therapy were reported separately. In addition, malignancies occurring during treatment and mortality were noted.

To determine effectiveness outcomes, patients with clinical disease activity at baseline (defined by HBI >4 or SCCAI >2 points) were analysed. Effectiveness outcomes included: clinical response, clinical remission, corticosteroid-free clinical remission and clinical remission combined with biochemical remission. Clinical response was defined as a reduction of at least 3 points in HBI or 3 points in SCCAI compared to baseline. Clinical remission was defined as HBI ≤4 or SCCAI ≤2 points. Biochemical remission was defined as a C-reactive protein (CRP) ≤5 mg/L and a faecal calprotectin (FCP) level ≤250 µg/g (when available). All effectiveness outcomes were measured at week 52.

Statistical analysis

Data analyses were performed using IBM SPSS Statistics for Windows, version 23.0. Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR) depending on the normality of the underlying distribution. Variables are compared using an independent T-test or Mann Whitney U test. Categorical variables are presented as counts and percentages and compared by using the chi-square test. Multivariable binary logistic regression was used to assess the association between comorbidities and outcomes of interest. The regression analyses were performed as complete case analyses, the maximum number of missing cases per inserted variable was one. Potential confounders were agreed upon beforehand and used in all multivariable binary logistic regression models. These variables included: age, sex, IBD type, disease duration and concurrent medication at baseline (no concurrent medication, steroid or immunomodulator use, steroid and immunomodulator use). In the safety analysis with the outcome *adverse events requiring treatment discontinuation*, multivariable analysis including only age and CCI was performed due to the small number of outcomes. To account for differences in treatment duration in the safety analyses, treatment duration was added

as a variable in the regression model. When statistical significance was reached in the 'all patients' analysis, we performed an additional multivariable analysis with CCI as categorical variable (categories 0,1,2 or ≥3) in the model. To assess the impact of CCI on drug survival, a multivariable cox proportional hazards model was used with the above mentioned confounders, using treatment duration as time and treatment cessation as outcome. Patients were analysed on an intention-to-treat basis. A two-sided p value of <.050 was considered statistically significant.

Ethical consideration

The study was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboudumc (institutional review board: 4076). All patients gave their informed consent prior to inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Baseline characteristics

In the ICC Registry, 410 cases (203 vedolizumab and 207 ustekinumab) were enrolled and assessed on the presence of comorbidities using the CCI. Ninety-five patients had one or more comorbidities, of which 49 (51.6%) received vedolizumab treatment and 46 (48.4%) received ustekinumab. Sixty-three (15.4%) patients were aged 60 years or older, 140 (34.1%) between 40 and 60 years and 206 (50.2%) <40 years, 36 patients aged 60 years or older were treated with vedolizumab, 27 patients aged 60 years or older with ustekinumab. Baseline characteristics are presented in table 1 comparing patients with and without comorbidities. An additional table comparing baseline characteristics of vedolizumab and ustekinumab treated patients is presented separately in supplementary table 1.

Mean age in patients with comorbidities was 50.1 years (SD 16.1) and mean age in patients without comorbidities 39.4 years (SD 14.0, p<.001). Both groups were predominantly female: 60.0% and 56.5%, respectively (p=.546). In patients with comorbidities, 71 patients (74.7%) were diagnosed with CD and 23 patients (24.2%) with UC. Median treatment duration and median follow-up time did not differ between patients with and without comorbidities (51.9 weeks (23.0-101.4) vs. 48.9 weeks (23.5-94.3), p=.460 and 102.4 (52.0-104.0) vs. 102.4 (52.0-104.0), p=.427, respectively). Montreal classification did not differ between groups, except for age at diagnosis, which was higher in patients with comorbidities. Disease duration was comparable between the two groups (12.4 years (4.9-19.9) vs. 11.0 years (5.8-18.8)). Clinical disease activity and medication use at baseline did not differ between patients with and without comorbidities, although patients with comorbidity reported less biological use in their medical history compared to patients without comorbidity.

Table 1. Baseline characteristics

		One or more comorbidities (n=95)	No comorbidity (n=315)	P-value
Treatment				.646
Vedolizumab	N (%)	49 (51.6)	154 (48.9)	
Ustekinumab	N (%)	46 (48.4)	161 (51.1)	
Age (years)	Mean (SD)	50.1 (16.1)	39.4 (14.0)	<.001
Sex - female	N (%)	57 (60.0)	178 (56.5)	.546
Body Mass Index	Mean (SD)	25.2 (5.0)	23.7 (4.5)	.029
IBD Type				.375
Crohn's Disease	N (%)	71 (74.7)	256 (81.3)	
Ulcerative Colitis	N (%)	23 (24.2)	57 (18.1)	
IBD-Unclassified	N (%)	1 (1.1)	2 (0.6)	
Disease duration (years)	Median (IQR)	12.4 (4.9-19.9)	11.0 (5.8-18.8)	.697
Treatment duration (weeks)	Median (IQR)	51.9 (23.0-101.4)	48.9 (23.5-94.3)	.501
Follow-up time (weeks)	Median (IQR)	102.4 (52.0-104.0)	102.4 (52.0-104.0)	.427
Montreal classification				
Age at diagnosis				<.001
≤16 years	N (%)	7 (7.4)	71 (22.5)	
17-40 years	N (%)	57 (60.0)	204 (64.8)	
>40 years	N (%)	31 (32.6)	40 (12.7)	
Disease location (CD)¶				.845
Ileum	N (%)	21 (29.6)	80 (31.4)	
Colon	N (%)	26 (36.6)	84 (32.9)	
Ileocolonic	N (%)	24 (33.8)	91 (35.7)	
Upper GI involvement (CD)¶	N (%)	5 (7.0)	18 (7.1)	.996
Disease behaviour (CD)¶				.348
Inflammatory	N (%)	37 (52.1)	135 (52.9)	
Stricturing	N (%)	22 (31.0)	65 (25.5)	
Penetrating	N (%)	9 (12.7)	50 (19.6)	
Unknown	N (%)	3 (4.2)	5 (2.0)	
Peri-anal disease (CD)¶	N (%)	8 (11.3)	49 (19.4)	.117
Disease location (UC/IBD-U)¶				.892
Proctitis	N (%)	2 (8.3)	4 (6.8)	
Left-sided colitis	N (%)	11 (45.8)	25 (42.4)	
Pancolitis	N (%)	10 (41.7)	28 (47.5)	
Unknown	N (%)	1 (4.2)	2 (3.4)	
Prior intestinal resections	N (%)	43 (45.3)	148 (47.0)	.768
Prior anti-TNF therapy (ever use anti-TNF)	N (%)	85 (89.5)	311 (98.7)	<.001
Prior vedo therapy	N (%)	10 (21.7)	72 (44.7)	.005
Prior uste therapy	N (%)	1 (2.0)	6 (3.9)	.535
Clinical disease activity				
HBI	Median (IQR)	8.0 (5.0-10.0)	7.0 (5.0-10.0)	.079
SCCAI	Median (IQR)	5.0 (3.0-7.0)	6.0 (3.5-9.0)	.519
Biochemical disease activity				
CRP, mg/L	Median (IQR)	6.0 (3.0-16.0)	8.0 (2.0-21.0)	.319
FCP, µg/g	Median (IQR)	552.0 (197.5-1223.8)	932.5 (296.8-1999.5)	.044

Table 1. Continued.

		One or more comorbidities (n=95)	No comorbidity (n=315)	P-value
Concomitant medication				.953
No immunosuppressants	N (%)	44 (46.3)	142 (45.2)	
Corticosteroid or immunomodulator	N (%)	42 (44.2)	139 (44.3)	
Both corticosteroid and immunomodulator	N (%)	9 (9.5)	33 (10.5)	

SD; Standard Deviation, N; Number, IBD; Inflammatory Bowel Disease, IQR; interquartile range, CD; Crohn's disease, GI; gastrointestinal, UC; ulcerative colitis, IBD-U; IBD-Unclassified, anti-TNF; anti-tumor necrosis factor, HBI; Harvey Bradshaw Index, SCCAI; simple clinical colitis activity index, CRP; c-reactive protein, FCP; fecal calprotectin. Missing data: age 1 missing; BMI 134 missing; disease duration 1 missing; treatment duration 1 missing; follow-up time 1 missing; disease location (CD) 1 missing; upper GI involvement 1 missing; perianal disease 3 missing; HBI 10 missing; SCCAI 2 missing; CRP 87 missing; FCP 180 missing; concomitant medication 1 missing ¶maximum extent until exclusion.

Baseline comorbidity prevalence

Prevalence of comorbidities at baseline is presented in table 2. The most prevalent comorbidities were cardiovascular disease (congestive heart failure, myocardial infarction, peripheral vascular disease and cerebrovascular accident (CVA) or transient ischemic attack (TIA)), connective tissue disease, pulmonary disease (chronic obstructive pulmonary disease (COPD) or asthma) and diabetes. The prevalence of comorbidities was numerically but not statistically significant higher in vedolizumab treated patients. However, more cardiovascular and pulmonary diseases were present in the vedolizumab treated group (cardiovascular: 20 (9.9%) versus 7 (3.4%), p=.031 and pulmonary: 16 (7.9%) versus 7 (3.4%), p=.048).

Age, comorbidity and safety outcomes

Infections

Infections, classified as mild, moderate, and severe, are presented in supplementary table 2a. The most frequently observed infections were related to the upper respiratory tract and flu-like symptoms. In total, 4.5 infections of any classification per 10 patient years of exposure occurred during follow-up, 6.4 infections in patients with comorbidities and 3.9 in patients without comorbidities. 5.9 infections of any classification per 10 patient years of exposure occurred in patients aged ≥60 years, compared to 3.1 in patients aged between 40 years and 60 years and 5.0 in patients aged <40 years.

2.1 severe infections per 10 patient years of exposure occurred in patients with comorbidities and 0.6 in patients without comorbidities. In patients aged 60 years or older, 1.2 severe infections per 10 patient years of exposure occurred in patients aged 60 years or older, 0.4 in patients aged between 40 and 60 years and 1.4 in patients younger than 40.

Table 2. Baseline comorbidity prevalence

		Vedolizumab (n=203)	Ustekinumab (n=207)	P-value
Charlson Comorbidity Index	N(%)			0.247
0		154 (75.9)	161 (77.8)	
1		26 (12.8)	33 (15.9)	
2		8 (3.9)	6 (2.9)	
≥3		15 (7.4)	7 (3.4)	
Diabetes				
Uncomplicated (1)		7 (3.4)	8 (3.9)	
End-organ damage (2)		2 (1.0)	0 (0.0)	
Liver disease				
Mild (1)		0 (0.0)	2 (1.0)	
Moderate to severe (3)		4 (2.0)	2 (1.0)	
Solid Tumor				
Localized (2)		3 (1.5)	1 (0.5)	
Metastatic (6)		0 (0.0)	0 (0.0)	
Leukaemia (2)		0 (0.0)	0 (0.0)	
Lymphoma (2)		2 (1.0)	1 (0.5)	
AIDS (6)		0 (0.0)	0 (0.0)	
Chronic kidney disease (2)		8 (3.9)	5 (2.4)	
Congestive heart failure (1)		6 (3.0)	1 (0.5)	
Myocardial infarction (1)		9 (4.4)	3 (1.4)	
Pulmonary disease (1)		16 (7.9)	7 (3.4)	
Peripheral vascular disease (1)		1 (0.5)	1 (0.5)	
CVA or TIA (1)		4 (2.0)	2 (1.0)	
Dementia (1)		1 (0.5)	0 (0.0)	
Hemiplegia (2)		0 (0.0)	0 (0.0)	
Connective tissue disease (1)		11 (5.4)	21 (10.1)	
Peptic ulcer (1)		2 (1.0)	4 (1.9)	
Total number of comorbidities		76	58	0.523

AIDS; acquired immune deficiency syndrome, CVA; cerebrovascular accident, TIA; transient ischemic attack. Numbers next to each comorbidity represent number of points given according to CCI. Categories of CCI were compared between groups by using chi square test, total number of comorbidities by using Mann-Whitney U Test.

The CCI was not associated with the occurrence of any infection during treatment in all patients (OR 1.277, 95% CI .998-1.634, p=.052). However, in vedolizumab treated patients the CCI was significantly associated with the occurrence of any infection during treatment (OR 1.387, 95% CI 1.022-1.883, p=.032), which was independent of age, sex, IBD type, disease duration, concurrent medication and treatment duration. No significant association between the CCI and any infection was observed in ustekinumab treated patients (table 3a).

Age at baseline was not associated with the occurrence of any infection during treatment in all patients (OR .984, 95% CI .966-1.003, p=.109), or in vedolizumab (OR .985, 95% CI .961-1.009, p=.219) and ustekinumab (OR .987, 95% CI .956-1.018, p=.397) treated patients separately (table 3a).

Table 3a. Safety analysis – any infection

All patients	**OR**	**95% CI**	**p-value**
CCI	1.277	0.998-1.634	.052
Age at baseline (years)	.984	0.966-1.003	.109
Sex (female)	.930	.586-1.476	.757
Crohn's Disease (ref. UC/IBDU)	.907	.478-1.722	.766
Disease duration (years)	1.011	.986-1.037	.393
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.155	.718-1.856	.552
Steroid and immunomodulator	.809	.361-1.816	.607
Treatment duration (weeks)	1.014	1.007-1.020	.000
Treatment (ustekinumab)	.758	.449-1.282	.301
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.387	1.022-1.883	.036
Age at baseline (years)	.985	.961-1.009	.219
Sex (female)	.746	.397-1.401	.362
Crohn's Disease (ref. UC/IBDU)	1.007	.520-1.952	.983
Disease duration (years)	.993	.958-1.030	.720
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.067	.550-2.070	.849
Steroid and immunomodulator	.683	.251-1.857	.455
Treatment duration (weeks)	1.012	1.004-1.019	.002
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.134	.720-1.788	.587
Age at baseline (years)	.987	.956-1.018	.397
Sex (female)	1.174	.584-2.363	.652
Disease duration (years)	1.025	.987-1.064	.197
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.187	.594-2.373	.627
Steroid and immunomodulator	.959	.229-4.012	.954
Treatment duration (weeks)	1.017	1.005-1.028	.005

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified; All patients: 409 patients included in analysis of which 119 reached endpoint; VEDO: 203 patients, endpoint: 70 patients; UST: 206 patients included in analysis of which 49 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Hospitalizations

A total of 138 hospitalizations occurred during treatment, 5.0 per 10 patient years of exposure in patients with comorbidities and 2.7 in patients without comorbidities. 3.4 hospitalizations per 10 patient years of exposure occurred in patients aged ≥60 years, 2.9 in patients aged between 40 and 60 years and 3.5 in patients aged younger than 40 years. The majority of hospitalizations were IBD-related (78 hospitalizations, 56.5%) or infection or malignancy

related (35 hospitalizations, 25.4%). Fourteen hospitalizations (10.1%) were classified as other and 15 (8.0%) as unknown. Hospitalizations are presented in supplementary table 2b.

The CCI was independently associated with the occurrence of one or more all-cause hospitalizations during treatment in all patients (OR 1.450, 95% CI 1.119-1.879, p=.005) and in both vedolizumab (OR 1.586, 95% CI 1.127-2.231, p=.008) and ustekinumab treated patients (OR 1.623, 95% CI 1.035-2.546, p=.035) separately (table 3b). Patients using concurrent immunosuppressive medication at baseline were also at a higher risk of hospitalization during both vedolizumab and ustekinumab treatment (steroid or immunomodulator use: OR 1.928, 95% CI 1.123-3.311, p=.017, steroid and immunomodulator use: OR 3.684, 95% CI 1.650-8.229, p=.001). A CCI of three points or higher was significantly and independently associated with hospitalization during treatment (OR 4.943, 95% CI 1.778-13.738, p=.002) when analysing the CCI as a categorical variable (categories 0,1,2 or ≥3) in all patients. Furthermore, we observed a strong and independent impact of cardiovascular disease (comprising the CCI categories myocardial infarction, congestive heart failure, peripheral vascular disease and CVA/TIA) on all-cause hospitalizations in vedolizumab treated patients (OR 3.954, 95% CI 1.048-14.924, p=.042). Age at baseline was not associated with the occurrence of one or more hospitalizations during treatment in all patients (OR .986, 95% CI .965-1.008, p=.204), or in vedolizumab (OR .986, 95% CI .958-1.014, p=.313) and ustekinumab (OR .986, 95% CI .951-1.021, p=.418) treated patients separately (table 3b).

Next, safety analyses for hospitalizations were performed while including only the IBD-related and infection or malignancy related hospitalizations as an outcome. We found that in all patients (OR 1.349, 95% CI 1.007-1.806, p=.045) and in ustekinumab patients (OR 1.625, 95% CI 1.002-2.634, p=.049) the CCI was associated with IBD- and infection or malignancy related hospitalizations. We did not find this association in vedolizumab patients separately (OR 1.388, 95% CI .933-2.066, p=.105).

Adverse events

Adverse events are listed in supplementary table 2c and are classified as possibly or probably related to treatment. 3.4 adverse events per 10 patient years of exposure were reported in patients with comorbidities and 2.7 in patients without comorbidities. 2.9 adverse events per 10 patient years of exposure were reported in patients aged ≥60 years, 3.4 in patients aged 40 to 60 years and 2.5 in patients <40 years. There was no significant association between age, the CCI and occurrence of adverse events in all patients and in vedolizumab or ustekinumab treated patients when analysed separately (supplementary table 3).

