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Alimentary Tract

Frailty risk and treatment strategy in elderly-onset inflammatory bowel disease. A Norwegian nationwide population-based registry study

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ABSTRACT

Background/Aims: To determine real-world medical and surgical treatment patterns in elderly-onset inflammatory bowel disease in a nationwide cohort, and to investigate associations between frailty and treatment choices.

Methods: Norwegian health registries were used to identify adult-onset (born 1950–1989) and elderly-onset (born 1910–1949) patients with Crohn's disease (CD) and ulcerative colitis (UC) diagnosed 2010–2017 (n = 13,006). Patients were classified as no, low and intermediate/high frailty risk after the Hospital Frailty Risk Score. Outcomes included use of medical and surgical treatment.

Results: Within five years, elderly-onset patients received less biologics (13% [CD], 7% [UC]) and immunomodulators (24% [CD], 11% [UC]), and major surgery was more frequent (22% [CD], 9% [UC]) than in adult-onset. Respective log rank tests were significant ($p < 0.01$). Compared to no frailty risk groups, elderly-onset UC with intermediate/high frailty risk had lower probability of starting biologics (4% versus 9%), immunomodulators (7% versus 13%) and 5-aminosalisylic acids (66% versus 84%), and elderly-onset CD with intermediate/high frailty risk had higher probability of starting prednisolone (67% versus 49%). Respective log rank tests were significant ($p < 0.05$).

Conclusions: Elderly-onset patients received less biologics and immunomodulators and a larger proportion underwent major surgery. Frailty risk in elderly-onset patients was associated with increased use of prednisolone, and less use of 5-aminosalisylic acids, immunomodulators and biologics.

1. Introduction

Existing evidence suggests that fewer patients with elderly-onset inflammatory bowel disease (IBD) receive biologics [1–5] and immunomodulators (IMs) compared to younger patients [1–7]. Reports on surgery rates are much more diverse, ranging from lower or equal surgery rates [1,2,6,7] to recent studies reporting increased rates in elderly [3,5,8]. Although treatment differences in elderly-onset IBD are documented in previous studies, population-based studies with nationwide coverage are limited [3,5], most studies have been performed in years before biologics became a common treatment option, and very few studies have pursued why these differences exist. Treatment of older patients with IBD might be complicated by comorbidities, polypharmacy and frailty. The latter is an increasingly important assessment criterion for personalized treatment in geriatric medicine [9].

Frailty describes a state where the individual has an increased vulnerability and a decline in reserve capacity. Compared to a fit individual, a frail patient does not have the same resistance. Minor stressors, e.g. a urinary tract infection or a new medication, can re-

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sult in large deteriorations from normal functioning level [10]. Although the risk of frailty seems to increase with comorbidity and age, these factors can exist independently of each other, meaning that a patient with multiple comorbidities or of high age can still be defined as a fit individual [10]. Hence, frailty scores contribute with valuable information on patients' health status beyond comorbidity, also in IBD patients [11]. Frailty in elderly IBD patients is associated with increased complication rates and poorer outcomes [11–16].

Frailty has previously been associated with presence of inflammatory markers in older adults [17]. Recent studies also suggest a connection between disease activity and frailty in IBD patients [18]. Further, frailty scores have been reported to decrease after response to tumour necrosis factor inhibitors (TNFi) [19], and initiation of biologic treatment may be a predictor for improved frailty status during follow-up [20]. If frailty is connected to disease activity, and effective treatment can improve frailty status, it is important to establish whether frailty status at the time of diagnosis is associated with choice of treatment in IBD.

We aimed to i) determine real-world medical and surgical treatment patterns in elderly-onset IBD in comparison to adult-onset IBD in a Norwegian nationwide cohort, and ii) to explore associations between frailty and treatment choices.

2. Materials and methods

2.1. Objectives

We conducted a nationwide observational cohort study by using data from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). To determine differences in treatment patterns, patients were grouped after age and frailty risk.

2.2. Data and source population

The source population included all individuals registered with ≥1 IBD diagnosis codes K50 (Crohn's disease [CD]) or K51 (ulcerative colitis [UC]) according to the International Classification of Diseases (ICD-10) between 2008 and 2017 in NPR. NPR is an administrative registry with nationwide coverage and includes diagnosis and procedure codes on in- and outpatient contacts for publicly funded specialist healthcare, which accounts for 85% of healthcare funding in Norway [21]. Unique personal identification numbers make it possible to follow individuals over time. Data were linked to NorPD, which comprises electronic registrations of dispensed drug prescriptions by Norwegian pharmacies from 2004 and forward. IBD prescriptions were defined as pharmacy claims with IBD diagnosis codes (ICD-10 codes K50 or K51, or code D94 of the International Classification of Primary Care), or 5-aminosalicylic acids (5-ASA) or budesonide prescriptions.

