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

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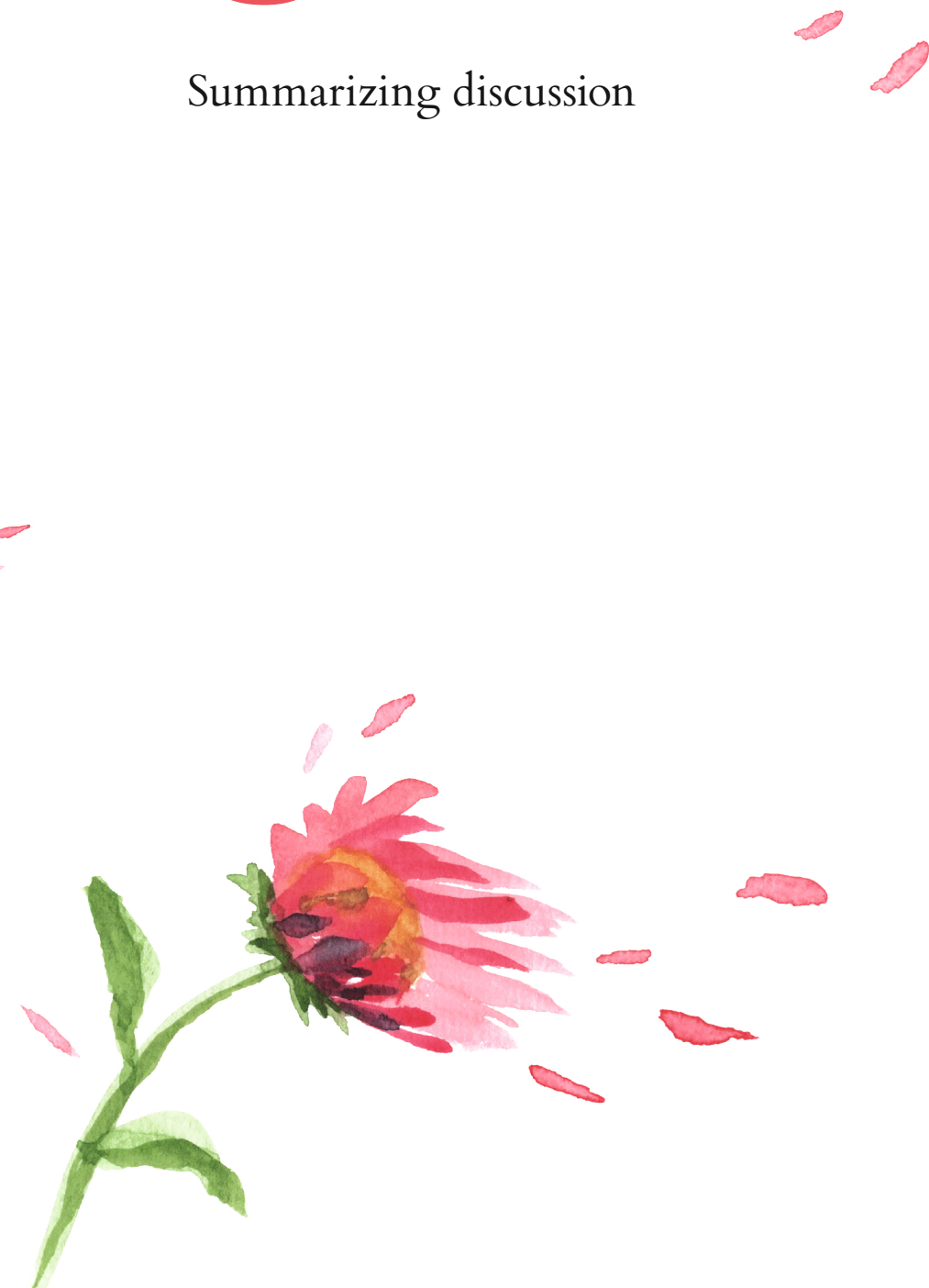
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Summarizing discussion



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 Comorbidity 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 $CCI \geq 3$ 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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