In total, 0.3 adverse events per 10 patient years of exposure were classified as a reason for treatment discontinuation, 0.8 in patients with comorbidities and 0.2 in patients without comorbidities (supplementary table 4). In patients aged ≥60 years, 0.1 adverse event per 10 patient years of exposure was classified as a reason for treatment discontinuation, in patients aged 40 to 60 years 0.5 and in patients aged <40 years 0.3.

Table 3b. Safety analysis - hospitalization

All patients	**OR**	**95% CI**	**p-value**
CCI	1.450	1.119-1.879	.005
Age at baseline (years)	.986	.965-1.008	.204
Sex (female)	1.521	.903-2.561	.115
Crohn's disease (ref. UC/IBDU)	2.655	1.245-5.663	.012
Disease duration (years)	1.006	.978-1.035	.675
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.928	1.123-3.311	.017
Steroid and immunomodulator	3.684	1.650-8.229	.001
Treatment duration (weeks)	.999	.992-1.006	.857
Treatment (ustekinumab)	.580	.336-1.004	.052
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.586	1.127-2.231	.008
Age at baseline (years)	.986	.958-1.014	.313
Sex (female)	1.558	.759-3.200	.227
Crohn's disease (ref. UC/IBDU)	3.468	1.523-7.897	.003
Disease duration (years)	.969	.927-1.012	.156
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.618	.737-3.550	.230
Steroid and immunomodulator	4.503	1.551-13.071	.006
Treatment duration (weeks)	.996	.987-1.004	.329
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.623	1.035-2.546	.035
Age at baseline (years)	.986	.951-1.021	.418
Sex (female)	1.427	.652-3.122	.374
Disease duration (years)	1.042	.999-1.086	.054
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	2.269	1.051-4.901	.037
Steroid and immunomodulator	1.861	.436-7.945	.402
Treatment duration (weeks)	1.008	.996-1.021	.179

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified; All patients: 409 patients included in analysis of which 90 reached endpoint; VEDO: 203 patients, endpoint: 51 patients; UST: 206 patients included in analysis of which 39 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable

The CCI was not associated with these adverse events that led to treatment discontinuation (supplementary table 5). Two patients with comorbidities were diagnosed with a malignancy and discontinued medication: one patient on vedolizumab aged ≥60 years had a peritonitis carcinomatosa originating from the digestive tract and one patient aged between 40 to 60 years on ustekinumab had a peritoneal carcinoma. Three patients without comorbidities

were diagnosed with a malignancy; one died (see below) and two patients discontinued treatment: one patient aged 40 to 60 years on vedolizumab had progression of a known anaplastic oligodendroglioma and one patient on ustekinumab aged ≥60 years was diagnosed with an unknown malignancy. Two patients without comorbidities died during treatment, both aged between 40 and 60 years: one patient on vedolizumab due to a thrombosis in the basilar artery and one patient on ustekinumab due to an abdominal sepsis after colonoscopic perforation after diagnosis of peritoneal carcinoma.

Age, comorbidity and effectiveness outcomes

Patients with active disease (HBI >4 or SCCAI >2) at baseline were included in the effectiveness analyses. The CCI was not associated with effectiveness outcomes (clinical remission, clinical response, corticosteroid-free clinical remission and combined biochemical and clinical remission) in all included patients. However, in ustekinumab treated patients, a higher age at baseline was independently associated with a mildly higher rate of combined biochemical and clinical remission (OR 1.043, 95% CI 1.003-1.085, p=.036). Results are presented in supplementary tables 6a, 6b, 6c and 6d.

Age and the CCI were not associated with drug survival in all patients (age: HR .991, 95% CI .977-1.004, p=.985 and CCI: HR 1.002, 95% CI 0.847-1.184, p=0.985), or in vedolizumab or ustekinumab treated patients separately (age: HR .996, 95% CI ,979-1.013, p=.617 and CCI: HR 0.899, 95% CI 0.725-1.115, p=0.333 and age: HR .977, 95% CI .955-1.000, p.054 and CCI: HR 1.349, 95% CI 0.998-1.823, p=0.051).

DISCUSSION

This study aimed to assess the impact of age and comorbidities on safety and effectiveness outcomes in vedolizumab and ustekinumab treated IBD patients using data from the Dutch ICC Registry. In contrast to age, the presence of comorbidities was independently associated with impaired safety outcomes in both vedolizumab and ustekinumab treated patients. Comorbidities were independently associated with the occurrence of any infection during vedolizumab treatment, and with all-cause hospitalization during both vedolizumab and ustekinumab treatment. No association between age, comorbidities and impaired effectiveness outcomes was found.

Clinical trials frequently follow strict exclusion criteria regarding advanced age and the presence of comorbidities such as biochemic abnormalities, the presence of an unstable or uncontrolled medical disorder[15] or a history of cancer.[17] In our real-life cohort, 15.4% of the included patients was aged 60 years or older. The prevalence of comorbidities according to the CCI was 24.1% in vedolizumab and 23.7% in ustekinumab treated patients. Most of these patients would have been excluded from clinical trials. As a result, little data on comorbidities and their prevalence and especially relevance in IBD is available.[11] The prevalence of

comorbidities found in our prospective cohort is comparable to a retrospective study by Khan et al., in which 63.759 IBD patients who initiated corticosteroids, immunomodulators or biologic therapy were analysed. In this study, 25.7% of the overall cohort had one or more comorbidities according to the CCI.[22] However, other studies using the same CCI, have shown a wide range of comorbidity prevalence. In these studies, the prevalences ranged from less than one-fifth to more than two-thirds of the included patients with one or more comorbidities.[12 23]

In our study, we found no association between age and safety outcomes. This finding is comparable with a recently published meta-analysis by Piovani et al., which found no evidence of an increased risk of any infection in older IBD patients treated with biologics[9] but in contrast to a meta-analysis published last year in older patients exposed to biologics.[7] However, next to age, we also assessed the presence of comorbidities. In our study, comorbidities were independently associated with safety outcomes in both vedolizumab and ustekinumab treated patients. In both treatment groups, an increase in the CCI was significantly associated with all-cause hospitalization during treatment. Analysing the CCI as a categorical variable (categories 0,1,2 or ≥3), the presence of three points or higher was significantly associated with all-cause hospitalization during treatment. Furthermore, we performed safety analyses regarding hospitalizations including only IBD- and infection or malignancy related hospitalizations as an outcome. In this analysis we found the CCI to be significantly associated with IBD- and infection or malignancy related hospitalizations in all patients and in ustekinumab patients, but not in vedolizumab patients. An increase in CCI was associated with any infection during treatment in vedolizumab (OR 1.387, 95% CI 1.022-1.883, p=.036), but not in ustekinumab treated patients (OR 0.998, 95% CI 0.611-1.630, p=.994). While earlier studies showed an association between comorbidities and adverse events for immunomodulators,[14] this association was not found for vedolizumab or ustekinumab in our study.

Although the impact of age and comorbidities was analysed for vedolizumab and ustekinumab treated patients separately, these analyses do not allow a direct comparison between both treatment groups for safety outcomes due to selection bias. An increase in CCI was associated with IBD-related and infection or malignancy related hospitalizations in the ustekinumab group, and with any infection during treatment in the vedolizumab group. In our study, only CD patients, and not UC patients, on ustekinumab were included. Furthermore, ustekinumab treated patients had a higher percentage of previous anti-TNF therapy, or previously failed on vedolizumab therapy (supplementary table 1). Besides this, since vedolizumab is considered to be a safe treatment option due to its supposed gut-specific mechanism of action it is likely that patients who were at an increased infection risk were initiated on vedolizumab therapy. This hypothesis is supported by the fact that vedolizumab treated patients had a higher absolute number of comorbidities and a higher number of patients with a high CCI (a score of three or more). Especially a higher number of cardiovascular diseases and pulmonary diseases was observed in these patients.

The association between the presence of comorbidity and impaired safety outcomes found in this study could be explained by the fact that comorbidity is a predictor of impaired immunity and frailty which could lead to impaired safety outcomes.[24] Furthermore, medication interactions due to polypharmacy as a consequence of comorbidity could influence the results. However, the route of metabolism of ustekinumab and the working mechanism of vedolizumab have not fully been characterized. [25-27]

No association between age, comorbidities and impaired effectiveness outcomes was found in our study. In line with this observation, prior studies in IBD patients receiving other biologicals, did also not find an association between age, comorbidities and impaired effectiveness outcomes.[8,28] For example, Lobatón et al. studied the impact of comorbidities in anti-TNF treated patients, and found no association between comorbidities (CCI>0) and efficacy outcomes.[28] In our study, an independent association between an increasing age and a higher rate of biochemical and clinical remission in ustekinumab treated patients was observed. This further underlines the fact that the effectiveness of biological therapies is no less in patients of advanced age. Overall, we did not find a significant impact of age and CCI on drug survival, although in ustekinumab patients both age and CCI were borderline significant. With an increasing age, patients tended to have a lower chance of therapy cessation (HR .977, 95% CI .955-1.000, p=.054) and with increasing points on the CCI patients tended to have a higher chance of therapy cessation (HR 1.349, 95% CI 0.998-1.823, p=0.051).

The results of our study have several clinical implications. First, although age in itself was not associated with impaired safety outcomes, patients with comorbidities were older. Therefore, we advise treating gastroenterologists to be aware of this higher prevalence of comorbidities in older IBD patients and, when comorbidity is suspected, to perform adequate screening and referral as deemed necessary. Second, in particular a CCI of three points or higher and the presence of cardiovascular disease were associated with impaired safety outcomes (all-cause hospitalization). This sub analysis identified a group of patients with an especially elevated risk for impaired safety outcomes which should be monitored closely. Third, concomitant immunosuppressive medication use at baseline was associated with hospitalization during vedolizumab and ustekinumab therapy in our study and with infections in other studies.[29] Prior studies have shown no significant differences in effectiveness rates when comparing vedolizumab or ustekinumab monotherapy to vedolizumab or ustekinumab therapy combined with immunosuppressive medication.[19,20] Therefore, we discourage concomitant immunosuppressive medication use in patients in which multiple comorbidities are present as well.

Our study has several strengths. This is the first study assessing the impact of comorbidities next to age on therapy outcomes in vedolizumab and ustekinumab treated IBD patients. The ICC Registry is a large prospective real-life cohort without restricting in- and exclusion criteria and a nationwide coverage. Hence, the included patients are a representative cohort

from non-academic and academic centres, reflecting daily IBD care. Finally, comorbidity was assessed systematically, using a validated comorbidity index that allows external validity.

However, since this is an ongoing registry, not all patients were followed for the same time period. We intended to limit this by correcting for follow-up duration in safety analyses. It is possible that results of our study are subjected to ascertainment bias: patients with comorbidities generally have more hospital visits or physician contacts, and therefore, a safety outcome such as infection, could be noted more frequently in this group. However, to limit this type of bias, the ICC registry applies scheduled visits with automated reminders for strict adherence to protocol in all patients. The comorbidity index used, the CCI, is a commonly used index to assess the number and severity of comorbidities but is not specifically validated for IBD patients. Furthermore, not all comorbidities, such as neurological conditions, are accounted for in this index. An IBD validated comorbidity index is therefore needed.[11] Finally, the number of old or very old patients was low in this study, which could have led to an underestimation of the effect of old age or CCI on treatment safety.

In conclusion, this study demonstrates that comorbidities, and not age, are independently associated with any infection and hospitalizations in vedolizumab treated IBD patients and hospitalizations in ustekinumab treated IBD patients. Effectiveness of both treatments was not impaired by presence comorbidities or a higher age. These results underline the importance of assessing comorbidity status instead of age prior to initiating vedolizumab and ustekinumab therapy, in order to discuss additional safety risks and need for close monitoring in IBD patients with multiple comorbidities.

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Supplementary table 1. Baseline characteristics vedolizumab and ustekinumab treated patients

		Vedolizumab (n=203)	Ustekinumab (n=207)	P-value
Age (years)	Mean (SD)	42.2 (16.0)	41.6 (14.4)	.677
Sex - female	N (%)	112 (55.2)	123 (59.4)	.385
Body Mass Index	Mean (SD)	24.1 (4.4)	24.1 (4.9)	.965
IBD Type				NA
Crohn's Disease	N (%)	120 (59.1)	207 (100.0)	
Ulcerative Colitis	N (%)	80 (39.4)	NA	
IBD-Unclassified	N (%)	3 (1.5)	NA	
Disease duration (years)	Median (IQR)	10.2 (4.8-17.6)	12.2 (6.4-20.9)	.051
Treatment duration (weeks)	Median (IQR)	54.0 (19.9-104.0)	48.4 (24.4-55.1)	.005
Follow-up time (weeks)	Median (IQR)	104.0 (103.1-104.0)	52.0 (49.3-100.4)	.000
Montreal classification				
Age at diagnosis				.298
≤16 years	N (%)	34 (16.7)	44 (21.3)	
17-40 years	N (%)	129 (63.5)	132 (63.8)	
>40 years	N (%)	40 (19.7)	31 (15.0)	
Disease location (CD)				.277
Ileum	N (%)	34 (28.3)	67 (32.5)	
Colon	N (%)	37 (30.8)	73 (35.4)	
Ileocolonic	N (%)	49 (40.8)	66 (32.0)	
Upper GI involvement (CD)†	N (%)	12 (10.0)	11 (5.3)	.113
Disease behaviour (CD)				.953
Inflammatory	N (%)	65 (54.2)	107 (51.9)	
Stricturing	N (%)	32 (26.7)	55 (26.7)	
Penetrating	N (%)	21 (17.5)	38 (18.4)	
Unknown	N (%)	2 (1.7)	6 (2.9)	
Peri-anal disease (CD)	N (%)	19 (16.2)	38 (18.4)	.590
Disease location (UC/IBD-U)				NA
Proctitis	N (%)	6 (7.2)	NA	
Left-sided colitis	N (%)	36 (43.4)	NA	
Pancolitis	N (%)	38 (45.8)	NA	
Unknown	N (%)	3 (3.6)	NA	
Prior intestinal resections	N (%)	71 (35.0)	120 (58.0)	.000
Prior anti-TNF therapy (ever use anti-TNF)	N (%)	192 (94.6)	204 (98.6)	.031
Prior vedo/uste therapy	N (%)	7 (3.4)	82 (39.6)	NA
Clinical disease activity				
HBI	Median (IQR)	7.0 (5.0-10.0)	7.0 (5.0-11.8)	.782
SCCAI	Median (IQR)	5.0 (3.0-8.0)	NA	NA
Biochemical disease activity				
CRP, mg/L	Median (IQR)	7.0 (2.0-22.0)	8.0 (3.0-19.5)	.655
FCP, µg/g	Median (IQR)	898.0 (301.0-2016.0)	721.0 (228.5-1780.5)	.294
Concomitant medication				.000
No immunosuppressants	N (%)	74 (36.5)	112 (54.4)	
Corticosteroid or immunomodulator	N (%)	99 (48.8)	82 (39.8)	
Both corticosteroid and immunomodulator	N (%)	30 (14.8)	12 (5.8)	

SD; Standard Deviation, N; Number, IBD; Inflammatory Bowel Disease, NA; not applicable, IQR; interquartile range, CD; Crohn's disease, GI; gastrointestinal, UC; ulcerative colitis, IBD-U; IBD-Unclassified, anti-TNF; anti-tumor necrosis factor, HBI; Harvey Bradshaw Index, SCCAI; simple clinical colitis activity index, CRP; c-reactive protein, FCP; faecal calprotectin.
Montreal classification is reported as maximum extent until exclusion.

Supplementary table 2a. Safety outcomes – any infection

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
Mild infections	**25**	**66**	**91**
Gastrointestinal	1	9	10
Upper respiratory tract	13	27	40
Flu like symptoms	5	17	22
Cold sores	0	3	3
Soft tissue	0	4	4
Skin infections - other	2	2	4
Urinary tract	0	1	1
Fever of unknown origin	2	3	5
Other	2	0	2
Moderate infections	**17**	**39**	**56**
Gastrointestinal	2	3	5
Upper respiratory tract	2	11	13
Flu like symptoms	1	2	3
Soft tissue	1	2	3
Skin infections - other	4	2	6
Urinary tract	3	8	11
Fever of unknown origin	0	1	1
Lower respiratory tract	2	4	6
Herpes zoster	1	1	2
Gynaecological	0	1	1
Other	1	2	3
Unknown	0	2	2
Severe infections	**22**	**20**	**42**
Gastrointestinal	7	10	17
Upper respiratory tract	1	0	1
Lower respiratory tract	5	2	7
Herpes zoster	0	1	1
Urinary tract	1	1	2
Skin infections-other	0	1	1
Fever of unknown origin	1	1	2
Other	7	3	10
Unknown	0	1	1
Unknown severity	**2**	**0**	**2**
Urinary tract	1	0	1
Upper respiratory tract	1	0	1
Total infections	**66**	**125**	**191**

Supplementary table 2b. Safety outcomes - hospitalizations

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
IBD-related hospitalizations	**21**	**57**	**78**
Worsening of IBD	10	28	38
Ileus	1	13	14
Fistula or abscess	2	6	8
Surgical resection	8	10	18
Infection or malignancy related hospitalizations	**18**	**17**	**35**
Infection:	**17**	**16**	**33**
-Gastrointestinal infection	5	6	11
-Respiratory tract infection	3	2	5
-Urinary tract infection	1	1	2
-Fever of unknown origin	2	1	3
-Infected CVC line	6	1	7
-Infection or abscess after surgery	0	3	3
-Appendicitis with phlegmon	0	1	1
-Diarrhoea during antibiotic use	0	1	1
Malignancy:	**1**	**1**	**2**
-Peritonitis carcinomatosis originating from gastrointestinal tract	1	1	2
Other hospitalizations	**10**	**4**	**14**
Laparoscopic cholecystectomy	2	0	2
Cholecystitis	0	1	1
ERCP	1	0	1
Pulmonary embolism	0	1	1
Endoscopic submucosal dissection	0	1	1
CVC for parenteral nutrition	0	1	1
Postoperative pain after surgery	1	0	1
Mamma puncture	1	0	1
Osteonecrosis	1	0	1
Diverticulitis	1	0	1
Variceal bleeding	1	0	1
Suspected pancreatitis	1	0	1
Lumbago	1	0	1
Unknown	**6**	**9**	**15**
Total hospitalizations	**52**	**86**	**138**

CVC; central venous catheter, ERCP; endoscopic retrograde cholangiopancreatography. Four hospitalizations were categorized as both worsening of IBD and infection.