2.3. Case definition and study population

According to a previously published algorithm on similar data material [22], patients were included as incident IBD cases if they had i) at least two IBD diagnosis codes (K50 or K51) in NPR, or ii) at least one IBD diagnosis code in NPR and at least two IBD prescriptions in NorPD between 2010 and 2017. Patients with either IBD diagnosis code registrations in NPR prior to 2010 or IBD prescriptions 60 days prior to the first IBD diagnosis code in NPR were excluded. Date of diagnosis was set to the first recorded IBD diagnosis code or IBD prescription. Diagnosis was defined as the last recorded UC or CD diagnosis code for patients with both codes registered in NPR.

2.4. Age of onset

Due to privacy requirements of anonymized data from the registry owner (NPR), age was only available in ten-year birth cohorts and not year of birth. Patients born between 1950 and 1989 were classified as adult-onset (21–67 years old at diagnosis). Patients born between 1910 and 1949 were classified as elderly-onset (≥61 years old at diagnosis). This led to a small overlap between the age groups. E.g., for patients belonging to the 1950–1959 birth cohort diagnosed in 2012, age at diagnosis varies between 53 and 62 years depending on year of birth.

2.5. Medication

All drugs dispensed from Norwegian pharmacies are registered in NorPD with codes by the Anatomical Therapeutic Chemical Classification System (ATC). Biologics administered at hospitals are registered in NPR with their respective ATC code. Use of biologics, immunomodulators (thiopurines and methotrexate), prednisolone, budesonide and 5-ASA were obtained (Supplementary Table S1).

2.6. Surgery

The NPR comprises all surgical procedure codes for each individual hospital event. Procedures were classified as major surgery according to the NOMESCO Classification of Surgical Procedures (NCSP) (Supplementary Table S2). All surgical cases after date of diagnosis were included in time-to-event curves independently of prior surgical events.

2.7. Hospital frailty risk score

The Hospital Frailty Risk Score (HFRS) is a validated method for measuring frailty in elderly by using administrative data from healthcare registries. HFRS is based on 109 selected ICD-10 diagnosis codes with known associations to frailty [23]. Each code is allocated a specific score based on estimates of how much the condition or comorbidity increases frailty risk [23]. Corresponding to two recent papers on frailty in IBD [11,24], we categorized patients with HFRS =0 (no ICD-10 codes associated with frailty occurring in the patient records) as fit/no risk of frailty. Patients with HFRS >0 and <5 were categorized as low risk and patients with HFRS ≥5 were categorized as intermediate/high risk. Patients were scored according to ICD-10 codes in NPR two years prior to their IBD diagnosis.

2.8. Statistical analysis

Data were analysed using Python 3.8 and Stata, version 16.1. Cumulative probability of exposure to medical therapy or undergoing surgical procedures were presented by Kaplan-Meier curves. Patients were followed from date of diagnosis until outcome of interest (first registration with relevant medical or surgical therapy), censored at study end (31st Dec 2017) or time of death, whichever occurred first. The log rank test was used to test for statistical significance. In sensitivity analyses, major surgical events registered with cancer diagnosis codes (ICD-10 codes C00-C97) as the primary ICD-10 code were excluded, which did not alter the results significantly (data not shown). We constructed Cox proportional hazard models to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for initiating biologics or undergoing surgery. Models were adjusted for sex, age, frailty risk, previous treatment expo-

Table 1
Patient characteristics.

		Elderly-onset		Adult-onset	
Crohn's disease	Patients, *n* (%)	780	(18)	3514	(82)
	Male, *n* (%)	345	(44)	1625	(46)
	Median age at diagnosis (IQR)[a]	70	(67–76)	41	(31–50)
Ulcerative colitis	Patients, *n* (%)	1788	(21)	6924	(79)
	Male, *n* (%)	926	(52)	3760	(54)
	Median age at diagnosis (IQR)[a]	70	(67–77)	41	(31–51)

[a] Median age calculated from ten-year birth cohorts. Interquartile range (IQR) in parenthesis.

Table 2
Hospital Frailty Risk Score (HFRS) in the elderly-onset population.

Hospital Frailty Risk Score (HFRS)	Crohn's disease	Ulcerative colitis
No risk (HFRS = 0)	332 (43)	826 (46)
Low risk (HFRS > 0 and < 5)	345 (44)	731 (41)
Intermediate/high risk (HFRS ≥ 5)	103 (13)	231 (13)

sure (biologics/major surgery), prednisolone dependency and hospitalization. Major surgery, prednisolone dependency and hospitalization were time-dependent covariates. Prednisolone dependency was defined as a defined daily dose ≥10 mg consecutively for more than three months or restarting prednisolone within three months of ending the last prednisolone prescription. A p-value ≤ 0.05 was defined as statistically significant.

2.9. Ethical considerations

The study was approved by the NPR, the NorPD, the Norwegian Data Protection Authority and the Regional Committees for Medical and Health Research Ethics (application number 2016/113-1).

