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

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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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