Supplementary table 2c. Safety outcomes - adverse events

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
Possibly related adverse event	**32**	**75**	**107**
Skin and subcutis	13	20	33
Musculoskeletal or connective tissue	4	5	9
Vascular disorders	0	5	5
Eye disorders	1	3	4
Kidneys and urinary tract	1	1	2
Gastrointestinal	1	3	4
Worsening of IBD	0	1	1
Neoplasia (benign, malignant, including cysts and polyps)	2	0	2
Respiratory, thoracic and mediastinal disorders	0	1	1
Cardiac disorders	1	0	1
Hepatobiliary disorders	1	0	1
Nervous system disorder	0	2	2
Psychiatric disorder	0	1	1
Result of medication administration: infusion reaction	0	1	1
Result of medication administration: other	3	3	6
Other	5	29	34
Probably related adverse event	**3**	**12**	**15**
Skin and subcutis	1	3	4
Nervous system disorder	0	1	1
Result of medication administration: delayed hypersensitivity	0	1	1
Result of medication administration: infusion reaction	0	2	2
Result of medication administration: other	1	1	2
Other	1	4	5
Total adverse events	**35**	**87**	**122**

Supplementary table 3. Safety analysis – adverse events

All patients	**OR**	**95% CI**	**p-value**
CCI	1.228	.963-1.567	.098
Age at baseline (years)	1.008	.988-1.028	.426
Sex (female)	1.924	1.145-3.234	.013
Crohn's Disease (ref. UC/IBDU)	1.104	.526-2.317	.794
Disease duration (years)	.992	.966-1.019	.568
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.750	.452-1.243	.264
Steroid and immunomodulator	.428	.154-1.188	.103
Treatment duration (weeks)	1.006	.999-1.013	.090
Treatment (ustekinumab)	1.250	.702-2.226	.449
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.239	.908-1.692	.177
Age at baseline (years)	0.992	.964-1.021	.587
Sex (female)	1.931	.903-4.131	.090
Crohn's Disease (ref. UC/IBDU)	1.024	.475-2.209	.951
Disease duration (years)	1.014	.973-1.057	.510
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	0.835	.387-1.801	.646
Steroid and immunomodulator	0.834	.262-2.653	.759
Treatment duration (weeks)	1.012	1.003-1.021	.009
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.181	.779-1.789	.435
Age at baseline (years)	1.022	.993-1.051	.133
Sex (female)	2.337	1.108-4.927	.026
Disease duration (years)	.979	.945-1.014	.235
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.749	.376-1.492	.411
Steroid and immunomodulator	.000	.000	.999
Treatment duration (weeks)	.996	.984-1.008	.531

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified; All patients: 409 patients included in analysis of which 90 reached endpoint; VEDO: 203 patients, endpoint: 41 patients; UST: 206 patients included in analysis of which 49 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 4. Safety outcomes – adverse events requiring treatment discontinuation

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
Adverse events requiring treatment discontinuation	**8**	**6**	**14**
Skin and subcutis	1	0	1
Musculoskeletal or connective tissue	2	2	4
Nervous system disorder	1	0	1
Result of medication administration: infusion reaction	1	1	2
Result of medication administration: other	0	1	1
Other	3	2	5

Supplementary table 5. Safety analysis – adverse events requiring discontinuation

All patients	**OR**	**95% CI**	**p-value**
CCI	1.444	.920-2.267	.110
Age at baseline (years)	.996	.955-1.038	.843
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.189	.603-2.347	.617
Age at baseline (years)	1.005	.947-1.066	.870
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	2.000	.986-4.059	.055
Age at baseline (years)	.984	.926-1.046	.613

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; All patients: 409 patients included in analysis of which 11 reached endpoint; VEDO: 203 patients, endpoint: 5 patients; UST: 206 patients included in analysis of which 6 reached endpoint Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 6a. Effectiveness analysis – clinical remission

All patients	**OR**	**95% CI**	**p-value**
CCI	.930	.680-1.261	.638
Age at baseline (years)	1.007	.986-1.028	.509
Sex (female)	.846	.500-1.430	.533
Crohn's Disease (ref. UC/IBDU)	1.313	.612-2.816	.485
Disease duration (years)	.977	.949-1.005	.104
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.846	.497-1.442	.540
Steroid and immunomodulator	.930	.400-2.161	
Treatment (Ustekinumab) (ref. vedolizumab)	2.314	1.289-4.153	.005
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.048	.726-1.512	.802
Age at baseline (years)	.994	.967-1.023	.695
Sex (female)	1.037	.484-2.220	.926
Crohn's Disease (ref. UC/IBDU)	1.282	.582-2.823	.538
Disease duration (years)	.979	.936-1.023	.339
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.717	.322-1.597	.416
Steroid and immunomodulator	.882	.299-2.601	.819
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	.776	.457-1.317	.347
Age at baseline (years)	1.026	.992-1.060	.132
Sex (female)	.707	.336-1.489	.362
Disease duration (years)	.968	.930-1.008	.115
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.015	.491-2.097	.968
Steroid and immunomodulator	.996	.243-4.076	.996

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 289 patients included in analysis of which 105 reached endpoint; VEDO: 154 patients, endpoint: 41 patients; UST: 135 patients included in analysis of which 46 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 6b. Effectiveness analysis – clinical response

All patients	**OR**	**95% CI**	**p-value**
CCI	.949	.704-1.278	.730
Age at baseline (years)	.995	.975-1.016	.656
Sex (female)	.985	.585-1.658	.955
Crohn's Disease (ref. UC/IBDU)	.715	.344-1.490	.371
Disease duration (years)	.992	.965-1.021	.594
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.031	.608-1.750	.909
Steroid and immunomodulator	.932	.405-2.145	.868
Treatment (Ustekinumab) (ref. vedolizumab)	2.975	1.652-5.358	.000
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.178	.826-1.680	.366
Age at baseline (years)	.982	.954-1.010	.214
Sex (female)	.993	.468-2.104	.985
Crohn's Disease (ref. UC/IBDU)	.711	.331-1.531	.384
Disease duration (years)	.992	.951-1.035	.722
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.104	.501-2.433	.807
Steroid and immunomodulator	.862	.287-2.594	.792
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	.630	.361-1.101	.105
Age at baseline (years)	1.013	.981-1.046	.436
Sex (female)	.984	.468-2.066	.965
Disease duration (years)	.983	.945-1.022	.394
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.995	.481-2.058	.989
Steroid and immunomodulator	1.236	.301-5.072	.768

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 286 patients included in analysis of which 114 reached endpoint; VEDO: 153 patients, endpoint: 45 patients; UST: 133 patients included in analysis of which 69 reached endpoint. Multivariable binary logistic regression was used, CCI was analyzed as a continuous variable.

Supplementary table 6c. Effectiveness analysis – corticosteroid-free clinical remission

All patients	**OR**	**95% CI**	**p-value**
CCI	.922	.673-1.265	.616
Age at baseline (years)	1.003	.982-1.025	.784
Sex (female)	.780	.458-1.327	.359
Crohn's Disease (ref. UC/IBDU)	1.386	.636-3.019	.412
Disease duration (years)	.972	.944-1.000	.054
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.770	.449-1.323	.344
Steroid and immunomodulator	.940	.402-2.195	.886
Treatment (Ustekinumab) (ref. vedolizumab)	2.298	1.270-4.155	.006
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	.992	.671-1.467	.969
Age at baseline (years)	.992	.964-1.022	.607
Sex (female)	1.054	.484-2.295	.894
Crohn's Disease (ref. UC/IBDU)	1.312	.586-2.935	.509
Disease duration (years)	.979	.935-1.025	.368
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.609	.268-1.380	.235
Steroid and immunomodulator	.863	.292-2.551	.789
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	.834	.493-1.412	.449
Age at baseline (years)	1.018	.985-1.052	.291
Sex (female)	.594	.280-1.260	.174
Disease duration (years)	.961	.923-1.001	.056
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.962	.464-1.995	.916
Steroid and immunomodulator	1.066	.258-4.406	.930

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 289 patients included in analysis of which 101 reached endpoint; VEDO: 154 patients, endpoint: 39 patients; UST: 135 patients included in analysis of which 62 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 6d. Effectiveness analysis – biochemical and clinical remission

All patients	**OR**	**95% CI**	**p-value**
CCI	1.082	.766-1.528	.656
Age at baseline (years)	1.018	.991-1.045	.184
Sex (female)	1.346	.667-2.715	.407
Crohn's Disease (ref. UC/IBDU)	1.086	.410-2.873	.869
Disease duration (years)	0.980	.946-1.016	.281
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.335	.659-2.704	.423
Steroid and immunomodulator	1.984	.717-5.485	.187
Treatment (Ustekinumab) (ref. vedolizumab)	1.664	.770-3.597	.195
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.035	.642-1.667	.888
Age at baseline (years)	0.997	.961-1.035	.887
Sex (female)	1.541	.553-4.290	.408
Crohn's Disease (ref. UC/IBDU)	0.955	.348-2.622	.929
Disease duration (years)	0.990	.934-1.050	.740
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.232	.412-3.687	.709
Steroid and immunomodulator	2.022	.531-7.695	.302
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.264	.721-2.215	.413
Age at baseline (years)	1.043	1.003-1.085	.036
Sex (female)	1.210	.445-3.288	.709
Disease duration (years)	.974	.929-1.022	.283
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.516	.588-3.912	.389
Steroid and immunomodulator	1.690	.301-9.477	.551

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 286 patients included in analysis of which 46 reached endpoint; VEDO: 153 patients, endpoint: 21 patients; UST: 133 patients included in analysis of which 25 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

6

Deficits in geriatric assessment associate with disease activity and burden in older patients with inflammatory bowel disease

Clinical Gastroenterology and Hepatology 2021

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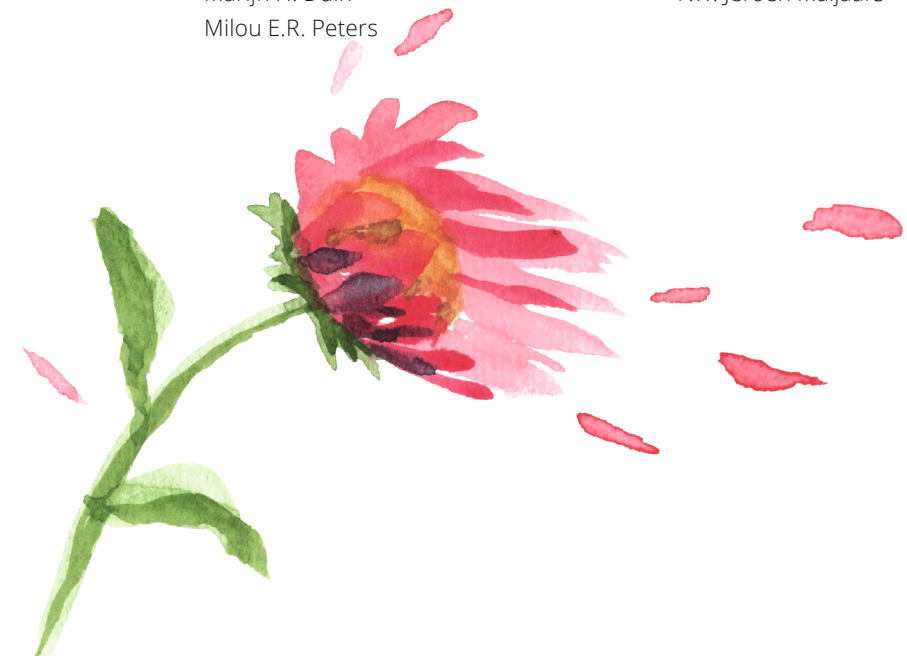

ABSTRACT

Background & aims We aimed to perform geriatric assessment in older inflammatory bowel disease (IBD) patients to evaluate which IBD characteristics associate with deficits in geriatric assessment and the impact of deficits on disease burden (health-related quality of life (HRQoL)).

Methods A prospective multicenter cohort study including 405 consecutive outpatient IBD patients aged ≥65 years. Somatic domain (comorbidity, polypharmacy, malnutrition), impairments in (instrumental) activities of daily living, physical capacity (handgrip strength, gait speed), mental (depressive symptoms, cognitive impairment), and social domain (life-partner) were assessed. Deficits in geriatric assessment were defined as ≥2 abnormal domains; 2-3 moderate and 4-5 severe deficits. Clinical (Harvey Bradshaw Index >4/partial Mayo Score >2) and biochemical (C-reactive protein ≥10 mg/L and/or calprotectin ≥250 µg/g) disease activity and disease burden (short Inflammatory Bowel Disease Questionnaire) were assessed.

Results Somatic domain (51.6%) and activities of daily living (43.0%) were most frequently impaired. 160 (39.5%) patients had moderate deficits in their geriatric assessment, 32 (7.9%) severe. Clinical and biochemical disease activity associated with deficits (clinical: aOR 2.191, 95% CI 1.284-3.743, p=.004, biochemical: aOR 3.358, 95% CI 1.936-5.825, p<.001). Deficits in geriatric assessment independently associate with lower HRQoL.

Conclusions Deficits in geriatric assessment are highly prevalent in older patients with IBD. Patients with active disease are more prone to deficits, and deficits associate with lower HRQoL, indicating higher disease burden. Prospective data validating impact of frailty and geriatric assessment on outcomes are warranted to further improve treatment strategies.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated disease characterised by a relapsing and remitting course.[1] The incidence and prevalence of IBD in older patients is rising, it has been estimated that in the next decade older patients with IBD will represent more than one-third of all IBD patients.[2] Older patients form a challenging patient population due to heterogeneity in somatic, functional, mental, and social abilities compared to younger patients.[3] These geriatric domains are measured by a geriatric assessment and then integrated into an overall level of frailty. Research on geriatric impairments in older patients is gaining attention. In older cancer patients for example, frailty is associated with poor functioning and high symptom burden during and following treatment, independent of disease-related factors.[4] Also, in adult patients with liver cirrhosis, physical frailty is associated with waitlist mortality, regardless of ascites or hepatic encephalopathy.[5] More recently, Kochar et al. found frailty to be associated with infections in adult patients with IBD receiving immunosuppressive medication,[6] and with mortality in all IBD patients.[7] However, up until now, no evidence is available on the prevalence of deficits in geriatric assessment in older patients with IBD and no prospective studies have been performed on their impact on adverse health outcomes or quality of life.[8]

Therefore, we aimed to assess the prevalence of deficits in geriatric assessment in older IBD patients and to evaluate which IBD disease characteristics associate with these deficits. Furthermore, we will evaluate the impact of deficits in geriatric assessment on health-related quality of life (HRQoL).

MATERIALS AND METHODS

Study design and population

This study reports the baseline data of a prospective multicentre cohort study performed in the outpatient departments and infusion centres of six hospitals in the Netherlands. In the Leiden University Medical Centre (LUMC, Leiden), patients were included from November 2016 - February 2020, in the Haga Teaching Hospital (HagaZiekenhuis, The Hague) patients were included from December 2017 – July 2018, in the Haaglanden Medical Centre (HMC, The Hague) from March 2019 – February 2020, in the Maastricht University Medical Centre (MUMC, Maastricht) from April 2019 – May 2019, in the Alrijne Hospital (Alrijne, Leiden and Leiderdorp) from November 2019 – February 2020 and in the Groene Hart Ziekenhuis (GHZ, Gouda) from October 2019 – February 2020.

Patient selection

Eligible patients were asked to participate during their regular visit. 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). Exclusion criteria were inability or unwillingness to participate or sign informed consent and the presence of a language barrier (no Dutch or English). The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed.[9]

Data collection

Study data were collected face-to-face and a geriatric assessment (see below) was performed by trained medical students. Assessments approximately took between 15 to 45 minutes per patient. Demographic and IBD characteristics included age, sex, weight, height, disease type, disease duration and disease behaviour and location according to the Montreal classification[10] (maximum extent at inclusion), current and previous IBD medications and prior IBD-related surgery. Educational level was noted, high educational level was defined as higher vocational or university. Previous hospitalizations (both all-cause and IBD-related) occurring three years prior to the inclusion date were noted. All patient characteristics were verified using the electronical medical record. Clinical disease activity was measured through the Harvey Bradshaw Index (HBI) for CD patients[11] and partial Mayo score (pMS)[12] for UC or IBD-U patients. Active disease was defined by a HBI of >4 or a pMS >2. Laboratory values (Hemoglobin (Hb) and C-reactive protein (CRP)) and fecal calprotectin (FCP) were extracted from the electronical medical record if tests were performed within three months of baseline. Blood Hb levels were divided by lower limit of normal (LLN): 7.5 mmol/L for female and 8.5 mmol/L for male sex. 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. IBD-related disability was measured with the IBD Disability Index (IBD-DI).[13] HRQoL was assessed using the short Inflammatory Bowel Disease Questionnaire (sIBDQ)[14] (low score equals low HRQoL).