3. Results

3.1. Patient characteristics

The study population included 4294 (33%) CD patients and 8712 (67%) UC patients of whom 780 (18%) and 1788 (21%) were elderly-onset (Table 1). More than half of elderly-onset CD (57%) and UC (54%) patients had an increased frailty risk (Table 2).

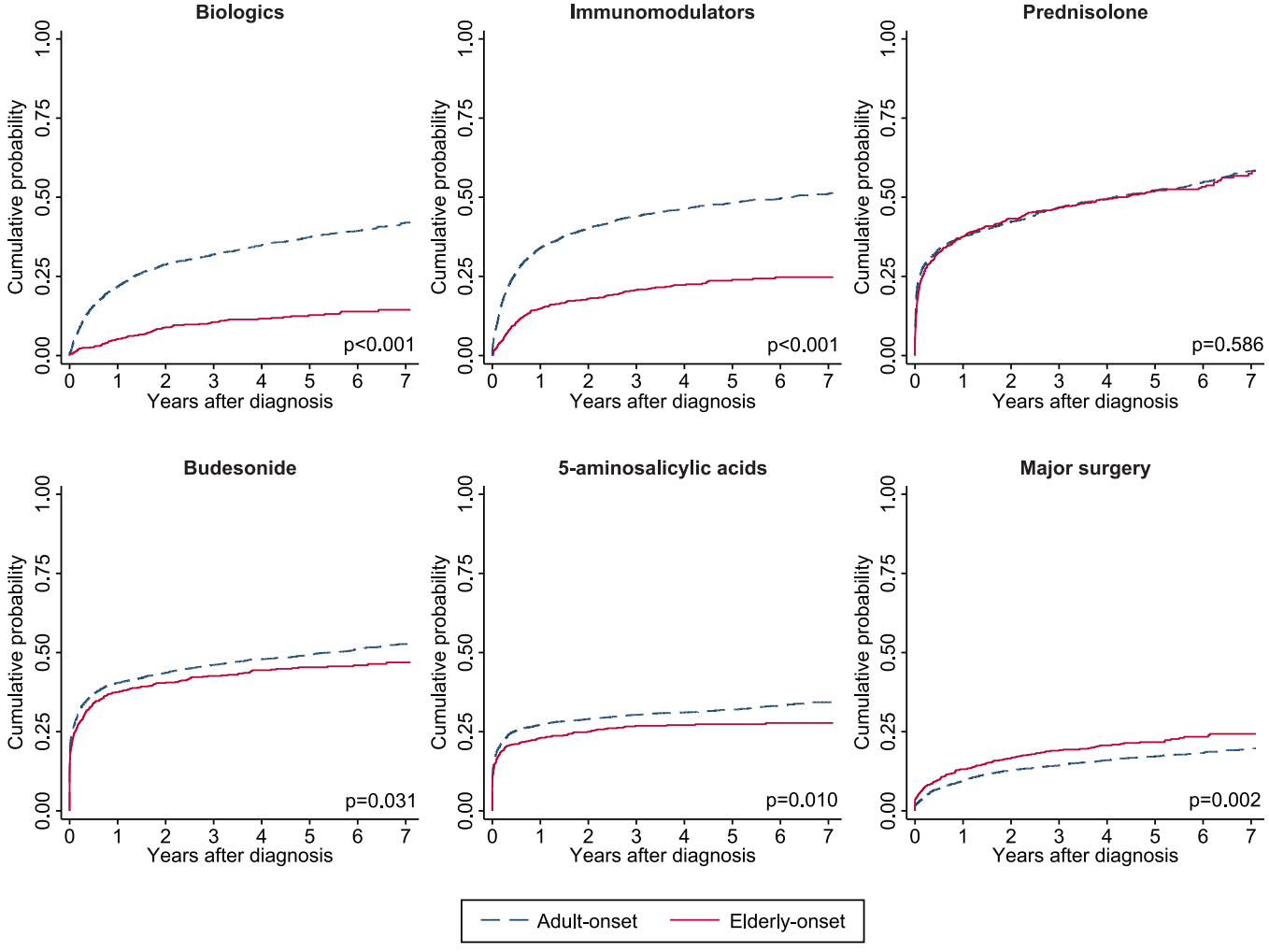

Fig. 1. Kaplan-Meier plot estimating time from diagnosis to treatment for Crohn's disease.

