Frailty in inflammatory bowel diseases: an emerging concept

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***Abstract*:** Inflammatory bowel diseases (IBD), consisting of Crohn's disease and ulcerative colitis, are chronic remitting, relapsing inflammatory conditions of the gastrointestinal tract. While traditionally a disease of younger ages, the number of older adults with IBD is rising rapidly. Patients with IBD often experience geriatric syndromes at earlier ages. Older adults with IBD have poorer disease and treatment-related outcomes compared with younger adults with IBD. Applying the principles of geriatrics to understanding a chronic disease in older adults may improve health span. Better tools are needed to stratify IBD patients who are at high risk for adverse events. Frailty is a geriatric construct that may approximate biologic age. Frailty is a complex, multi-dimensional syndrome that leads to increased vulnerability to stress and decline of reserve across multiple physiologic systems. In this review, we present the leading conceptual models of frailty and discuss the applications of frailty in immune-mediated diseases. We also review chronic conditions where frailty has been applied successfully as a tool for risk stratification. Finally, we discuss in the detail the growing body of literature highlighting the relationship between frailty and IBD, the epidemiology of frailty in IBD, and ramifications of frailty in IBD.

Keywords: aging, Crohn's disease, frailty, geriatrics, inflammation, inflammatory bowel diseases, ulcerative colitis

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Epidemiology of geriatric inflammatory bowel diseases

Inflammatory bowel diseases (IBD), consisting of Crohn's disease and ulcerative colitis (UC), are chronic remitting, relapsing inflammatory conditions of the gastrointestinal tract. The incidence and prevalence of IBD are rising globally, with many traditionally low incidence regions, such as the global south, reporting increasing numbers of people diagnosed with IBD.[1] There are approximately 7 million people worldwide living with IBD.[1] IBD is traditionally diagnosed in younger adults, with the peak incidence occurring in the third and fourth decade of life. However, studies report a bimodal peak of incidence, with the second peak occurring in the seventh decade of life.[2] Recent data suggest that at least 20% of incident IBD diagnoses occur in adults ⩾60 years.[3] In fact, one study demonstrated that the median age at diagnosis is significantly increasing over time from 33 years before 1990 to 47 years after 2010.[4]

As a chronic condition, with improved disease-related knowledge and more effective treatments, the IBD-specific death rate has decreased 16% between 1990 and 2017. In parallel to the rapidly aging population and increasing lifespan, the number of older adults with IBD is rising.[5] In 2015, the United States (US) Centers for Disease Control (CDC) estimated that 26% of Americans with IBD are 65 years and older.[6] A robust modeling study using 2008 data projects that the number of adults ⩾60 years with IBD will increase >200% by the year 2030.[7] Although IBD is less fatal, the years of life lived with disability (YLD) has doubled over time.[1] As expected, older adults

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bear the brunt of this disability, with the peak of YLD being in the seventh decade of life.[1] With the increasing recognition that health-span is as important as life-span, applying principles from geriatrics to the study and care of older patients with IBD may alleviate some burden of disability.[8]

IBD and aging

Patients with IBD often experience geriatric syndromes at earlier ages. It is well described that adults with IBD are at increased risk for osteoporosis, hip fractures, polypharmacy, serious infections and malignancies, independent of treatment.[9–14] One recent study demonstrated that adults with IBD are also at greater risk for impaired neurocognitive and psychomotor function.[15] Other studies raise the possibility of an association between IBD and increased risk for cognitive decline with states such as Parkinson's disease and Alzheimer's dementia.[16,17]

Older adults with IBD have poorer disease and treatment-related outcomes compared with younger adults with IBD.[18–20] The approved and available treatment options for IBD have proliferated rapidly over the past two decades. Early and effective immunosuppression with biologic agents is the main stay of treatment for moderate-to-severe IBD, both Crohn's disease and UC.[21,22] Despite a growing armamentarium of steroid-sparing immunologic therapies, older adults with IBD are significantly less likely to receive steroid-sparing therapy and more likely to receive corticosteroids.[23,24] Corticosteroid use has significant sequela, conferring a markedly higher risk for venous thromboembolism, fracture, and infections in older adults with IBD.[25]