Geriatric assessment

The purpose of a geriatric assessment is to systematically explore geriatric domains as a reflection of patients' health: the somatic, functional, mental and social domain.[15] In this study, the functional domain was further specified in activities of daily living and physical capacity, resulting in an overall of five different domains. A domain was deemed abnormal when one or more components of a domain were abnormal. To compare patients with deficits in geriatric assessment to patients without deficits, we divided our population in no deficits, moderate deficits and severe deficits. Moderate deficits was defined as two or three impaired domains, severe deficits as four or five impaired domains.

The somatic domain comprises the presence of multiple comorbidities, polypharmacy or malnutrition. Comorbidity was assessed using the Charlson Comorbidity Index (CCI), a weighted index taking into account the number and severity of 16 predefined comorbidities.[16] Age was not included in the CCI. The presence of multiple comorbidities was defined as a CCI ≥3. Polypharmacy was defined as the use of five or more non-IBD prescription medications.[17]

Malnutrition was assessed using the Mini Nutritional Assessment (MNA) short form. Patients are categorized as being at *no risk of malnutrition (*>11 points), *at risk of malnutrition (*8-11 points) or *malnutrition* (≤7 points). Both at risk of malnutrition and malnutrition were considered abnormal.[18]

The functional domain includes activities of daily living and physical capacity. Activities of daily living were assessed by the Katz Index of Independence in Activities of Daily Living (ADL) which consists of six items, each scored with zero, one or two points[19] and the Lawton Instrumental Activities of Daily Living (IADL) with eight items, each scored with one to three points.[20] Patients were defined as impaired in ADL when a score of ≥1 was reached. IADL scores were sex-adjusted: questions on food preparation, housekeeping and laundry were not taken into account for the male sex. A total IADL score for both sexes of ≥1 was considered abnormal. Physical capacity was measured by handgrip strength and gait speed. A JAMAR hand dynamometer (Patterson Medical, Warrenville, IL) was used to assess isometric handgrip strength. Patients were instructed to sit in an upright position, with the elbow of the dominant hand flexed at 90°, and forearm and wrist in neutral position.[21] Grip strength was measured three times on the dominant hand in the second handle setting. The mean value of three measurements was thereafter stratified by sex and body mass index (BMI), according to Fried et al.[22] Gait speed was assessed with a 4-meter gait speed test at usual pace.[23] Gait speed was stratified by sex and height, according to Fried et al.[22]

The mental domain comprises depression and cognitive function. Depression was assessed by the Geriatric Depression Scale (GDS-15) ranging from 0-15 points. A score of ≥6 points was considered indicative of depression.[24] Cognitive function was assessed using the Six Item Cognitive Impairment Test (6-CIT)[25], a short cognition test with a maximum score of 28 points. A score of ≥8 points is indicative of cognitive impairment. The 6-CIT has been validated against the Mini-Mental State Examination (MMSE) and has been demonstrated to have high diagnostic accuracy.[25] The social domain was considered impaired when patients did not have a life-partner, as the presence of a partner indicates a high chance of loneliness and social isolation and provides social support which has been hypothesised to buffer effects of stressful events.[26, 27]

Statistical analyses

Data analyses were performed using IBM SPSS Statistics for Windows, version 25. Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR) and compared using an independent T-test or Mann Whitney U test. Categorical variables are presented as numbers and percentages and compared using a chi-square test. Logistic regression was performed to assess factors associated with geriatric deficits. Linear regression was used to evaluate the association between the number of impaired geriatric domains, IBD disease activity and HRQoL (measured by sIBDQ). A sensitivity analysis was added using the sIBDQ while excluding three questions regarding 'fatigue', 'depression' and 'relaxing' as these questions are less IBD-specific. All regression

analyses were performed as complete case analyses. Potential confounders were agreed upon beforehand (age, sex, IBD type (CD versus UC/IBD-U), educational level). As no data were available on prevalence of geriatric deficits in older patients with IBD no sample size calculation was performed. We aimed to include as many patients as possible. A p-value of <.05 was considered statistically significant.

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

Overall, 547 patients were approached for participation. Out of these, 405 were included (figure 1). Overall median age was 70 years (IQR 67-74) at baseline, 191 patients (47.0%) were diagnosed with CD. Eighty-five (21.7%) patients had clinical disease activity, 93 (26.7%) biochemical disease activity (elevated CRP or FCP) and 68 (29.7%) an elevated FCP (table 1). Biochemical disease activity was available in 348 patients, FCP in 229 and endoscopic disease activity in 141 patients. Patients included in a referral hospital (LUMC or MUMC) did not differ significantly from patients included in a general hospital regarding disease activity or frailty status.

The results of the geriatric assessment are presented in table 2. To visualize the number of impaired geriatric domains, we plotted the number of patients against the number of impaired geriatric domains per patient (figure 2). 192 patients (47.4%) had geriatric deficits, 160 patients moderate (2-3 deficits) and 32 severe deficits (4-5 deficits). Several differences were noted between these patients, as displayed in table 1.

Disease activity

Active disease, when assessed by clinical indices, was more often present in patients with geriatric deficits (14.9% in patients without deficits, 27.7% in patients with moderate and 39.9% in patients with severe deficits, p=.001)) and when assessed by biochemical disease indices (17.1% (31/181) versus 37.7% (52/138) and 34.5% (10/29), p<.001). An elevated FCP was also more often present in patients with geriatric deficits (table 1).

A higher frequency of impaired somatic domain (69.9% versus 45.1%, p<.001) was observed in biochemically active IBD, also when all three components (comorbidity, polypharmacy and (risk of) malnutrition) were analysed separately. An impaired physical capacity (30.1% versus 19.6%, p=0.038) was mainly observed in patients with biochemically active disease, which was mainly explained by a difference in abnormal gait speed (30.1% versus 19.6%, p=.023, supplementary figure 1). To further explore differences between active and non-

active IBD patients regarding impairments in geriatric domains we performed a sub-analysis by defining elevated FCP as ≥50 instead of ≥250 µg/g. Especially polypharmacy (44.9% versus 27.8%, p=.014), abnormal IADL (27.8% versus 15.3%, p=.038) and abnormal gait speed (9.2% versus 1.4%, p=.031) were more often present in patients with FCP ≥50 µg/g (supplementary figure 1).

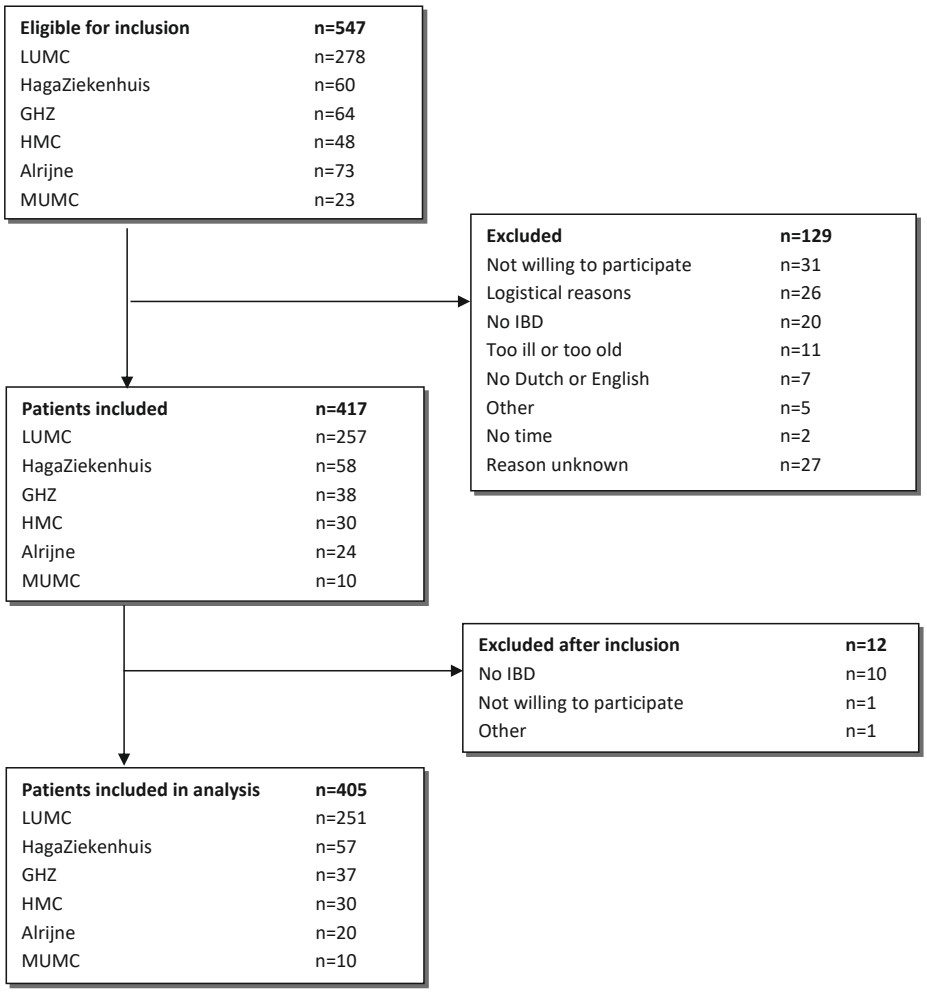

Figure 1. Flowchart patient inclusion. Logistical reasons are researcher- or hospital-related logistical reasons such as no consulting room available or due to different hospital locations. No time means patient had no time; too ill or too old means patient thinks he or she is too ill or too old to participate.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

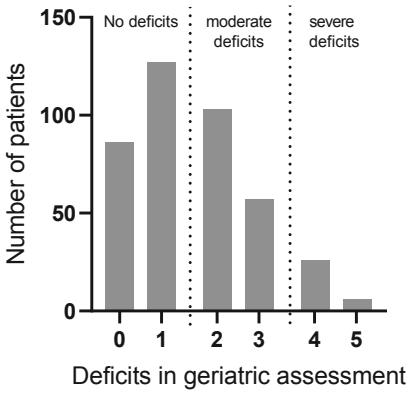

Figure 2. Prevalence of the number of deficits in geriatric assessment.

Older-onset

Thirty percent of patients had older-onset IBD, defined as an age of onset ≥60 years. Older-onset patients had a higher age at cohort entry (71.5 (68-76) versus 70 (67-72), p<.001) and more often biochemical disease activity (44.6% (52/118) versus 17.8% (41/230), p<.001), elevated FCP (48.2% (41/85) versus 18.8% (27/144), p<.001) and endoscopic disease activity (61.5% (32/52) versus 37.1% (33/89), p=.005). Older-onset patients were more often impaired in mental domain, mainly cognitive impairment (16.9% versus 6.7%, p=.001), and in their physical capacity, both handgrip strength (24.3% versus 16.4%, p=.048) and gait speed (11.8% versus 3.0%, p<.001, supplementary figure 2). This difference between older-onset and non-older onset remained present when analysing biochemically active and biochemically inactive patients separately. In patients with biochemically inactive disease, older-onset patients had a higher rate of cognitive impairment (16.7% versus 6.3%, p=.012), abnormal handgrip strength (22.7% versus 15.3%, p=.134) and abnormal gait speed (9.1% versus 2.6%, p=.027, supplementary figure 2). HRQoL did not differ between older-onset and non-older-onset patients.

Factors associated with deficits in geriatric assessment

A multivariate analysis was performed to assess factors associated with deficits in geriatric assessment (table 3). IBD disease activity, as assessed using clinical disease indices, biochemical disease indices or elevated FCP, was independently associated with the presence of deficits. Also, being female and having a previous all-cause hospitalization was associated with the presence of deficits.

Impact of deficits in geriatric assessment on HRQoL

Both clinical and biochemical disease activity and the number of deficits in geriatric assessment were associated with a lower HRQoL (supplementary figure 3, supplementary table 1). Elevated FCP and endoscopic disease activity did not associate with HRQoL (supplementary figure 4, supplementary table 1). Both clinical disease activity and the

number of deficits in geriatric assessment were also independently associated with a lower HRQoL (table 4). The association between deficits in geriatric assessment and HRQoL did not change when clinical disease activity was replaced by biochemical disease activity or by elevated FCP alone. After excluding the questions regarding fatigue, depression and relaxing from the sIBDQ, the number of deficits in geriatric assessment remained associated with a lower HRQoL. Four out of five geriatric domains impacted HRQoL independent of clinical disease activity: mental domain (B -6.810, 95% CI -8.847, -4.772, p=.000), somatic domain (B -3.182, 95% CI -4.653, -1.711, p=.000), activities of daily living (B -2.787, 95% CI -4.363, -1.210, p=.001) and physical capacity (B -2.544, 95% CI -4.401, -.686, p=.007).

DISCUSSION

In this study, we provide the first prospective data on geriatric assessment in older patients with IBD. Almost fifty percent had two or more deficits in geriatric assessment.. Active IBD was associated with the presence of deficits in geriatric assessment and additionally, number of deficits independently associated with a lower HRQoL, demonstrating a higher IBD symptom burden in patients with geriatric deficits.

Older patients form a challenging patient population due to heterogeneity in geriatric assessment. Impairments in geriatric assessment reflect the overall level of frailty.[28] Recently published studies provide evidence for an association between the presence of frailty and negative health outcomes.[6 7 29] However, in these retrospective studies, frailty is measured by ICD codes and, while malnutrition[6 7] and comorbid conditions[29] are the defining domains in those studies, other geriatric domains are not well represented. Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis following a stressor[28] and comprises a spectrum which is best measured by a comprehensive geriatric assessment.[15] The most frequently abnormal domains in our study were the somatic domain, especially polypharmacy, and activities of daily living. In total, almost half of all assessed IBD patients had two or more deficits in their geriatric assessment. No other evidence on the prevalence of deficits in geriatric assessment in older IBD patients is currently present. Frailty rates in IBD patients have been described by Kochar et al. (5-7%)[6 7] and Qian et al (32.7%).[29] However, in these papers frailty is described in a retrospective manner by using ICD codes and in IBD patients of all ages. By using a geriatric assessment, we not only detected already established diagnoses, but also discovered new deficits. This finding further stresses the importance of prospective research on frailty in older patients with IBD by using a geriatric assessment.

Disease activity, both clinical and biochemical (CRP or FCP) was independently associated with geriatric deficits. Although CRP corresponds with disease activity and is therefore frequently used as an inflammatory marker during IBD treatment,[30] it is linked to many diseases and correlates with frailty, poor physical activity and cognitive decline.[31] For this reason, we

performed the analyses on biochemical disease activity separately for FCP alone and found an association between elevated FCP and geriatric deficits. The association between IBD disease activity and geriatric deficits could be explained by several mechanisms. Patients with polypharmacy or malnutrition have a higher chance of developing an IBD-flare.[17 32] The association between depression and disease activity has been established before,[33] but a link between IBD disease activity and cognitive function has also been described previously.[34] Also, mechanisms related to inflammation contribute to muscle wasting .[35] In addition, as ADL comprise stool incontinence, disease activity including frequent bowel movements, could easily cause impairments in ADL. The association between active inflammation and frailty in older patients has also been confirmed in RA.[36]

Older-onset patients had more deficits in geriatric assessment, mainly in physical capacity and cognition. It could be hypothesized that the recent inflammatory state in patients with older-onset IBD, contributes to triggering or exaggerating underlying geriatric deficits.

Furthermore, we found that female sex was predictive of deficits in geriatric assessment. This has also been found in earlier studies[22 29] and could be due to a higher symptom reporting or poorer perceived health and greater vulnerability to frailty via extrinsic effects on sarcopenia.[22 37 38]

We found an independent association between an increasing number of deficits in geriatric assessment and a decreasing HRQoL. This finding suggests that geriatric impaired and therefore frail older patients with IBD experience a higher disease burden, independent of present disease activity. In patients with cancer, this association has also been found.[4]

One of the strengths of this study is that we included IBD patients in tertiary, peripheral and teaching hospitals. However, as we aimed to conduct a study with as little study burden as possible, biochemical and endoscopic data of patients were extracted from the electronical medical record and not performed for study purposes. Therefore, no firm conclusions can be drawn on the association between endoscopic disease activity and outcomes of interest due to lower data availability. However, because of this low study burden, we created a low barrier for patients to participate and therefore generated a representative cohort.

In conclusion, our findings underline the importance of assessing the presence of frailty in older patients with IBD, as the prevalence of geriatric deficits we found is high. Patients with active disease were more prone to geriatric deficits and patients with geriatric deficits had a higher symptom burden. Prospective data validating the influence of frailty and geriatric deficits on negative health outcomes are warranted. As the population ages, we should strive to work towards a multidisciplinary evaluation of older patients with IBD to aim for the best possible treatment goals, while accounting for biological age based risk factors.

Table 1. Characteristics of older inflammatory bowel disease patients with deficits in geriatric assessment.