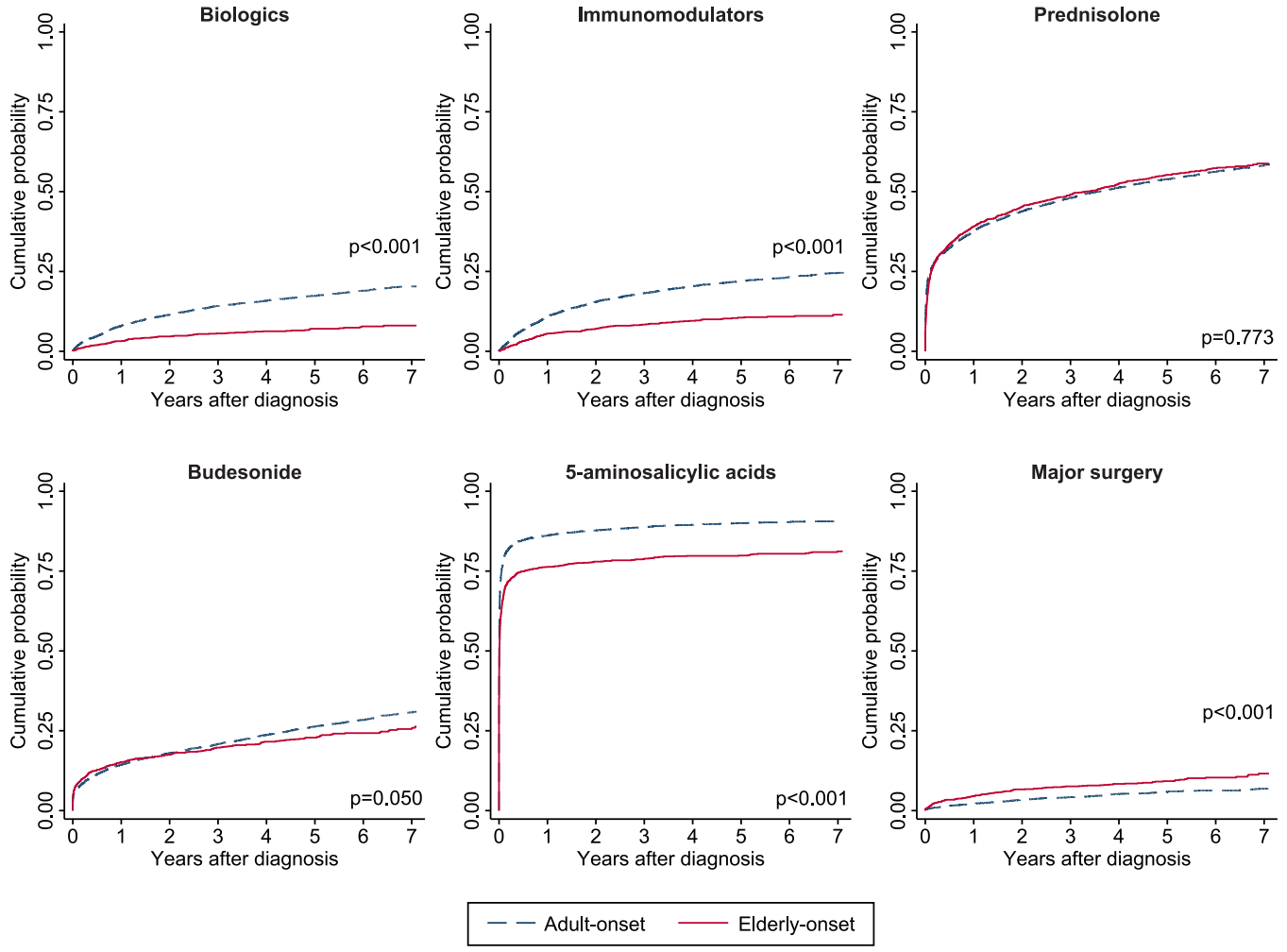

Fig. 2. Kaplan-Meier plot estimating time from diagnosis to treatment for ulcerative colitis.

3.2. Treatment exposure in elderly-onset and adult-onset IBD

Time from diagnosis to treatment is shown in Figs. 1(CD) and 2(UC).

Five years after diagnosis, 13% (CD) and 7% (UC) elderly-onset had received biologics compared to 37% (CD) and 17% (UC) in the adult-onset group, and 24% (CD) and 11% (UC) of elderly-onset patients and 48% (CD) and 22% (UC) of adult-onset patients had received IMs. All respective log rank tests were significant ($p < 0.001$). A subgroup analysis of the elderly-onset group only showed no trend towards shorter time from diagnosis to first biologic for elderly-onset patients diagnosed in 2010–11, 2012–13, 2014–15 and 2016–17 (Supplementary Figure S1). Among the biologic recipients, only a small fraction was registered with other biologics than TNFis as their first biologic treatment in both elderly-onset (2.4% [CD] and 0.9% [UC]) and adult-onset (0.9% and 1.1%, respectively) patients.