The infrequent use of effective steroid-sparing therapies in older adults with IBD may be due to a paucity of older adults included in trials of IBD therapies. A review of randomized controlled trials of medications approved for the treatment of IBD revealed that less than 1% of patients were 65 years and older.[26] The lack of high quality data on treatment safety, efficacy, and applicability to older adults may explain why older adults with IBD are often sub-optimally treated without targeted immunosuppression.[24] The reluctance to use effective treatments may result in increased need for surgery, which is associated with high morbidity and mortality.[18] Older adults with UC have a 57% higher rate of colectomy and significantly higher rates of post-operative infections and mortality.[18,19] The use of less effective treatments may also explain the poorer disease-related outcomes experienced by older patients with IBD. Crohn's patients diagnosed $\geqslant$65 years have nearly six times the IBD-specific mortality of younger adults.[19] Older adults with severe acute UC have nearly five times the mortality of younger adults.[20]

One important reason for lower use of effective IBD treatments for older adults may be the clinical practice of using chronologic age to estimate risk, rather than overall health and functional status. The existing literature on treatment efficacy and safety in older IBD patients comprises largely of retrospective studies assessing chronologic age without consideration of function, reserve, and vulnerability.[27–29]

Frailty

While there is no universally accepted definition of frailty, it is most often described as a complex, multi-dimensional syndrome that leads to increased vulnerability to stress and decline of reserve across multiple physiologic systems and thereby increases the risk of adverse health outcomes.[30] Frailty is associated with aging, yet is independent of age.[31] Frailty can be disentangled from other markers of vulnerability in older adults, such as multi-morbidity and disability.[32] Most frail individuals are multi-morbid; however, fewer multi-morbid adults are frail.[33] Frailty predicted mortality independent of multi-morbidity,[34] suggesting that while they have a bi-directional relationship, frailty may be the common pathway toward a significant adverse outcome.

Currently, there are two leading conceptual models of frailty. The phenotype model of frailty, championed by Linda Fried, defined individuals as frail if they had three of the following five interrelated attributes: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength.[35] Using this model, 7% of community swelling adults $\geqslant$65 years were characterized as frail. An alternative model of frailty, pioneered by Kenneth Rockwood, counting up to 92 parameters encompassing symptoms, signs, laboratory values, disease states, and disabilities in order to define frailty as an accumulation of these deficits.[36]

Using this model, approximately 20% of a general population of adults ⩾65 years were identified as frail. Measurements of frailty are varied and can be tailored to a population of interest, as has been done in many disease states.[37–39] To date, there is no standardized definition of frailty in the literature.[40] Regardless of how frailty is measured, it signifies a vulnerability to age-related stressors.[30] It is a dynamic process with transitions between being non-frail, pre-frail, and frail over time, suggesting that is modifiable.[41]

Frailty is associated with an increased risk of mortality in older adults.[42] Applying the Fried frailty phenotype, older, community-dwelling, adults who were frail had a 7-year adjusted hazard ratio (HR) for death of 1.63 compared with those who were not frail.[35] Applying the Rockwood Frailty Index in a community-dwelling population of older adults, the HR for death in those who were frail was 1.57.[36] In a seminal prospective study of trajectories of disability in community-dwelling adults in the last year of life, frailty was identified as the leading cause of death[42] These data lend support to frailty as a construct that accounts for general health reserve better than age and co-morbidities alone.[30,43]

While the biologic basis of frailty is not clearly elucidated, it is well described that frailty is associated with an increase in systemic inflammatory markers.[44–47] One hypothesis on the etiopathogenesis of frailty is that components of the innate immune system, such as chemokine signaling, catecholamine-cortisol system, interferons, and immune-competent cells commune with and influence each other in a network of biochemical reactions. This complex interplay has resulted in challenges to developing a reproducible model to study the interaction between inflammation and frailty.[48]

Frailty is most often associated with aging. There are a number of changes to the immune system that occur with age. With advancing age, as the number of lymphoid-based hematopoietic stem cells (HSCs) decline, myeloid-based HSCs predominate, B and T cells exhibit reduced rates of proliferation and higher levels of apoptosis, a pro-inflammatory cascade is generated.[49] Multiple studies have demonstrated that older adults often have elevated serum concentrations of interleukin (IL)-6, C-reactive protein (CRP), and tumor necrosis factor (TNF)-α.[44,45,50–52] These changes to the immune system can start occurring as early as the sixth decade of life.[49]

The relationship between chronic inflammation and aging-related processes has been encapsulated in the term 'inflammageing.'[53] Inflammageing is the hypothesis that aging is intrinsically an inflammatory process; it is the downstream effect of chronic stressors including mitochondrial dysfunction, epigenetic alternations, cellular senescence, chronic infections, gut microbial changes, and intrinsic immune cell defects to name a few stressors. In turn, inflammageing contributes to multi-morbidity, sarcopenia, and disability, all aspects often referred to as geriatric syndromes.