		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
Age at baseline	Median (IQR)	69.0 (67.0-72.0)	71.0 (68.0-75.0)	72.5 (70.3-79.8)	<.001
Sex (Female)	N (%)	82 (38.5)	81 (50.6)	25 (78.1)	<.001
BMI	Mean (SD)	25.9 (3.5)	26.1 (5.0)	27.1 (5.8)	.378
Educational level (high)	N (%)	75 (36.1)	45 (29.6)	1 (3.6)	.002
Current smoker	N (%)	20 (9.4)	11 (8.8)	5 (15.6)	.435
IBD Type					.029
CD	N (%)	85 (39.9)	86 (53.8)	20 (62.5)	
UC	N (%)	121 (56.8)	69 (43.1)	12 (37.5)	
IBD-U	N (%)	7 (3.3)	5 (3.1)	0 (0.0)	
Current ostomy					.132
No ostomy	N (%)	200 (93.9)	148 (92.5)	26 (81.3)	
Ileostomy	N (%)	11 (5.2)	10 (6.3%)	5 (15.6)	
Colostomy	N (%)	2 (0.9)	2 (1.3)	1 (3.1)	
Previous all-cause hospitalization	N (%)	56 (26.3)	62 (38.8)	19 (59.4)	<.001
Previous IBD-related hospitalization	N (%)	20 (9.4)	18 (11.3)	12 (37.5)	<.001
Disease duration	Median (IQR)	21.0 (8.0-39.0)	24.0 (6.0-40.8)	15.5 (7.3-43.8)	.964
Older-onset	N (%)	64 (30.0)	58 (36.3)	14 (43.8)	.213
Age at diagnosis					.908
≤16 years	N (%)	5 (2.3)	3 (1.9)	1 (3.1)	
17-40 years	N (%)	79 (37.1)	58 (36.3)	10 (31.3)	
>40 years	N (%)	129 (60.6)	99 (61.9)	21 (65.5)	
Disease location (CD)					.623
Ileum	N (%)	23 (27.1)	25 (29.1)	3 (15.0)	
Colon	N (%)	18 (21.2)	13 (15.1)	4 (20.0)	
Ileocolonic	N (%)	44 (51.8)	48 (55.8)	13 (65.0)	
Upper GI involvement (CD)	N (%)	6 (7.1)	4 (4.7)	1 (5.0)	.818
Disease behaviour (CD)					.718
Inflammatory	N (%)	39 (45.9)	32 (37.2)	8 (40.0)	
Stricturing	N (%)	24 (28.2)	30 (34.9)	5 (25.0)	
Penetrating	N (%)	22 (25.9)	24 (27.9)	7 (35.0)	

Table 1. 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
Peri-anal disease (CD)	N (%)	24 (28.2)	19 (22.1)	3 (15.0)	.432
Disease location (UC/IBD-U)					.281
Proctitis	N (%)	19 (14.8)	10 (13.5)	2 (16.7)	
Left-sided colitis	N (%)	40 (31.3)	29 (39.2)	7 (58.3)	
Pancolitis	N (%)	69 (53.9)	35 (47.3)	3 (25.0)	
Hb (mmol/L divided by LLN)	Mean (SD)	1.06 (0.11)	1.05 (0.13)	1.07 (0.13)	.313
CRP (mg/L)	Median (IQR)	3.0 (1.7-4.0)	3.0 (2.0-6.0)	3.0 (2.0-9.6)	.027
FCP (µg/g)	Median (IQR)	82.0 (26.3-187.5)	172 (51.0-484.0)	108 (32.0-244.0)	.004
Elevated FCP (FCP ≥250 µg/g)	N (%)	23 (21.3)	41 (40.2)	4 (21.2)	.007
Biochemical disease activity (CRP≥10 mg/L or FCP≥250 µg/g)	N (%)	31 (17.1)	52 (37.7)	10 (34.5)	<.001
Endoscopic disease activity	N (%)	35 (46.7)	24 (42.9)	6 (60.0)	.627
HBI	Median (IQR)	2.0 (1.0-3.0)	3.0 (2.0-5.0)	3.0 (2.0-7.0)	.003
pMS	Median (IQR)	0.0 (0.0-1.0)	1.0 (0.0-2.0)	1.0 (0.0-2.5)	.010
Clinical disease activity (HBI>4/pMS>2)	N (%)	31 (14.9)	43 (27.7)	11 (39.9)	.001
No current IBD therapy	N (%)	38 (17.8)	40 (25.0)	8 (25.0)	.216
Current mesalamine	N (%)	101 (47.4)	58 (36.3)	11 (34.4)	.066
Current prednisone or budesonide	N (%)	14 (6.6)	19 (11.9)	6 (18.8)	.036
Current immunomodulatory therapy	N (%)	36 (16.9)	38 (23.8)	7 (21.9)	.263
Current biological therapy	N (%)	50 (23.5)	51 (31.9)	6 (18.8)	.113
Prior IBD-related surgery	N (%)	77 (36.2)	63 (39.4)	16 (50.0)	.317
SIBDQ	Mean (SD)	62.3 (5.8)	58.4 (4.9)	50.7 (12.1)	<.001
IBD-DI	Mean (SD)	13.8 (10.3)	22.7 (13.8)	31.2 (19.5)	<.001

No deficits: 0-1 deficits in geriatric assessment, moderate deficits: 2-3 deficits in geriatric assessment, severe deficits: 4-5 deficits in geriatric assessment. High educational level: higher vocational or university level.

IQR=Interquartile range; SD=standard deviation; BMI=Body Mass Index; IBD=Inflammatory Bowel Disease; CD=Crohn's disease; UC=ulcerative colitis; IBD-U=IBD-Unclassified; Hb=hemoglobin; mmol/L, millimole per liters; LLN=lower limit of normal; CRP=c-reactive protein; FCP=fecal calprotectin; HBI=Harvey-Bradshaw Index; pMS=partial Mayo Score; sIBDQ=short IBD questionnaire (health-related quality of life); IBD-DI=IBD-disability index.

Previous hospitalization: in 3 years before inclusion. Only oral IBD therapy was noted. Male LLN Hb: 8.5 mmol/L, female 7.5 mmol/L.

Valid percentages are reported, missing data: BMI 1; educational level 17; Hb 68; CRP 81; FCP 176; Biochemical disease activity 57; endoscopic disease activity 264; clinical disease activity 14; sIBDQ 6.

Table 2. Geriatric characteristics of 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.

Table 3. Univariable and multivariable logistic regression analyses on factors associated with deficits in geriatric assessment in older patients with inflammatory bowel diseases

	Univariable analyses			Multivariable analyses		
Covariate	**Odds of frailty**	**95% CI**	**P-value**	**Adjusted odds of frailty †**	**95% CI**	**P-value**
Age in years	1.115	1.067-1.165	.000	1.107	1.056-1.160	.000
Sex (female)	1.969	1.325-2.927	.001	1.939	1.263-2.978	.002
Crohn's disease	1.856	1.250-2.755	.002	1.799	1.179-2.743	.006
Educational level (high)	.609	.393-.944	.027	.730	.459-1.162	.185
Clinical disease activity	2.390	1.455-3.927	.001	2.192	1.284-3.743	.004
Biochemical disease activity	2.857	1.736-4.702	.000	3.358	1.936-5.825	.000
Elevated FCP	2.188	1.213-3.948	.009	2.721	1.376-5.379	.004
Endoscopic disease activity	.952	.490-1.850	.885	.907	.427-1.919	.799
Previous all-cause hospitalization	2.046	1.346-3.109	.001	1.994	1.267-3.137	.003
Previous IBD-related hospitalization	1.787	.978-3.266	.059	1.551	.800-3.006	.194
Previous IBD-related surgery	1.235	.827-1.844	.303	.963	.573-1.617	.886
IBD therapy						
-Corticosteroid use	2.034	1.018-4.063	.044	1.876	.905-3.887	.091
-Immunomodulator use	1.458	.889-2.392	.135	1.316	.761-2.274	.326
-Biological use	1.275	.812-2.000	.291	1.463	.875-2.448	.147

Deficits in geriatric assessment: ≥2 deficits in geriatric assessment, high educational level: higher vocational or university level. Biochemical disease activity=C-reactive protein ≥10 mg/L and or fecal calprotectin ≥250 µg/g. FCP=fecal calprotectin; IBD=inflammatory bowel disease

† Each covariate adjusted for age, sex, Crohn's disease and educational level.

Analyses were performed as complete case analysis

Table 4. Multivariable regression analysis of the association between number of deficits in geriatric assessment and the short Inflammatory Bowel Disease Questionnaire in older patients with inflammatory bowel disease

		Unstandardized coefficient B	**95% Confidence Interval**	**P-value**
Age in years		.189	.035, .342	.016
Sex (female)		-1.854	-3.303, -.404	.012
Educational level (high)		-1.085	-2.596, .425	.158
IBD type (CD)		-.849	-2.248, .551	.234
Clinical disease activity		-5.360	-7.065, -3.656	.000
Number of impaired geriatric domains				
	0	*Reference*		
	1	-1.078	-3.011, .856	.274
	2	-2.908	-4.992, -.825	.006
	3	-6.001	-8.491, -3.511	.000
	4	-8.638	-12.259, -5.017	.000
	5	-19.666	-26.549, -12.782	.000

Deficits in geriatric assessment: ≥2 deficits in geriatric assessment, clinical disease activity : Harvey Bradshaw index >4 or partial Mayo Score >2, high educational level: higher vocational or university level. Analysis performed as complete case analysis, 375 patients were included in multivariable analysis. CD=Crohn's disease.

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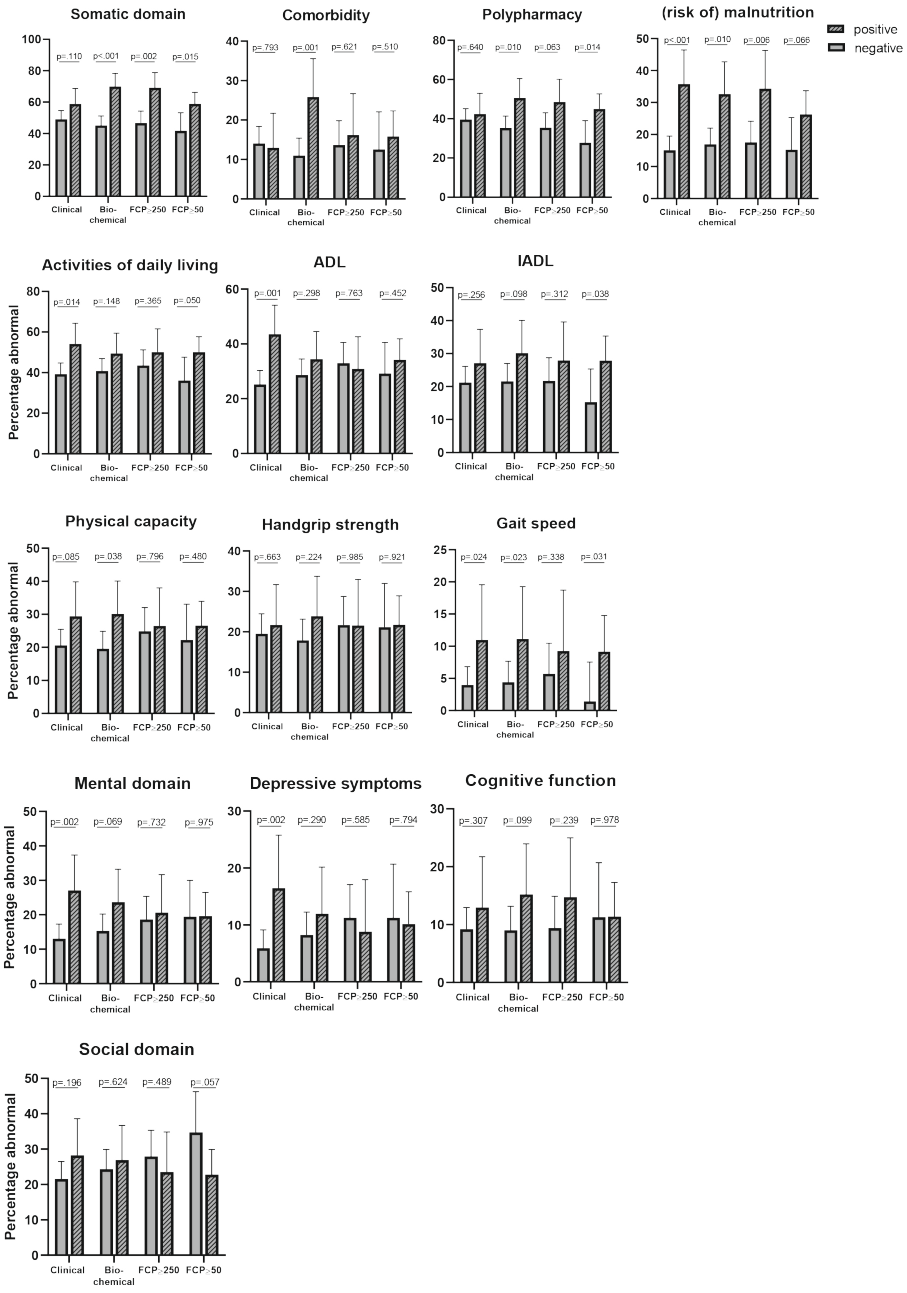
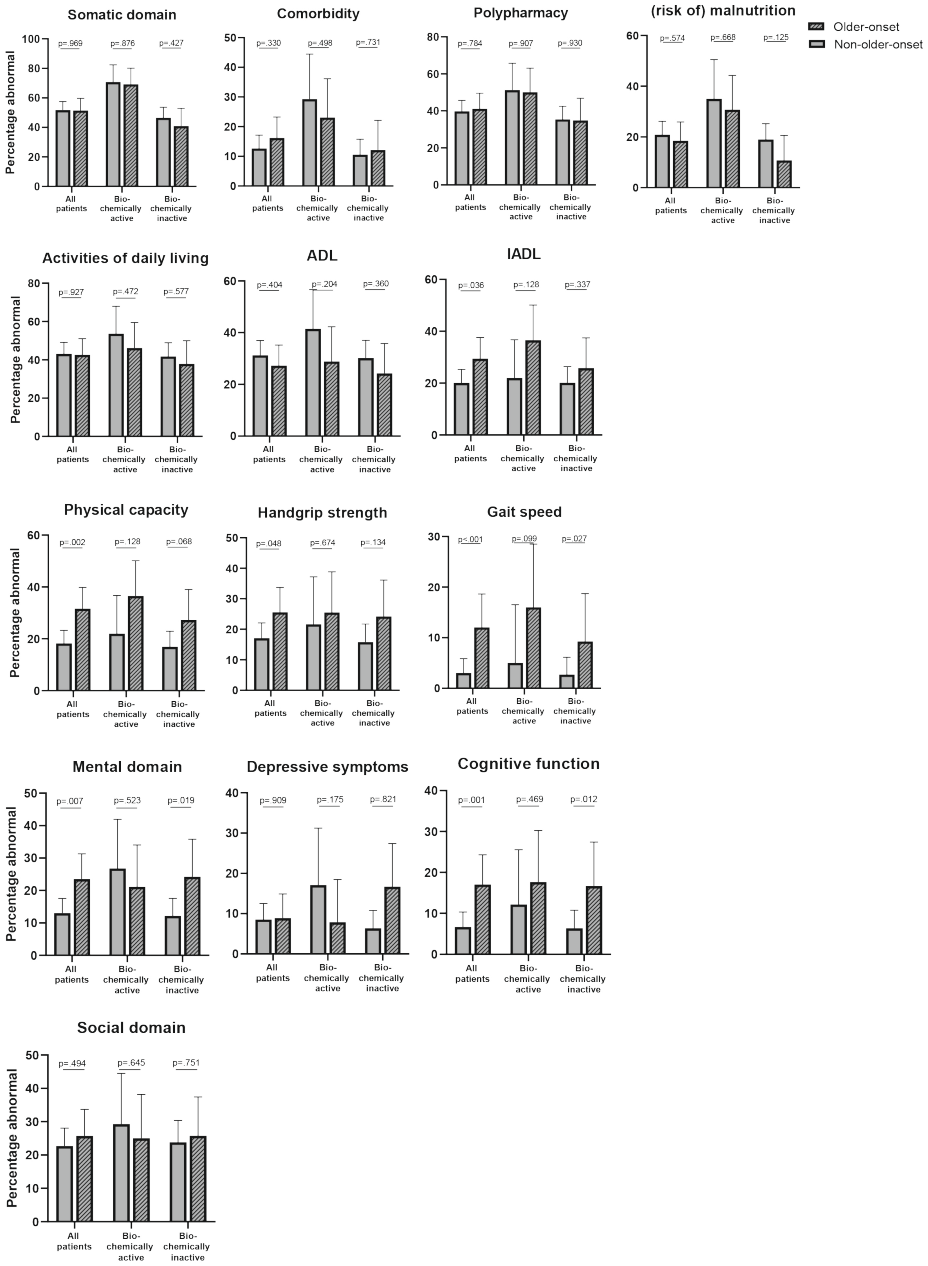
Supplementary table 1: Univariable regression analyses of the association between number of deficits in geriatric assessment and short Inflammatory Bowel Disease Questionnaire.