The use of prednisolone did not differ between the elderly-onset and adult-onset groups ($p = 0.586$ [CD] and $p = 0.773$ [UC]). The use of budesonide was lower in the elderly-onset CD group (cumulative probability after five years 45%) compared to the adult-onset group (49%). The log rank test was significant ($p = 0.031$). After five years, 27% (CD) and 80% (UC) of elderly-onset patients had received 5-ASA compared to 32% (CD) and 90% (UC) of adult-onset patients. The log rank tests were significant ($p = 0.010$ and $p < 0.001$, respectively).

Elderly-onset patients had higher cumulative probability of undergoing major surgery within five years (22% [CD] and 9% [UC]) compared to adult-onset patients (17% and 6%, respectively). Both log rank tests were significant ($p = 0.002$ [CD] and $p < 0.001$ [UC]).

3.3. Treatment exposure in elderly-onset patients grouped by frailty risk

For elderly-onset UC patients, the intermediate/high frailty risk group had a lower cumulative probability of starting biologics (4%) and IMs (7%) within five years after diagnosis compared to the no frailty risk group (9% and 13%, respectively). The log rank tests were significant ($p = 0.014$ and $p = 0.014$, respectively). (Fig. 3). In elderly-onset CD, the cumulative probability of receiving IMs within five years was higher in the no risk group (28%) than in the intermediate/high risk (20%) and low risk (21%) groups, but the log rank tests remained non-significant ($p = 0.339$ and $p = 0.094$, respectively, Fig. 3).

For elderly-onset CD patients, the cumulative probability of starting prednisolone within five years was higher in the intermediate/high risk group (67%) than in the no risk (49%) and low risk (51%) groups (Fig. 4). The log rank tests were significant ($p < 0.001$ and $p = 0.002$, respectively). For elderly-onset UC patients, the use of 5-ASA was lower in the intermediate/high risk group (66%) compared to the no risk (84%) and low risk (79%) groups (Fig. 4). The log rank tests were significant ($p < 0.001$).

For elderly-onset CD patients, the use of surgery between the three frailty risk groups was comparable (Fig. 3). For elderly-onset UC, the cumulative probability of undergoing major surgery within