Study of frailty in chronic immune-mediated conditions

As frailty is linked closely with inflammation, it stands to reason that frailty should be more prevalent in those with chronic immune-mediated diseases. The study of frailty in chronic immune-mediated diseases is sparse. However, there is an emerging body of literature about frailty in rheumatologic conditions.

Of the rheumatologic conditions, frailty has been most studied in rheumatoid arthritis (RA). In a cohort of patients of all ages with RA, 17% met the definition of frail and 32% were pre-frail, which was significantly higher than healthy controls.[54] In another cohort of working age individuals with RA, 15% of patients 18–65 years met criteria for frailty.[55] In patients with rheumatologic conditions, frailty appears to be associated with disease activity. Two separate studies of frailty in RA patients report that a higher disease activity index correlated with an increased prevalence of frailty.[54,56] Using a validated RA-specific cumulative deficit frailty index, frailty was found to be associated with advanced age and high disease activity.[57,58] A study of frailty in patients with systemic sclerosis found that patients with diffuse systemic sclerosis had higher scores (worse) on a frailty index than patients with limited systemic sclerosis. Furthermore, the score on the frailty index did not increase in a linear manner with age.[59] These studies highlight the close relationship between systemic inflammation and frailty, independent of age.

Frailty helps identify those at increased risk of vulnerability in the face of a stressor. Studies of the implications of frailty in patients with chronic inflammatory conditions are also nascent. In RA patients, frailty was associated independently with worsening physical function.[60] Using a systemic lupus erythematosus (SLE)-specific frailty index, one group reported that the prevalence of frailty in this cohort of both older and younger adults was 27%, and conferred a HR of 1.59 for mortality.[38,61] A study of frailty in older patients with ANCA-associated vasculitis also found that frailty conferred an increased risk for longer hospitalizations and mortality, independent of age and co-morbidities.[62] However, many patients in these studies were treated with corticosteroids, which may certainly contribute to frailty. Better defining the relationship between frailty, medications used to treat chronic immune-mediated diseases, and disease activity itself will be important to further the study of frailty.

Taken together, these studies of frailty in patients of all ages with chronic rheumatologic conditions suggest that chronologic age underestimates biological age in patients with chronic systemic inflammatory conditions. Therefore, frailty may be a more accurate construct to prognosticate outcomes in patients with chronic immune-mediated conditions rather than age, demographic, and disease-specific parameters alone.[63]

Frailty as a risk stratification construct

Frailty has perhaps been studied most robustly as a risk stratification measure in the pre-operative setting. Using a five-point score that combines the frailty phenotype and cumulative deficit models, a prospective study of older adults found that frailty independently predicts post-operative complications, length of hospitalization, and discharge to a facility better than other commonly used risk models such as the American Society of Anesthesiologists' score and Lee's revised cardiac risk index.[64] Another study reveals that frailty remains an important predictor of adverse post-surgical outcomes regardless of age, surgical discipline, and surgical risk.[65] A study conducted in a large Veterans Administration Surgical Quality Improvement Program database further supports the principle that a frailty screening should be universally applied in the preoperative setting to identify patients who are at high risk for even low-risk surgical procedures.[66] The 2012 Best Practice Guidelines, jointly published by the American College of Surgeons and the American Geriatrics Society, includes a frailty score validated for surgical patients as part of the optimal preoperative evaluation of geriatric patients.[67]

Physical function evaluations have been in routine use in oncology for decades to risk stratify adults undergoing cancer treatments. The more widely used instruments are the ECOG (Eastern Cooperative Oncology Group) Performance Status and the Karnofsky Index.[68,69] However, the multi-dimensional aspect of frailty has resulted in a growing interest in studying frailty as a risk-stratification construct in oncology and comparing frailty with existing physical function measures.[70,71] In myelodysplastic syndromes, frailty was found to be independently predictive of infection-related mortality.[72] In a study of colon cancer patients $\geqslant$70 years, frailty was independently associated with 1- and 5-year post-surgical survival.[73] A frailty index also predicted mortality from chemotherapy in advanced colon cancer patients[74,75] In another study of cancer patients $\geqslant$65 years, weak grip strength – a measure of frailty – predicted chemotherapy toxicity but not mortality, while the ECOG score predicted mortality but not treatment toxicity.[76] In retrospective regression models controlling for tumor characteristics, age, body mass index, number of medications, and chemotherapy, a phenotypic frailty score was significantly associated with radiotherapy fatigue while the Karnofsky score was not.[77] In a prospective study of patients with solid tumors referred for a geriatric assessment, phenotypic frailty predicted a recommendation to switch to supportive and palliative treatment rather than the initial treatment plan while the ECOG performance status did not.[78] While a frailty-based evaluation is not yet in widespread clinical use in oncology to date, it is increasingly recognized that frailty is a more comprehensive risk assessment construct than existing performance measures.