	Unstandardized coefficient B	95% Confidence Interval	p-value
Age in years	.020	-.137, .176	.805
Sex (female)	-2.946	-4.490, -1.402	.000
Educational level (high)	.444	-1.257, 2.145	.608
IBD type (CD)	-1.651	-3.212, -.089	.038
Clinical disease activity	-6.758	-8.553, -4.963	.000
Biochemical disease activity	-4.621	-4.621, -.731	.007
Elevated FCP	-2.038	-4.510, .433	.106
Number of impaired geriatric domains			
0	*Reference*		
1	-1.332	-3.312, .648	.187
2	-3.961	-6.032, -1.889	.000
3	-6.188	-8.603, -3.773	.000
4	-10.409	-13.670, -7.149	.000
5	-22.118	-28.609, -15.627	.000

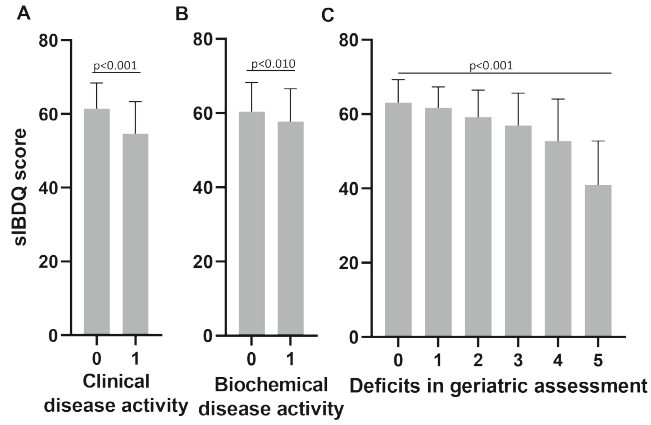
High educational level: higher vocational or university level. Clinical disease activity: Harvey Bradshaw index >4 (Crohn's disease) or partial Mayo Score >2 (ulcerative colitis), biochemical disease activity: CRP≥10 mg/L or FCP≥250 µg/g. CD=Crohn's disease, FCP=fecal calprotectin.



Supplementary figure 1: Prevalence of deficits in geriatric assessment in older patients with inflammatory bowel disease, by clinical disease activity, biochemical disease activity and elevated fecal calprotectin. Percentages and 95% confidence intervals are plotted and groups are compared using a Chi square test. Clinical disease activity : HBI>4 or pMS>2. Biochemically active=c-reactive protein ≥10 mg/L and or FCP ≥250 µg/g); elevated FCP= fecal calprotectin ≥250 µg/g. ADL= Katz Index of Independence in Activities of Daily Living, IADL= Lawton Instrumental Activities of Daily Living



Supplementary figure 2: Prevalence of deficits in geriatric assessment in older patients with inflammatory bowel disease, comparing older-onset with non-older-onset in all patients, biochemically active and biochemically inactive patients Percentages and 95% confidence intervals are plotted and groups are compared using a Chi square test. Biochemically active=C-reactive protein ≥10 mg/L and or fecal calprotectin ≥250 µg/g. ADL= Katz Index of Independence in Activities of Daily Living, IADL= Lawton Instrumental Activities of Daily Living



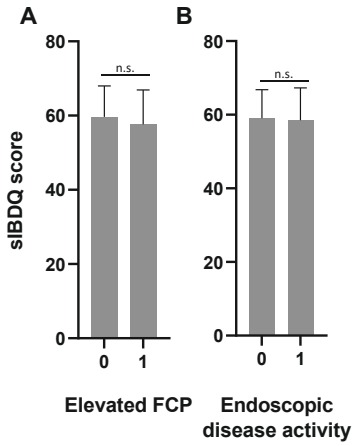
Supplementary figure 3. Health-related quality of life measured by the short Inflammatory Bowel Disease Questionnaire (sIBDQ) in older patients with inflammatory bowel diseases (IBD). Means and standard deviations are plotted.

Means with standard deviations are plotted and groups are compared with an independent samples-T-test (A and B) or one-way ANOVA (C). Clinical disease activity: Harvey Bradshaw Index >4/partial Mayo Score >2, biochemical disease activity: C-reactive protein ≥10 mg/L and/or calprotectin ≥250 µg/g.

A sIBDQ score in older patients with IBD with (1) and without (0) clinical disease activity.

B sIBDQ score in older patients with IBD with (1) and without (0) biochemical disease activity

C sIBDQ score in older patients with IBD with no (0) to five (5) deficits in geriatric assessment



Supplementary figure 4: Health-related quality of life measured by the short Inflammatory Bowel Disease Questionnaire (sIBDQ) in older patients with inflammatory bowel diseases (IBD), by fecal calprotectin (FCP) and endoscopic disease activity.

Means with standard deviations are plotted and groups are compared with an independent samples-T-test. Elevated FCP=fecal calprotectin ≥250 µg/g.

A. sIBDQ score in older patients with IBD with an elevated FCP (1) and with low FCP (0).

B. sIBDQ score in older patients with IBD with endoscopic disease activity (0) and without endoscopic disease activity (0).

7

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

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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.

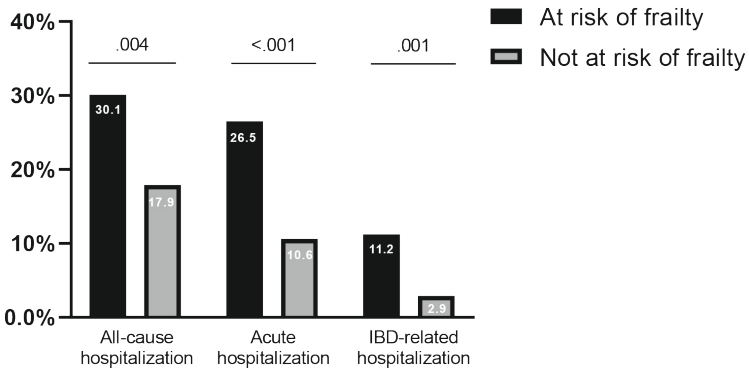

Figure 1. Hospitalizations during 18 months follow-up in older patients with Inflammatory Bowel Disease by frailty screening

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

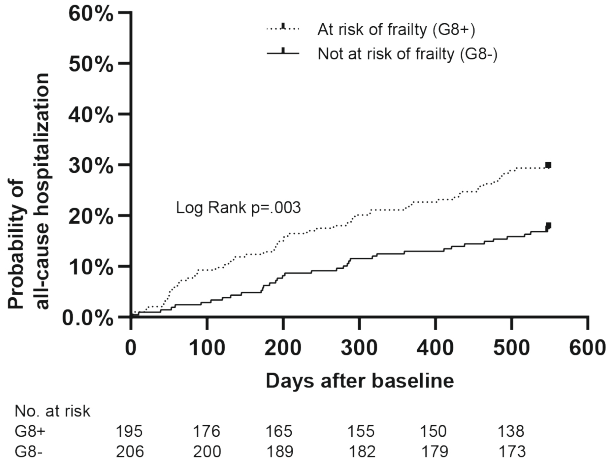

Figure 2. Probability of all-cause hospitalization according to frailty screening in older patients with Inflammatory Bowel Disease.
Kaplan Meier figure is displayed, frailty screening was performed using Geriatric 8 questionnaire

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.

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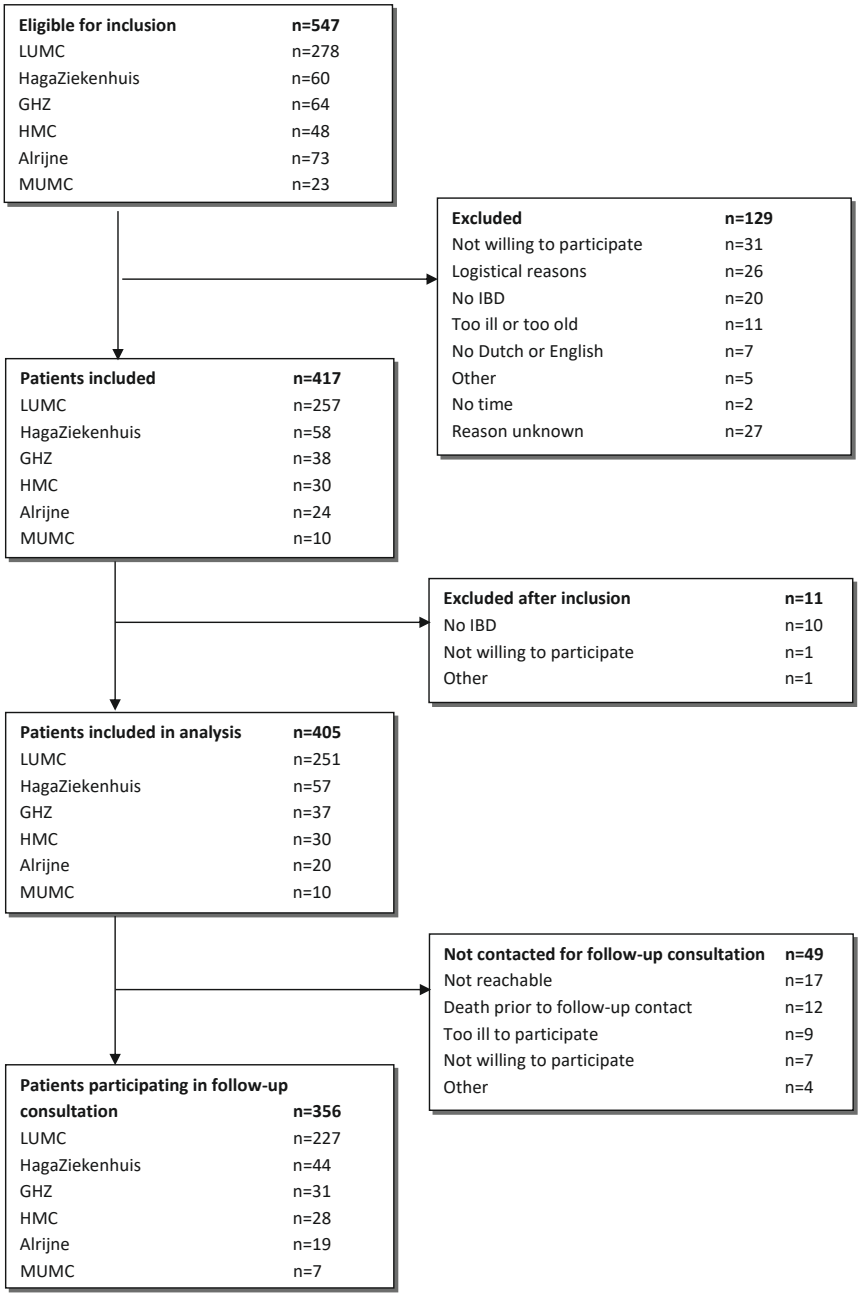

Supplementary figure 1. Flowchart patient inclusion.
Logistical reasons are researcher- or hospital-related logistical reasons such as no consulting room available or due to different hospital locations. No time means patient had no time; too ill or too old means patient thinks he or she is too ill or 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.

8

Summarizing discussion

MAIN FINDINGS

This thesis has three main findings. First, we found that characteristics of frailty influence therapy choices and treatment goals in current practice. However, physicians do not systematically assess frailty and evidence on frailty and (components of a) geriatric assessment in association with health outcomes is very scarce. Therefore we conclude that the decisions based on characteristics of frailty in treatment of IBD are currently based on gut feeling rather than evidence-based medicine.

Second, in patients with IBD of all ages using anti-TNF therapy, comorbidity independently associates with safety outcomes (serious infections and malignancies), but not with effectiveness of therapy. In patients of all ages with IBD on vedolizumab or ustekinumab, comorbidity also associates with safety outcomes. Again, comorbidity was not associated with effectiveness of therapy. An important note is that age did not associate with any of the outcomes of interests in both studies.

Third, the prevalence of frailty was assessed in a cohort of older patients with IBD, while performing both a geriatric assessment including five geriatric domains and a frailty screening. Deficits in geriatric domains were highly prevalent: 39.5% had moderate deficits (deficits in two or three domains) and 7.9% severe (deficits in four or five domains). Out of all patients, 48% screened at risk of frailty. At baseline we found that patients with disease activity are more prone to deficits in their geriatric assessment, and that presence of deficits independently associates with higher disease burden. Patients screened at risk of frailty and patients with deficits in their geriatric assessment both have a higher risk of acute and IBD-related hospitalization during follow-up and patients at risk of frailty have a higher risk of decline in both quality of life and functional status.

IMPLICATIONS FOR CLINICAL PRACTICE

The European Crohn's and Colitis Organisation (ECCO) advises to account for frailty rather than age in treatment of older patients with IBD, as reported in their topical review published in 2017.[1] In **Chapter 2** of this thesis we found that the need for clinically applicable research in older patients is high. Treatment decisions are sometimes based on aspects of frailty in daily clinical practice, however, looking at the scarcity of literature as described in **Chapter 3** and the fact that currently frailty is not systematically assessed in daily practice, these treatment decisions are based on a gut-feeling and not on evidence-based medicine. The advice published by the ECCO therefore currently fails to guide clinical decision making in older patients with IBD.

Professionals often encounter moments needing decision making, for example when a patient is developing symptoms under current medical treatment and there is need to

step-up medication. The results described in **Chapter 4 and 5** endorse clinical application of comorbidity indices such as the Charlson Comorbitidy Index (CCI) next to IBD specific characteristics in this decision-making process. In **Chapter 4**, we found cardiovascular disease to be associated with a higher risk of infections during anti-TNF therapy in patients with IBD of all ages. In **Chapter 5**, we identified patients on vedolizumab and ustekinumab with elevated risk for impaired safety outcomes which should be monitored closely: patients with a CCI≥3 and, again, patients with cardiovascular disease. Furthermore, we found that patients treated with concomitant immunosuppressive medication are at a higher risk for hospitalization during both vedolizumab and ustekinumab therapy. From this thesis follows the recommendation to screen every patient with IBD for comorbidities prior to the start of new medication, to discuss the additional risks and perform close monitoring or opt for alternative options. Besides, we discourage concomitant immunosuppressive medication use next to biologicals in patients in which multiple comorbidities are present.

Next to comorbidity assessment, this thesis provides evidence on using frailty screening in older patients with IBD. Although the current place in treatment of IBD in older patients is not yet established, in **Chapter 6 and 7** we have shown that frailty in older patients with IBD is associated with higher disease burden, and higher risk of hospitalization and decline in functional status and quality of life. We therefore advise to screen older patients with IBD for risk of frailty at the outpatient department regularly. Physicians should be aware of their patient's frailty and when in doubt, a geriatrician should be consulted and multidisciplinary care should be initiated where necessary and possible. Multiple interventions are available to improve disease burden and possibly risk of negative health outcomes.

Last, physicians should be aware of the fact that treatment goals relevant to older patients are often related to independence and quality of life and could also depend on frailty status. We recommend physicians to ask their patients about goals which are relevant to them, as for an older patient with IBD, short term goals such as quality of life and independence could be equally or even more important than conventional outcomes such as endoscopic remission or mucosal healing.

IMPLICATIONS FOR FUTURE RESEARCH

Including measures of frailty in IBD research

Further research must point out how frailty screening can help physicians to optimize treatment for frail older patients with IBD and how it could guide clinical decision making. Ideally, to include frailty screening in the clinical decision-making process, we need prospective data on the association between risk of frailty, measured prior to start of therapy, and outcomes on safety and effectiveness. As only seven percent of all randomized controlled trials (RCTs) is specifically designed for older patients and less than 1% of participants in RCTs regarding IBD medications is aged 65 years or older, it is unlikely that

the evidence regarding frailty in older patients with IBD will be provided by RCTs.[2,3] Registry studies and prospective cohort studies are therefore of priceless value. In IBD care, registry studies such as the ICC registry are customary and widely implemented in the Netherlands to monitor IBD patients starting novel therapies. Frailty screening has to be included in such registry studies. The G8 questionnaire is convenient to use because it is easy to administer and doesn't require additional instructions or instruments. Although three out of eight questions cover food intake or weight loss and are thereby closely linked with IBD symptoms, we found that risk of frailty was independent of disease activity associated with outcomes of interest.

To further evaluate the interplay between frailty and outcomes of therapy an observational study including older patients with IBD in need for step-up of therapy can be rolled out. At inclusion patients have to be screened for frailty and after this, patients can be allocated to two different therapies, equally distributing patients at risk of frailty between both. In **Chapter 2** we found that professionals tend to prescribe vedolizumab in favor of other biologicals in older patients. An explanation for could be that vedolizumab supposedly has a gut-specific working mechanism and is therefore safer in older patients. In the light of this theory, we could randomize patients either for vedolizumab or for anti-TNF therapy. In this way we can analyze the association between frailty and outcomes in both vedolizumab and anti-TNF and assess if vedolizumab is indeed safer in older patients with IBD at risk of frailty.

Researching trajectories of frailty and interventions to promote resilience

A few studies in other research fields have suggested that a worsening of frailty status over time is predictive of negative health outcomes. A study by Lai et al. in adult patients with liver cirrhosis found that worsening of physical frailty was associated with waitlist mortality or delisting. This association was independent of both baseline physical frailty and liver cirrhosis severity (MELD-Na score).[4] In our cohort described in **Chapter 6 and 7**, we performed geriatric assessment in 150 patients at both baseline and after 18 months. In patients with worsening frailty over time, we can investigate if a higher risk of hospitalization or other negative health outcomes is present.