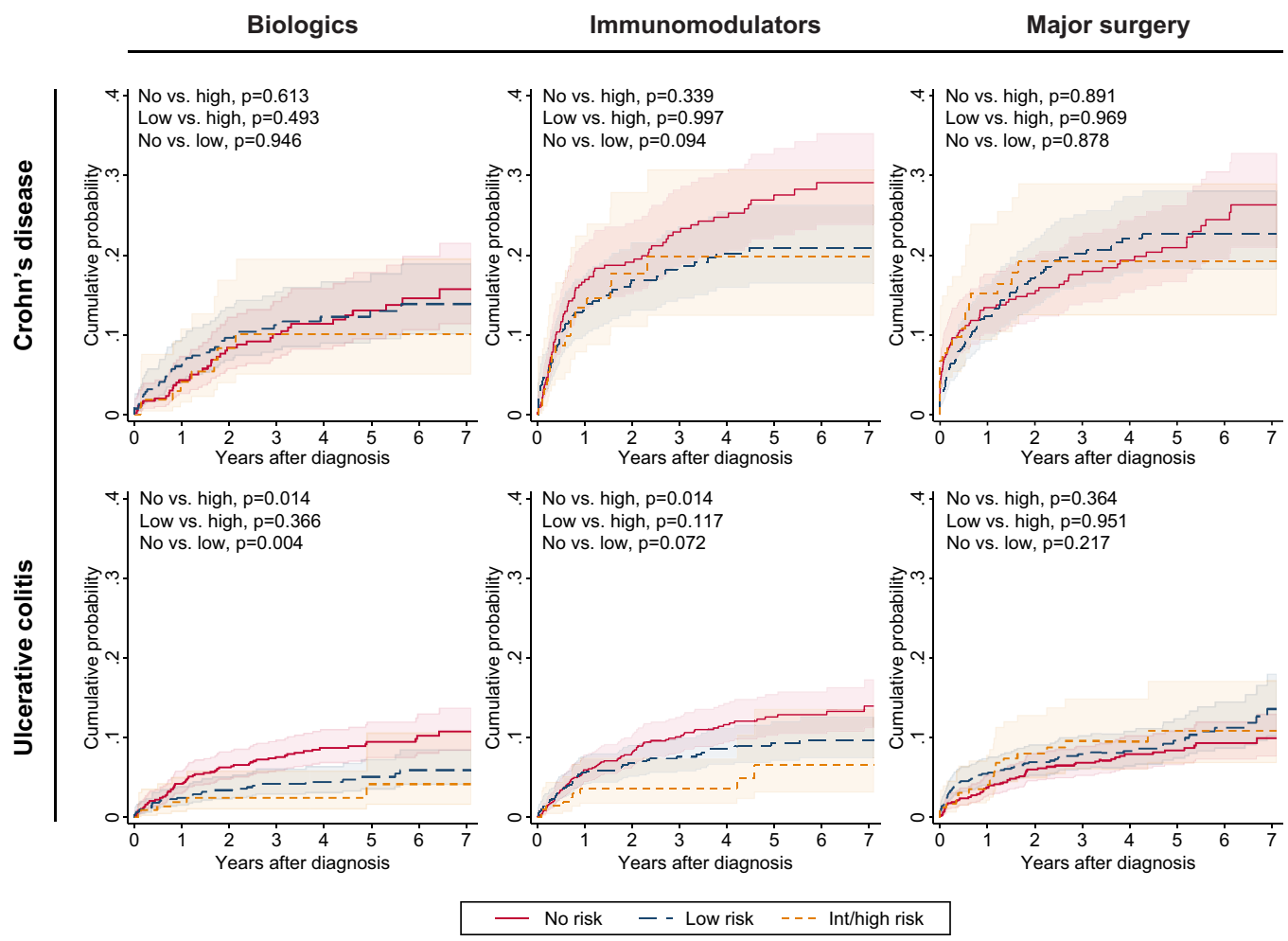

Fig. 3. Kaplan-Meier plot estimating time from diagnosis to treatment. Patients are grouped by diagnosis (Crohn's disease [CD] and ulcerative colitis [UC]) and frailty risk. Frailty risk was assessed by Hospital Frailty Risk Score (HFRS) with following cut-offs; HFRS =0 (no risk), HFRS >0 and <5 (low risk) and HFRS ≥5 (intermediate/high risk).

five years increased with higher frailty risk, but the log rank test was non-significant (Fig. 3).

Five-year cumulative probabilities of all treatments are listed in Supplementary Table S3.

3.4. Hazard ratios for biologic treatment and major surgery

In multivariable Cox proportional hazards models, patients with intermediate/high frailty risk (CD: HR 0.61, 95% CI 0.45–0.84, $p < 0.005$. UC: HR 0.63, 95% CI 0.43–0.93, $p = 0.02$) had lower probability of starting biologics when compared to patients with no frailty risk (Supplementary Figure S2). Increased frailty risk was not significantly associated with probability of undergoing major surgery for either CD or UC (Supplementary Figure S3).

4. Discussion

In this nationwide, population-based study we report differences in medical treatment and major surgery between elderly-onset and adult-onset IBD. Frailty risk in the elderly-onset IBD population was associated with increased use of prednisolone, and lower use of 5-ASA, IMs, and biologics.

4.1. Treatment patterns in elderly-onset and adult-onset IBD

In line with studies from other countries, we found less use of biologics and IMs among elderly-onset patients compared to the adult-onset population [3,4]. The proportion of elderly patients exposed to IMs in the present study was similar to findings in a Swedish nationwide study by Everhov et al. [3]. However, the use of biologics in elderly-onset patients (13% [CD] and 7% [UC]) was higher in the present study than reports from Sweden (6% and 2%, respectively) [3] and Denmark (5.7% of all elderly-onset IBD cases) [5]. A higher probability of starting biologics in the present study could be partly explained by incomplete recordings of biologic infusion therapy in Swedish registries [25] and that the Danish study did not separate on CD and UC diagnoses. The use of biologics in IBD has increased consistently in Scandinavia from 2010 to 2017 [26], and, thus, a lower proportion of biologics would be expected in both the Swedish (patients diagnosed 2006–2013) and Danish (2001–2020) cohorts compared to the present cohort (2010–2017). However, the present study revealed that the cumulative probability of starting biologics in the elderly-onset population was rather constant from 2010 to 2017, implying that the previously shown increased use of biologics in Norway [27] is mainly attributable to treatment of younger patients, and that the treatment gap between elderly and younger patients is expanding. In the present study, the elderly-onset population had a higher probability of undergoing major surgery within five years after diagnosis, which corre-