In gastrointestinal diseases, frailty has been best characterized in patients with end stage liver disease (ESLD).[79] A frailty index tailored for patients with liver diseases identified ESLD patients at greater risk for mortality while awaiting liver transplantation independent of ascites and hepatic encephalopathy, both of which are well-established risk factors for decompensation.[80] Given the aging liver transplantation wait-list, a frailty

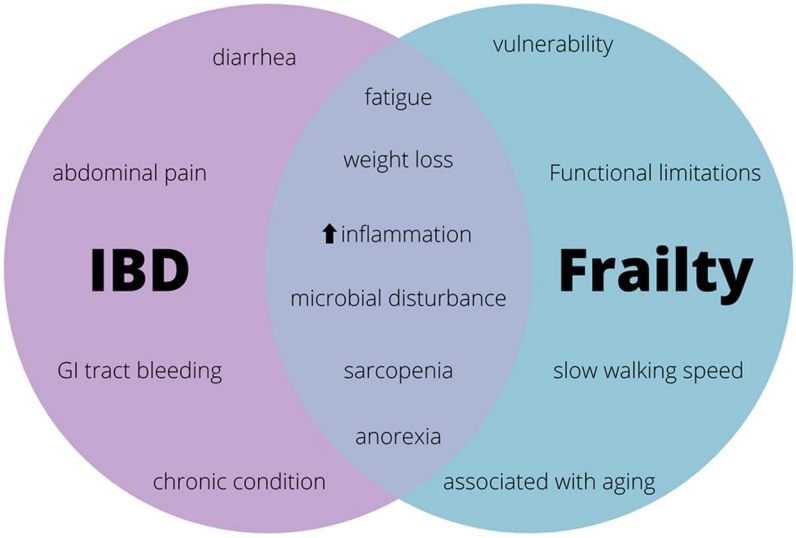

Figure 1. Features of inflammatory bowel diseases and frailty.
GI, gastrointestinal.

assessment is increasingly a critical component of the liver transplant evaluation.[81]

Frailty in IBD

Inflammatory bowel diseases, both Crohn's disease and UC, are systemic, chronic, remitting, relapsing diseases of bacterial dysbiosis resulting in altered immune function with amplified inflammation.[82] Severe IBD often manifests with many features associated with frailty, such as weight loss, fatigue, and sarcopenia (Figure 1). In humans, frailty is associated with reduced microbial diversity and depletion of saccharolytic and butyrate-producing bacteria.[83–87] Intriguingly, several of these changes resemble those in IBD and other related conditions including fatigue and sarcopenia.[83,86–89] This lends further credence to the hypothesis that frailty may be a relevant construct in IBD.

The earliest studies of frailty in IBD were in the operative setting. The initial study evaluated frailty as risk factor for outcomes after ileoanal pouch creation in the American National Surgical Quality Improvement Program database from 2005 to 2012. In a cohort of 2493 patients undergoing IPAA creation, patients with one or more frailty related diagnosis code were found to have a numerically higher number of post-operative complications and increased length of stay than those without a frailty trait, although the differences were not statistically different.[90] The definition of frailty used in this study limit the interpretation and clinical applicability of this study. In the same database, a study applying a frailty index validated in the database to a cohort of 943 patients who underwent a colectomy for UC, found that frailty was an independent and significant predictor of septic and cardiopulmonary complications, serious morbidity, re-operation, and overall mortality.[91]

A 2019 systematic review on the use of the Comprehensive Geriatric Assessment in patients with IBD identified 27 studies that included at least one geriatric assessment in the study.[92] However, none of these studies focused on older adults or present sub-group analysis of data specific to older adults. Domains such as somatic, functional, mental, and social, were assessed. However, no studies assessed frailty specifically. This review highlighted the void of studies of geriatric assessments in older adults with IBD and specifically regarding frailty, a multi-dimensional construct that may be more comprehensive than any one domain of the geriatric assessment.