The next step would be to investigate how interventions aimed at reversing frailty and thereby promoting resilience could mitigate this risk. One could postulate that by using interventions aimed at improving deficits in geriatric domains such as nutritional and physical status, or depression, the risk of negative health outcomes could be reduced. A very interesting research design would be to screen patients for frailty prior to biological therapy, and to offer half of them a program aimed at improving certain aspects of their frailty such as referring patients to a dietician or physiotherapist. During their treatment we could monitor if frailty status improves and if we can reduce the risk for negative health outcomes.

Including outcomes relevant for older patients in research

Quality of life in older patients with IBD is mostly determined by factors related to independence and health status, as we found in **Chapter 2**. Also, we saw that several older patients find incontinence one of the most disabling IBD-symptoms, because it influences their independence. In both research and daily practice professionals should be focusing on endpoints which are relevant to older patients.

The first step to make the evidence regarding patient related outcomes in older patients more robust is to gather the ideas we have found in **Chapter 2** and test them in a quantitative manner. Currently, we are working with the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) to make a survey combining the results of **Chapter 2** with input from a focus group of older patients with IBD, to make a survey which will be distributed to patients throughout Europe. In this manner we can quantify which treatment goals are important in our population of interest in a larger population.

When the above-mentioned evidence is available, these patient related outcomes can be included in both daily practice and in research. In observational studies in older patients measures regarding functional status, such as (instrumental) activities of daily living, can already be implemented.

CONCLUSION

Decisions which are currently being made in the treatment of older patients with IBD are for a large part based on gut-feeling rather than evidence-based medicine. From the results of this thesis, we advise to screen older patients with IBD for comorbidity and frailty, especially prior to start of new medication. Measures of both comorbidity and frailty should be implemented in clinical trials and observational studies. Outcomes important for older patients should be prioritized in both clinical practice and in research to optimize care for older patients with IBD. In the end, we should strive to work towards an evidence-based and systematic approach in the treatment of older patients with IBD in which patients at risk of frailty will be selected on time. In this way, patients with frailty could be offered tailored medical care for their IBD and at the same time receive interventions aimed at improving their frailty.

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Appendix

NEDERLANDSE SAMENVATTING

Introductie

Inflammatoire darmziekten (Inflammatory Bowel Diseases, IBD) zijn chronische immuun gemedieerde ziekten. Hieronder vallen de ziekte van Crohn, colitis ulcerosa en ongeclassificeerde IBD. Typisch voor deze ziekten is een chronisch en terugkerend beloop waarbij er opvlammingen optreden, die gekenmerkt worden door ontstekingen van het maag-darmstelsel met hierbij passende klachten zoals buikpijn en diarree.[1] De populatie van patiënten met IBD omvat steeds meer oudere patiënten, meestal gedefinieerd als 65 jaar of ouder. Er wordt geschat dat in het volgende decennium meer dan een derde van alle IBD patiënten ouderen zullen zijn.[2]

IBD is niet te genezen en wordt behandeld door het in remissie brengen van de ziekte met medicijnen zoals corticosteroïden, en het in remissie houden door onderhoudstherapie te starten zoals immunomodulatoren of, als dit onvoldoende helpt, biologicals zoals bijvoorbeeld anti-tumour necrosis factor (anti-TNF) therapie, vedolizumab of ustekinumab. Biologicals zijn medicijnen die de werking van ontstekingseiwitten of afweercellen in het lichaam remmen.

Het behandelen van oudere patiënten kan een uitdaging zijn door de aanwezigheid van andere ziekten naast IBD (comorbiditeit) en geriatrische aandoeningen zoals geheugenproblemen. Daarom wordt in deze populatie in bepaalde gevallen een Comprehensive Geriatric Assessment (CGA) uitgevoerd. Dit is een uitgebreid multidisciplinair klinisch geriatrisch onderzoek waarbij de problemen van de oudere patiënt worden opgespoord en ook de capaciteiten en zorgbehoeften van de patiënt worden onderzocht.[3] Een groot onderdeel hiervan is het geriatrisch assessment. Dit assessment bestaat uit vier verschillende domeinen: het somatische, functionele, mentale en sociale domein. Het somatische domein bestaat uit het vaststellen van comorbiditeit, polyfarmacie en (risico op) ondervoeding. Het functionele domein bestaat uit het onderzoeken van de mate van afhankelijkheid in dagelijkse activiteiten en ook de fysieke capaciteit (deze laatste is in dit proefschrift apart genomen als domein, waardoor er in totaal vijf domeinen ontstonden). De fysieke capaciteit wordt gemeten door bijvoorbeeld de loopsnelheid of handknijpkracht. Het mentale domein bestaat uit het vaststellen van geheugenproblemen en depressie. Het sociale domein is de evaluatie van een sociaal netwerk en de support die een patiënt hieruit kan krijgen. Als er veel afwijkingen zijn in een geriatrisch assessment wordt een patiënt als kwetsbaar gezien. Dit betekent dat een patiënt vatbaarder is voor achteruitgang in zijn of haar gezondheid na een bepaalde gebeurtenis zoals bijvoorbeeld een ziekenhuisopname. Omdat een geriatrisch onderzoek zoals hierboven beschreven vaak tijdrovend is, worden patiënten meestal eerst gescreend voor kwetsbaarheid.[3] Als de screening dan afwijkend is, wordt het gehele assessment uitgevoerd.

In andere medische vakgebieden zoals de oncologie laat onderzoek dat uitgevoerd is bij oudere patiënten een verband zien tussen de aanwezigheid van kwetsbaarheid en uitkomsten als achteruitgang in functioneren, opname in het ziekenhuis of meer bijwerkingen van een bepaalde behandeling.[4 5] Op deze manier is (de screening van) kwetsbaarheid een belangrijk middel geworden in klinische besluitvorming in deze vakgebieden. Op het gebied van IBD is echter nog relatief weinig onderzoek verricht naar dit onderwerp.

Doel van dit proefschrift

Dit proefschrift heeft drie doelen. Het eerste doel is tweeledig. Aan de ene kant wordt onderzocht welke factoren bijdragen aan huidige therapiekeuzes en behandeldoelen bij oudere patiënten met IBD. Dit deel van het onderzoek is uitgevoerd door MDL-artsen met de specialisatie IBD, IBD-verpleegkundigen en IBD-patiënten te interviewen. Aan de andere kant wordt onderzocht of er in de huidige literatuur wetenschappelijk bewijs is voor het gebruik van kwetsbaarheidsscreening of een geriatrisch assessment bij de behandeling van IBD. Het tweede doel van dit proefschrift is om het verband te bepalen tussen de aanwezigheid van comorbiditeit bij de start van de behandeling met biologicals, enerzijds, en de veiligheid en effectiviteit van deze therapie, anderzijds. Als derde en laatste doel wordt de prevalentie van kwetsbaarheid in oudere patiënten met IBD onderzocht, en de relatie tussen deze kwetsbaarheid en gezondheidsuitkomsten zoals ziekenhuisopnames en infecties, functionele achteruitgang en kwaliteit van leven.

Samenvatting van de belangrijkste bevindingen

Ondanks dat er in de huidige literatuur of richtlijnen geen adviezen zijn omtrent het anders behandelen van oudere patiënten met IBD ten opzichte van jongere patiënten, blijkt uit meerdere onderzoeken dat oudere patiënten in de dagelijkse praktijk toch anders behandeld worden. Dit was de aanleiding voor het onderzoek beschreven in **Hoofdstuk 2**, waarin factoren worden geïdentificeerd die bijdragen aan dit verschil in behandeling. Er werd gevonden dat zowel leeftijd als (aspecten gerelateerd aan) kwetsbaarheid de behandelbeslissingen beïnvloeden, bij zowel professionals als bij patiënten. Bijvoorbeeld: veel professionals richten zich meer op doelen gerelateerd aan functionele status bij patiënten met kwetsbaarheidskenmerken, in plaats van puur het kijken naar vermindering van ziekteactiviteit. Wat daarnaast opviel was dat, ondanks dat studies hebben laten zien dat corticosteroïden zorgen voor bijwerkingen en negatieve uitkomsten,[6] sommige professionals kiezen voor een behandeling met corticosteroïden in oudere patiënten met IBD terwijl anderen hier juist faliekant tegen zijn.

In **Hoofdstuk 3** is systematisch alle literatuur omtrent het verband tussen kwetsbaarheid, (delen van) het geriatrisch assessment en gezondheidsuitkomsten in oudere patiënten met IBD onderzocht. Opvallend was dat er geen enkele studie was die specifiek voor oudere patiënten bedoeld was, en dat er ook geen studies waren die een subgroep-analyse hadden uitgevoerd naar oudere patiënten. Daarnaast was er geen enkele studie naar kwetsbaarheid, en ook niet naar cognitieve of functionele status. Daarom is verder gekeken naar de losse

domeinen (componenten van) een geriatrisch assessment. Uiteindelijk werden 27 studies gevonden waarin een of meerdere componenten van een geriatrisch assessment werden onderzocht in relatie met de bovengenoemde uitkomsten. Een derde van de onderzochte verbanden in deze studies was statistisch significant geassocieerd met een hoger risico op uitkomsten zoals ziekenhuisopnames, heropnames of een opvlamming van IBD. Kortom, na Hoofdstuk 2 en 3 valt te concluderen dat de behandeling van oudere patiënten met IBD vaak op het gevoel wordt gedaan, en niet zozeer op basis van resultaten van wetenschappelijke onderzoeken.

In **Hoofdstuk 4 en 5** is de rol van comorbiditeit bij patiënten met IBD die behandeld worden met biologicals onderzocht. In **Hoofdstuk 4** werden patiënten onder behandeling met de biological anti-TNF onderzocht. Comorbiditeit werd gemeten door te kijken of gastro-intestinale, hepatische, cardiovasculaire, pulmonale comorbiditeiten of diabetes mellitus aanwezig waren. Als comorbiditeit bij de start van anti-TNF therapie aanwezig was, gaf dit een hoger risico op bijwerkingen. Zo gaf de aanwezigheid van cardiovasculaire ziekten een drie keer zo hoog risico op ernstige infecties (onafhankelijk van leeftijd) in vergelijking met patiënten zonder cardiovasculaire ziekten. De aanwezigheid van twee of meer comorbiditeiten gaf een negen keer zo hoog risico op het ontwikkelen van een maligniteit (ook onafhankelijk van leeftijd). In **Hoofdstuk 5** werden patiënten onder behandeling met de biologicals vedolizumab (een α4β7 antilichaam) of ustekinumab (een antilichaam tegen IL-12 en IL-23) onderzocht. De Charlson Comorbidity Index (CCI) werd gebruikt om het aantal comorbiditeiten te kwantificeren. Dit is een index waarbij meerdere comorbiditeiten worden meegenomen en patiënten punten krijgen voor hoe ernstig de comorbiditeiten zijn.[7] Zo krijgt een patiënt met Diabetes Mellitus één punt, maar als er orgaanschade is door de Diabetes wordt deze als twee punten meegeteld. De CCI verschilde niet significant tussen de patiënten die met vedolizumab of met ustekinumab behandeld werden, alhoewel de patiënten die met vedolizumab werden behandeld meer cardiovasculaire ziekten hadden en ook vaker een hoge CCI-score hadden van drie of meer. Ook in dit hoofdstuk gaf comorbiditeit een hoger risico op bijwerkingen. Bij patiënten behandeld met vedolizumab gaf een hogere CCI een hoger risico op infecties (per punt stijging in de CCI 40% meer kans) en op ziekenhuisopnames (per punt CCI-stijging 60% meer kans). Dit was onafhankelijk van leeftijd, geslacht, type IBD, ziekteduur, en ander medicatiegebruik zoals corticosteroïden of immunomodulatoren. Als sub-analyse werd in deze groep gekeken of specifieke comorbiditeiten een hoger risico met zich meebrachten. Cardiovasculaire ziekten gaven een vier keer zo hoog risico op ziekenhuisopnames tijdens de behandeling met vedolizumab. In ustekinumab patiënten was de CCI niet geassocieerd met infecties, maar wel onafhankelijk met ziekenhuisopnames (per punt stijging in de CCI 60% meer kans). Als alle patiënten, dus zowel de patiënten met vedolizumab als ustekinumab, samen werden gegroepeerd, bleek dat patiënten met een CCI van drie of meer punten een bijna vijf keer zo hoog risico op ziekenhuisopnames hadden. Comorbiditeit was in beide hoofdstukken niet geassocieerd met effectiviteitsuitkomsten. Zowel in Hoofdstuk 4 als in Hoofdstuk 5 was leeftijd, gecorrigeerd voor comorbiditeit,

op geen enkele manier geassocieerd met een hoger risico op verminderde veiligheid of effectiviteit van de behandeling.

In **Hoofdstuk 6** wordt de prevalentie van beperkingen in geriatrische domeinen in ons multicenter cohort van oudere patiënten met IBD onderzocht. Daarnaast is gekeken in hoeverre IBD-karakteristieken zoals ziekteactiviteit en ziektelast samenhangen met deze beperkingen. In totaal werden in het geriatrisch assessment vijf domeinen onderzocht. Het viel op dat beperkingen in geriatrische domeinen vaak voorkomen: bij de 405 patiënten die werden onderzocht had 39.5% (160 patiënten) matige beperkingen (2 of 3 domeinen afwijkend uit een totaal van 5) en 7.9% (32 patiënten) ernstige beperkingen (4 of 5 domeinen afwijkend uit een totaal van 5). Zowel de aanwezigheid van klinische (klachten passend bij ziekteactiviteit) als biochemische ziekteactiviteit (verhoogde ontstekingswaarden in het bloed of in de ontlasting) hing samen met een hoger aantal beperkingen in geriatrische domeinen. Klinische ziekteactiviteit gaf een twee keer zo hoog risico, biochemische ziekteactiviteit een meer dan drie keer zo hoog risico. Hoe hoger het aantal beperkingen in het geriatrisch assessment was, des te hoger ook de IBD ziektelast. De conclusie is dat beperkingen in geriatrische domeinen, en dus kwetsbaarheid, samengaan met meer ziekteactiviteit en -last in onze populatie.

Het doel van **Hoofdstuk 7** is om in bovenstaand cohort van oudere patiënten met IBD te bepalen of kwetsbaarheid het risico verhoogt op ziekenhuisopnames en vermindering van kwaliteit van leven en functionele status. In dit hoofdstuk werd kwetsbaarheid op twee manieren bepaald. De eerste door middel van een screening met de G8 vragenlijst. Dit is een vragenlijst bestaande uit acht vragen, die zo het risico op kwetsbaarheid inschat.[8] De tweede door middel van het geriatrisch assessment (opnieuw met vijf domeinen zoals ook in hoofdstuk 6 beschreven). Achttien maanden na inclusie vonden er 136 ziekenhuisopnames van 96 patiënten plaats (23.7% van het totaal aantal patiënten), 103 daarvan waren acute ziekenhuisopnames van 74 patiënten (18.3%). Een afname in kwaliteit van leven werd bij 108 (30.6%) patiënten waargenomen, en een afname in functionaliteit in 46 (13.3%). Patiënten met een risico op kwetsbaarheid zoals gemeten met de G8 vragenlijst hadden een twee keer zo hoog risico op acute ziekenhuisopnames, patiënten met twee of meer beperkingen in geriatrische domeinen hadden een verhoogd risico op alle ziekenhuisopnames en ook specifiek op acute ziekenhuisopnames. Risico op kwetsbaarheid gaf een twee keer zo hoge kans op achteruitgang van kwaliteit van leven en een bijna vier keer zo hoge kans op functionele achteruitgang. Dit laatste zagen we niet terug bij de beperkingen in het geriatrisch assessment.

Discussie

Ondanks het feit dat kwetsbaarheid in de praktijk niet systematisch wordt gebruikt bij het behandelen van oudere patiënten met IBD, en het feit dat de literatuur over kwetsbaarheid bij IBD zeer schaars is, blijkt uit het onderzoek beschreven in dit proefschrift dat professionals op dit moment wel behandelbeslissingen en -doelen baseren op

aspecten van kwetsbaarheid. Deze beslissingen zijn eerder gebaseerd op gevoel dan op wetenschappelijk bewijs. In dit proefschrift wordt het eerste bewijs geleverd dat pleit voor het gebruik van comorbiditeitsindices en kwetsbaarheidsscreening bij oudere patiënten met IBD. Gebaseerd op onze resultaten adviseren wij clinici om oudere patiënten met IBD te screenen voor comorbiditeit voorafgaand aan de start van een nieuwe (biological) behandeling, bij voorkeur met een gestandaardiseerde index. Comorbiditeiten zouden geoptimaliseerd moeten worden voorafgaand aan de behandeling, en patiënten met een hoger risico (cardiovasculaire ziekten of een hoge CCI, met name drie punten of meer) zullen geïnformeerd moeten worden en goed gemonitord. Daarnaast zouden clinici zich bewust moeten zijn van de (mogelijke) aanwezigheid van kwetsbaarheid en de associatie tussen kwetsbaarheid en negatieve gezondheidsuitkomsten in oudere patiënten met IBD. Wanneer er twijfel is zal een geriater of internist-ouderengeneeskunde geconsulteerd moeten worden. Om ons verder te helpen hoe we kwetsbaarheidsscreening in de praktijk kunnen gebruiken, en hoe het ons kan helpen om therapie te optimaliseren voor oudere patiënten met IBD zal kwetsbaarheid veel meer meegenomen moeten worden in IBD-onderzoek. Uitkomsten die belangrijk zijn voor deze populatie, zoals kwaliteit van leven en functionele status, zullen meegenomen moeten worden in dergelijke onderzoeken, en ook in de praktijk zal hier meer aandacht voor moeten komen door te luisteren naar wat voor de patiënt zelf belangrijk is. Op deze manier werken we toe naar de beste behandeling voor kwetsbare oudere patiënten met IBD.