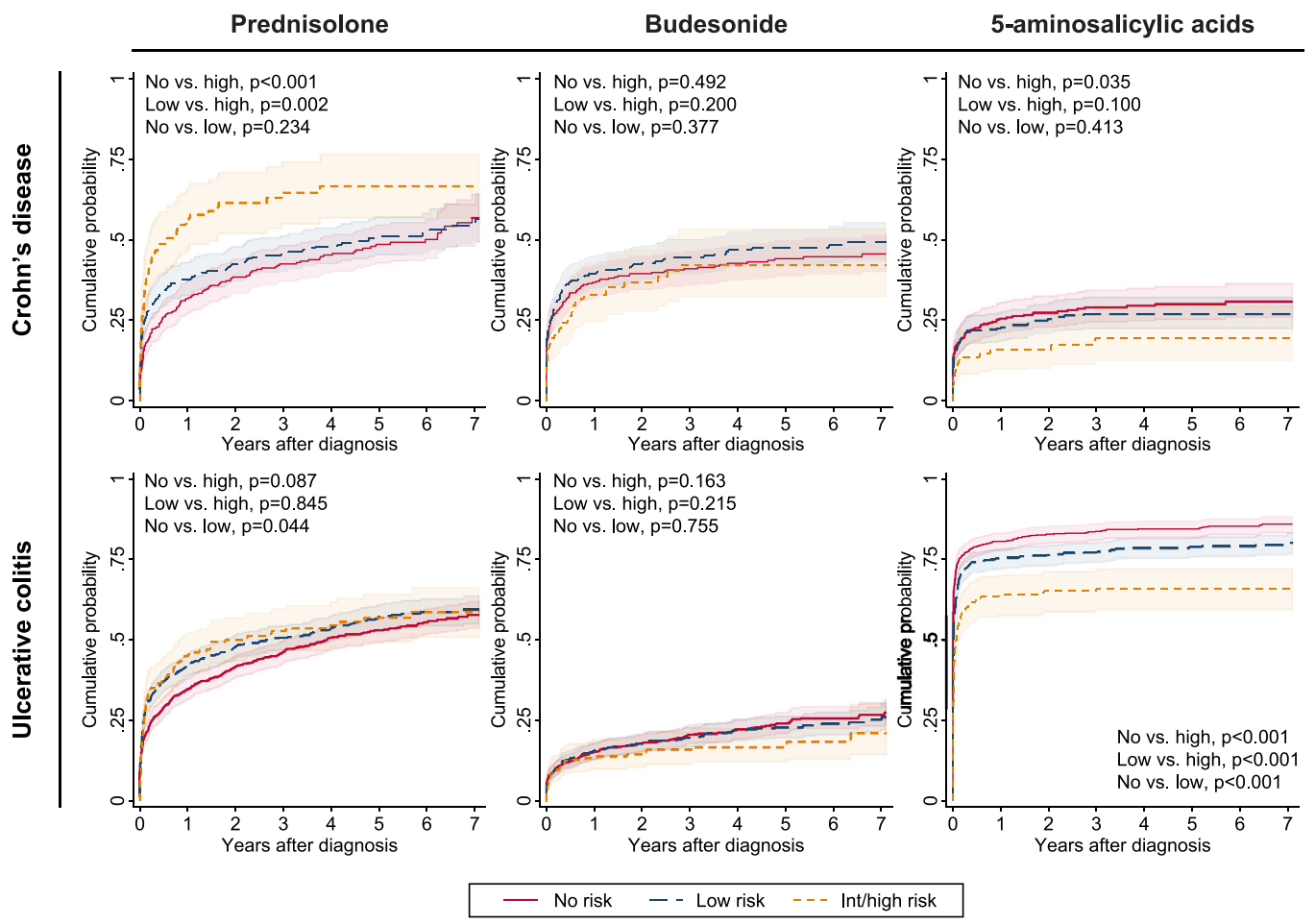

Fig. 4. Kaplan-Meier plot estimating time from diagnosis to treatment. Patients are grouped by diagnosis (Crohn's disease [CD] and ulcerative colitis [UC]) and frailty risk. Frailty risk was assessed by Hospital Frailty Risk Score (HFRS) with following cut-offs; HFRS =0 (no risk), HFRS >0 and <5 (low risk) and HFRS ≥5 (intermediate/high risk).

spond well with recent findings from Sweden [3]. More frequent surgery and lower use of biologics and IMs in elderly-onset IBD can suggest that clinical decision-making favours surgery for this patient group.

Since budesonide is considered non-systemic [28] and 5-ASA is considered safe for elderly patients [29], it was surprising that the cumulative probabilities of starting budesonide (CD) or 5-ASA (CD and UC) in elderly-onset patients were significantly lower than that in adult-onset patients. We would expect clinicians to opt for drugs with lower risk of side effects in elderly patients susceptible to experiencing complications. One possible explanation for the higher cumulative probability in adult patients is that this group might have a more active disease over time. Although current guidelines do not support the use of 5-ASA for CD [30], extensive use of 5-ASA in elderly has been reported [3,31]. Our results revealed that almost one third of elderly-onset CD patients received 5-ASA during five years of follow-up. This could be explained by the fact that elderly-onset CD patients often present with colonic disease [32], and that certain CD subgroups [33], such as Crohn colitis, could benefit from 5-ASA.

4.2. Assessment of frailty risk and its impact on treatment choices in elderly-onset IBD

The prevalence of frailty in IBD patients varies from 6% to 53.9% depending on study population and choice of frailty scoring system [34]. Many well-known and validated frailty assessment methods exist [23,35,36], but none have been fully validated in IBD populations. HFRS was developed as a tool to screen for frailty from health claims data and has been validated in a large cohort (hospitalized individuals >75 years of age) to identify patients with a greater risk of adverse outcomes (mortality, readmission rates and length of stay) [23]. HFRS has been used in several papers as a measurement for frailty risk in IBD patients [11,13-15,24], although the score remains to be validated for IBD patients, patients under 75 years of age and patients in non-hospitalized settings. However, the rationale for use of HFRS in registry-based IBD research is strengthened by similar findings in studies with comparable populations and methodology. For example, the prevalence and distribution of frailty risk in our study was similar to what was reported in a recent Swedish register study [24].