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ENGLISH SUMMARY

Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease, comprising Crohn's disease (CD), ulcerative colitis (UC) and IBD-Unclassified (IBD-U) and characterized by a relapsing and remitting inflammation of the intestines.[1] The number of older patients with IBD, defined as aged 65 years or older, is increasing. It is estimated that in the next decade more than one-third of all IBD patients will be older adults.[2] IBD is incurable and medical treatment consists of remission induction with corticosteroids, and maintenance therapy with immunomodulators or biologicals such as anti-tumour necrosis factor (anti-TNF) therapy, vedolizumab or ustekinumab targeting the immune system.

Providing adequate healthcare for older patients is often challenging due to the presence of multimorbidity and geriatric conditions, such as cognitive impairment. A Comprehensive Geriatric Assessment (CGA) is used to assess these conditions. This assessment is defined as a multidisciplinary evaluation in which problems are uncovered and resources and strengths of the patient are defined.[3] It includes a geriatric assessment which explores four different domains, namely the somatic, functional, mental and social domain. The somatic domain includes assessment of (co-)morbidities, polypharmacy and (risk of) malnutrition. The functional domain includes functional performance, measured by the level of independence in activities of daily living, and level of physical capacity, which can be measured by gait speed or handgrip strength. The latter was taken as an individual domain in the research described in this thesis, resulting in five domains. The mental domain includes cognitive performance and depression, the social domain includes the evaluation of the social support network. The above-mentioned assessment can be integrated into an overall level of frailty. Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis following a stress. Because a geriatric assessment is a time consuming effort, patients are often first screened for frailty. Based on findings of this screening, the more detailed assessment can be undertaken.[3] In other medical fields, research performed in older patients shows an association between the presence of frailty and adverse health outcomes, thereby presenting the use of frailty screening or a geriatric assessment as a valuable tool in clinical decision making.[4, 5] However, in IBD, little research has been performed on this topic.

Aim of this thesis

This thesis has three aims. The first is to research which factors contribute to current therapy choices and treatment goals in older patients with IBD by interviewing professionals and patients, and to quantify the current evidence on geriatric assessment and its relation with health outcomes in our population of interest. The second is to study the association between comorbidity, prior to start of medical therapy, and safety and effectiveness outcomes of these therapies in patients with IBD. The third is to assess the prevalence of

frailty and its association with health outcomes and functional decline and decline in quality of life in older patients with IBD.

Summary of key findings

Although current clinical guidelines do not advise different treatment strategies in older patients as compared to younger patients, several studies have shown that older patients do receive different treatments in daily practice. The aim of **Chapter 2** is to identify factors contributing to this difference by conducting interviews in patients and professionals. Age and frailty status influence choices regarding therapy goals and treatment modalities of both professionals and patients. For instance, many professionals aim towards functional goals such as maintaining independence when characteristics of frailty are present in an older patient with IBD. Although multiple studies have shown that corticosteroids cause negative health outcomes[6] and are therefore not advised for long-term use, it was found that several professionals opt for corticosteroid treatment in older patients while others are very reluctant.

In **Chapter 3** the literature on the association between frailty screening, (components of a) geriatric assessment, and adverse health outcomes in older patients with IBD is assessed. One of the main findings is that there were no studies specifically designed for older patients, or even studies performing subgroup analyses in older patients. Also, no studies researching frailty, cognitive status or functional performance in older patients with IBD were found. Therefore we focused on the domains (components) of a geriatric assessment. Twenty-seven studies were found in which one or more of these components were analyzed, In one-third of the associations described in these studies were described a higher risk between a component of a geriatric assessment and adverse health outcomes such as hospitalization or exacerbation of disease. In conclusion, from Chapter 2 and 3 we can conclude that treatment of older patients with IBD is often led by gut feeling, instead of evidence-based medicine.

In **Chapter 4 and 5** the role of comorbidity in patients with IBD undergoing treatment with biologicals was studied. In **Chapter 4** IBD patients treated with anti-TNF therapy were included. Comorbidity was measured by documenting gastro-intestinal, hepatic, cardiovascular and pulmonary comorbidities and presence of diabetes. Patients with cardiovascular disease had a three times higher risk of serious infections (independent of age) and patients with two or more comorbidities had a nine times higher risk of developing a malignancy during follow-up (again independent of age). In **Chapter 5**, patients treated with vedolizumab (an α4β7 antibody) or ustekinumab (a human IgG antibody targeting the p40 subunit of IL-12 and IL-23) were studied. In this study, we used the Charlson Comorbidity Index (CCI) to quantify comorbidity. This is a weighted index taking into account the number and severity of 16 pre-defined comorbidities.[7] CCI did not differ between vedolizumab and ustekinumab treated patients, however the vedolizumab-treated group had more cardiovascular diseases. In vedolizumab patients, the CCI was associated with infections during follow-up (per point

increase in CCI: 40% higher risk) and all-cause hospitalization (per point increase in CCI: 60% higher risk). This was independent of age, sex, IBD type, disease duration and the use of corticosteroids or immunomodulators. As a sub-analyses the relation between separate comorbidities and outcomes were studied. Patients with cardiovascular disease who were treated with vedolizumab had a four times higher risk of all-cause hospitalization. In ustekinumab treated patients, CCI was not associated with any infection, but was associated with hospitalization (per point increase in CCI: 60% higher risk). In all patients, both vedolizumab and ustekinumab, a CCI of 3 points or higher (compared with CCI categories 0, 1 or 2) was significantly and independently associated with hospitalization during treatment (five times higher risk). Comorbidity did not influence effectiveness outcomes in both studies. Furthermore, in both chapter 4 and 5, age, corrected for comorbidity, was not associated with higher risk of negative health outcomes.

In **Chapter 6**, the prevalence of deficits in geriatric domains is evaluated in a multicentre outpatient cohort of older patients with IBD. Furthermore, the association between IBD characteristics and these deficits in geriatric domains is being looked at, next to the impact of these deficits on disease burden. In total, five geriatric domains were evaluated in the geriatric assessment. The prevalence of deficits in geriatric domains was remarkably high. Out of 405 patients, a total of 160 (39.5%) patients had moderate deficits (2 or 3 out of 5 domains impaired) in their geriatric assessment; 32 (7.9%) severe (4 or 5 out of 5 domains impaired). Clinical (disease complaints) and biochemical (inflammation in blood or stool) disease activity associated with presence of deficits. Clinical disease activity gave a two-fold risk, biochemical disease activity more than three-fold risk. Deficits in geriatric domains were independently associated with a higher disease burden.

The objective of **Chapter 7** is to study frailty, measured by both geriatric assessment and frailty screening, in association with hospitalization and decline in quality of life and functional status in our cohort of older patients with IBD over the course of 18 months. Frailty screening was performed using the G8 questionnaire, consisting of eight questions estimating the risk of frailty.[8] All-cause hospitalizations occurred 136 times in 96 patients (23.7%), acute hospitalization 103 times in 74 patients (18.3%). Decline in QoL was experienced by 108 (30.6%) patients, decline in functional status by 46 (13.3%). Patients with a high risk of frailty had a two times higher risk of acute hospitalizations, and patients with severe deficits in geriatric domains (four or five) had a three times higher risk of all-cause and acute hospitalization. Risk of frailty had a two times higher risk for decline in quality of life and a three times higher risk for decline in functional status. Deficits in geriatric domains did not associate with decline in quality of life or functional status.

Discussion

Although frailty is currently not systematically assessed and literature on frailty in IBD is scarce, in daily clinical practice treatment decisions for older patients with IBD are often

already based on aspects of frailty. These treatment decisions are therefore mainly based on a gut feeling rather than evidence-based medicine. In this thesis, we provide the first evidence for the use of comorbidity indices and frailty screening in older patients with IBD.

Based on our results, we advise clinicians to screen older patients with IBD for comorbidity prior to start of treatment with biologicals, preferably by using a standardized comorbidity index such as the CCI. Comorbidities should be optimized prior to treatment and patients with a high risk for impaired safety outcomes (cardiovascular disease or a CCI≥3) should be informed and monitored closely. Furthermore, physicians should be aware of their patients' (risk of) frailty and its association with negative health outcomes, when in doubt, a geriatrician should be consulted. To guide us how frailty screening can help optimize treatment for older patients measures of frailty have to be included in conventional IBD research, in registry data, observational studies and randomized trials. Outcomes related to functional status and quality of life are specifically important to older patients, especially when frailty is present. These outcomes need to be implemented in both daily practice and in research, to eventually treat older patients with IBD in the best way possible.

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Asscher, V.E.R.; Rodriguez Girondo, M.D.M.; Fens, J.; Waars, S.N.; Stuyt, R.J.L.; Baven-Pronk, A.M.C.; Srivastava, N.; Jacobs, R.J.; Haans, J.J.L.; Meijer, L.J.; Klijnsma-Slagboom, J.D.; Duin, M.H.; Peters, M.E.R.; Lee-Kong, F.V.Y.L.; Provoost, N.E.; Tijdeman, F.; van Dijk, K.T.; Wieland, M.W.M.; Verstegen, M.G.M.; van der Meijs, M.E.; Maan, A.D.I.; van Deudekom, F.J.; van der Meulen-de Jong, A.E.; Mooijaart, S.P.; Maljaars, P.W.J.
Frailty associates with hospitalization and decline in quality of life and functional status in older patients with inflammatory bowel disease.
Submitted

Fons, A.B.; Asscher, V.E.R.; Stuyt, R.J.L.; Baven-Pronk, A.M.C.; van der Marel, S.; Jacobs, R.J.; Haans, J.J.L.; Mooijaart, S.P.; Eikelenboom, P.; van der Meulen-de Jong, A.E.; Kalisvaart, K.J.; Maljaars, P.W.J.
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Scientific Reports, 2017. DOI: 10.1038/s41598-017-09099-z
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CURRICULUM VITAE

Vera Elisabeth Rosa Asscher was born on the 22nd of August 1993 in Amsterdam, the Netherlands. In 2011, she graduated cum laude from the Vossius Gymnasium in Amsterdam. During high school, she completed the Pre-University College at Leiden University. In 2011, she started studying medicine at Leiden University, during which she participated in the Honours College. In this programme she followed courses on clinical epidemiology and performed research on immune responses in malaria infections under the supervision of dr. Sanne de Jong and prof. Maria Yazdanbakhsh. She was an active member of the Medical Faculty of Leiden Students (M.F.L.S.) and its sub-associaton Leids Medisch Dispuut Forestus. In 2012, she joined the Leiden student association L.V.V.S. Augustinus. As a part of her Bachelor's degree she completed an elective course on Traditional Chinese Medicine at Zhejiang Medical University, Hangzhou, China. Prior to her clinical rotations, Vera went to Nepal in 2015 for a clinical internship at Kanti Childrens' Hospital, Kathmandu, and afterwards travelled through Nepal and India. The internship was arranged by Stichting Medicine for ALL (SMALL), a foundation sponsoring medical therapy for children with cancer in Nepal. Vera joined the board of SMALL after her internship in Nepal and organized several benefit events during her six years as a board member. She conducted her senior clinical internship at the Haaglanden Medical Centre at the department of Internal Medicine and Gastroenterology and Hepatology and began her research on Inflammatory Bowel Disease (IBD) in older patients in 2017 as a scientific internship under the supervision of dr. Jeroen Maljaars and prof. dr. Simon Mooijaart. In 2018, she obtained her medical degree and continued this research as a PhD candidate. During her PhD research Vera supervised multiple master students during their scientific internship and she took place as a board member in the Young Initiative on Crohn's and Colitis (YICC) from 2018 to 2020, which unites young medical doctors and researchers with interest in IBD. Following her PhD research, she started working as a 'resident not in training' at the Gastroenterology and Hepatology department of the HagaZiekenhuis, The Hague. In May 2022 she began her residency in Internal Medicine, as the first part of her training to become a Gastroenterologist and Hepatologist.

DANKWOORD

Allereerst wil ik alle patiënten bedanken die deelnamen aan de studies beschreven in dit proefschrift. De interesse voor ons onderzoek en de bereidwilligheid om mee te doen vind ik bewonderenswaardig, deze contacten waren een van de lichtpuntjes van mijn dag als arts-onderzoeker.

Daarnaast een woord van dank aan de Maag-, Darm- en Leverartsen en IBD verpleegkundigen die aan de interviews deelnamen beschreven in hoofdstuk 2.

Dr. P.W.J. Maljaars, beste Jeroen, toen ik in 2016 een wetenschapsstage bij de MDL zocht werd mij een plek bij jou aangeraden, het zou een interessant onderwerp zijn en jij een 'heel vriendelijke en bekwame arts'. Niets bleek minder waar. Dankjewel voor het vertrouwen dat je vanaf het begin in mij had, ik kijk er naar uit om niet alleen op het gebied van onderzoek maar ook straks in de kliniek verder met je samen te werken.

Prof. Dr. S.P Mooijaart, beste Simon, ik zal niet snel vergeten dat wij elkaar een keer aan het begin van de werkdag tegenkwamen en jij ons gesprek afsloot met de woorden 'veel plezier vandaag!'. Jouw enthousiasme voor het onderzoek naar oudere patiënten ervaar ik als erg aanstekelijk, en na een afspraak met jou had ik vaak genoeg stof tot nadenken voor meerdere weken. Dank voor je onmisbare input!

Prof. Dr. J.E. van Hooft, beste Jeanin, dank voor het op een vakkundige en benaderbare manier begeleiden van mijn proefschrift naar de eindstreep.

Dr. A.E. van der Meulen, beste Andrea, dank voor het kritisch meelezen en het vanaf de zijlijn inspringen wanneer nodig.

Tijdens mijn onderzoek heb ik veel studenten begeleid. Dank allemaal voor jullie bijdrage! Speciaal woord van dank aan jou, Sanne, voor het opzetten van de ouderenstudie en mij inwerken aan het begin van mijn wetenschapsstage. Daarnaast heb ik met veel anderen samengewerkt. Specifiek wil ik Floor noemen, die mij de ins en outs van het uitvoeren van een systematic review heeft geleerd. En ook Arwen, dankzij jou leerde ik kwalitatief onderzoek uitvoeren, een hele andere tak van sport en verfrissend om met je samen te werken!

Lieve (oud) PhD collega's van het LUMC, dank voor alle gezellige momenten, de vele koffietjes en broodjes kroket. Ons hok zonder ramen zal ik niet snel vergeten, evenals belangrijke levenslessen zoals de waarde van koptelefoons met noise cancelling functie en het motto *eat that frog first thing in the morning*. Eem en Lau, dank voor alle gezellige etentjes, en het uitwisselen van recepten tijdens de COVID-19-tijd. Anne, ik ben blij dat jij als mijn opvolgster verder gaat, succes en vooral veel plezier!

Het laatste deel van dit proefschrift heb ik tijdens mijn ANIOS baan bij de MDL en vooropleiding bij de Interne Geneeskunde afgemaakt, dat was niet altijd makkelijk. Ik wil dan ook graag alle (oud) collega's van het HagaZiekenhuis bedanken voor hun steun tijdens deze tijd. Collega's van de MDL in het HagaZiekenhuis, jullie wil ik daarnaast ook bedanken voor het begeleiden van een dokter zonder klinische ervaring tijdens haar eerste stappen in de kliniek, en voor de groei die ik dankzij jullie heb doorgemaakt!

Lieve vrienden en vriendinnen, dank voor de nodige afleiding de afgelopen jaren. Chava, Isabelle, Marieke en Ozair, dank voor de extra steun (lees: duw in de rug) tijdens de COVID-19-tijd.

Eem en Chaaf, wat ben ik blij dat jullie vandaag naast mij staan! Eem, dank voor je eeuwige positiviteit, ik bewonder hoe jij elke terugslag of obstakel tijdens onze PhD in iets positiefs wist om te zetten. *Ga door, ook al zit het even tegen, ga door, ook al stroomt het van de regen.* Chaaf, dat jij mijn paranimf zou zijn was al duidelijk voordat ik überhaupt aan dit PhD traject begon. Bedankt dat ik altijd bij jou terecht kan met alles.

Lieve (schoon) familie, dank voor jullie oprechte interesse in mijn onderzoek en onvoorwaardelijke steun. Lieve Ida, over een paar jaar sta jij hier ook, ik ben nu al trots op je! Lieve papa, dankjewel voor het kritisch meedenken met mijn onderzoek en adviezen waar nodig vanuit een niet-medische invalshoek, en om jouw woordgrapje maar vast voor te zijn: ik ben er trots op om jouw dochter dokter doctor te zijn. Lieve mama, jouw doorzettingsvermogen en kracht zijn voor mij een voorbeeld, zonder jouw vele peptalks was deze PhD een stuk moeilijker geweest.

Lieve Martijn, in het laatste jaar van mijn arts-onderzoekers aanstelling was jij niet alleen mijn vriend en huisgenoot, maar ook mijn full-time collega tijdens de COVID-19-pandemie. Ik vind het knap dat je het al die maanden met mij in één ruimte hebt uitgehouden. Dankjewel voor je bereidheid om mee te denken waar nodig, en je relativerende en nuchtere blik. Ik kijk uit naar alle andere avonturen die wij gaan beleven, samen staan we sterk!

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