In two recent studies, Salvatori et al. showed that disease activity was an independent risk factor for being categorized as frail, and that clinically active disease was a predictive factor for remaining frail during follow-up [18,20]. In the present study, the use of prednisolone in elderly-onset CD was higher in the intermediate/high frailty risk group than in the no risk group. Use of prednisolone indicates presence of clinically active disease and thus supports an association between frailty and bowel inflammation as suggested by Salvatori et al. In elderly-onset UC patients, comparable use of prednisolone and major surgery in the three frailty risk groups suggests similar disease activity in all groups. Concurrently, low use of 5-ASA, biologics and IMs in the intermediate/high risk group implies inadequate medical treatment practice for this patient group.

For both CD and UC, results from the descriptive survival analyses were supported by findings in explorative, multivariable analyses. The latter showed that patients with higher frailty scores had

a lower probability of being prescribed biologics, also when adjusting for age. Since it has been shown that starting biologics in frail patients was associated with improved frailty status during follow-up [20] and that patients responding to TNFi therapy improved in pre-treatment frailty score [19], our finding in the present study of low use of biologics in frail patients may reflect a suboptimal treatment strategy for these patients. Future studies with access to clinical variables and disease activity assessment should pursue how frailty affects treatment choices and outcomes. Also, future treatment guidelines for older IBD patients should include suggestions for accessible and feasible frailty scores to be implemented in clinical practice.

4.3. Strengths and limitations

The study cohort was population-based, and data were collected from two high-quality nationwide registries, which limits information- and selection bias. Although IBD diagnosis codes remain to be validated in NPR and NorPD, other Scandinavian national registries have shown high validity [37–39], and it is likely that Norway follows the same standard as neighbouring countries with similar health registries.

Due to privacy requirements of anonymized data, age was only available in ten-year birth cohorts and thus a small number of true elderly-onset patients born 1950–57 could have been misclassified as adult-onset depending on their date of diagnosis. The adult-onset group was the largest group, and misclassification of some elderly-onset cases into this group should not have significant effect on the results.

Information on disease characteristics is not available in our health registries. This limited the possibilities of adjusting for disease activity and disease severity. Also, the reason and setting (e.g., emergency or not) for surgery were not obtainable.

Frailty risk was assessed at diagnosis, and the patient's status could change over time and thus decreased the effect in our estimates. We acknowledge that HFRS >0 is a strict definition of elevated frailty risk and could lead to an underestimation of the importance of frailty. Nevertheless, our study revealed significant findings with our applied cut-off. The limitations we encountered in this study underline the demand for frailty risk scores validated in IBD populations.

In conclusion, age of onset and frailty risk seem to impact both medical treatment and major surgery. Higher frailty risk was associated with a significantly lower probability of starting biologics. To personalize the treatment for older patients with IBD, we need more knowledge on how frailty impacts treatment effect and risk of adverse outcomes.

Authors' contributions

KA was involved in study design, statistical analysis, data interpretation, drafting and revising the manuscript. SSL and HOM were involved in study design, data acquisition, statistical analysis, data interpretation and revising the manuscript. AWM, BM and MLH were involved in study design, data interpretation, drafting and revising the manuscript. All authors read and approved the final manuscript.

Conflict of interest

K.A. reports consultant fees from Takeda outside the submitted work. S.S.L. reports grants and consultant fees from Takeda. A.W.M. reports grants from Takeda. B.M. reports consultant fees from Takeda, Janssen, AbbVie, Galapagos, Pfizer, Sandoz, Pharmacosmos as, Ferring as, Tillotts Pharma; speaker fees from Takeda, Janssen, Pfizer, AbbVie, Sandoz, Orion Pharma, Ferring as, Tillotts Pharma. H.O.M. reports grants and consultant fees from Takeda. M.L.H. reports speaker fees from Galapagos, Ferring, BMS, Janssen, AbbVie, Meda, Tillotts and Takeda; advisory boards for Takeda, Galapagos, BMS and AbbVie; investigator-initiated research grants from: Takeda, Pfizer, Tillotts and Ferring.

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Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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Conference presentation

Part of this work was presented as poster presentation at UEG Week Virtual 2020 and as oral presentation at Norwegian Gastroenterology Society Annual Meeting 2021.

Data availability statement

The data underlying this article were provided by the Norwegian National patient register (NPR) and the Norwegian Prescription Database (Nor-PD) by permission. Data cannot be shared publicly due to the privacy of the patients listed in the registries. Data are available from the NPR (https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr) and Nor-PD (http://www.reseptregisteret.no/) through an application process.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.02.002.

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