Subsequently, a retrospective study in an electronic health record (EHR)-based database was conducted to evaluate the prevalence and impact of frailty in patients with IBD. In a cohort of 11,001 patients of all ages with IBD, frailty was quantified using the validated Hospital Frailty Risk Score, a weighted composite of diagnosis codes validated to measure frailty.[93] The prevalence of

frailty increased from 4% in IBD patients <30 years to 25% in those ⩾90 years.[94] The impact of frailty was assessed longitudinally as well. Adjusting for age and comorbidity, frailty was associated independently with a threefold increase in mortality [odds ratio (OR) 2.90, 95% confidence interval (CI) 2.29–3.68). In a separate study in the same cohort assessing IBD patients initiating immunosuppression, including 1299 patients initiating anti-TNF therapy and 2676 patients initiating immunomodulator therapy, frail patients had a twofold increased risk of infections compared with non-frail IBD patients initiating anti-TNF (OR: 2.05) and immunomodulator (OR: 1.81) therapy.[95]

Another retrospective study in an EHR-based cohort that applied a frailty index demonstrated that frail IBD patients had a higher mean CRP than more robust IBD patients.[96] In this cohort of 1210 patients initiating anti-TNF therapy, IBD patients who were frail prior to treatment demonstrated an improvement in frailty in the year following treatment. Clinical response to anti-TNF therapy, determined using natural language processing technology, was associated with an improvement in frailty after treatment. The magnitude of improvement in frailty was similar in those 60 years and older as in those younger than 60 years. These data suggest that frailty and inflammation are dynamically linked. They also demonstrate that frailty in IBD patients may be a construct that is applicable to patients of all ages and a modifiable syndrome.

A retrospective cohort study using the US Nationwide Readmission Database from 2010 to 2013 reported that frailty, also defined by the Hospital Frailty Risk Score, was independently associated with a 57% higher risk of mortality, 21% higher risk of all-cause hospital readmission, and 22% higher risk for readmission for severe IBD.[97] A second study in the same database using a definition of frailty based on the Johns Hopkins Adjusted Clinical Groups of frailty-defining diagnoses, concluded that frailty predicted hospital re-admission while age did not. Interestingly, in this cohort, older age was associated with a lower risk of readmission after adjusting for covariates.[98] These data suggest that frailty may have more applicability than chronologic age alone in predicting adverse outcomes in patients with IBD. More recently, a claims-based study of frailty in IBD patients treated with biologic agents concluded that frailty was associated with an increased risk of serious infections only in patients treated with vedolizumab and not in patients with anti-TNF agents.[99] The published studies of frailty in IBD are summarized in Table 1.

Implications and future directions

As the population with IBD is rising rapidly, there is a pressing need to understand aging in adults with a chronic inflammatory condition. There is a knowledge void in both the biology of inflammation and aging as well as optimal risk stratification for older IBD patients. Similar principles can augment risk stratification tools for the increasingly multi-morbid population of younger adults with IBD. The early studies of frailty in IBD demonstrate great promise for frailty as a comprehensive modality to risk stratify IBD patients at greatest risk for adverse outcomes; however, studies published to date are retrospective. It is not yet know how to best measure frailty in IBD patients. It is possible that a cumulative deficit model of frailty will be suited for risk stratification of older adults with IBD, while the phenotype model of frailty will be most useful to understand the biology of aging with an inflammatory condition. Future studies should be directed toward appropriate frailty measures, prospectively delineating frailty features and determining the longitudinal implications of frailty in IBD patients to inform the importance of studying frailty in patients with IBD.

A focused frailty evaluation that will risk stratify older IBD patients prior to choosing medical and surgical treatment options will aid clinicians at the bedside both in medical decision making and patient counseling. The clinical implications of using frailty to risk stratify older adults with IBD are far reaching. Characterizing those who are physiologically more fit to withstand immunosuppressive therapies may expand access for more effective, steroid-sparing, therapies to older adults. Building on this study may result in more appropriate and tailored therapies to treat IBD to improve quality of life and decrease risk for surgery. Furthermore, if treating IBD may ameliorate the frailty syndrome itself, it is plausible that adverse outcomes related to frailty can also be longitudinally mitigated.

Using frailty as a construct to identify those who are at greater risk for adverse events can also allow

Table 1. Published studies of frailty in inflammatory bowel diseases.

First author	Journal	Data source	Frailty measure	Main conclusion
Cohan *et al.*[90]	Journal of Surgical Research	National surgical quality improvement program	Frailty trait count	Frailty is not significantly associated with complications or increased length of stay after IPAA procedures
Telemi *et al.*[91]	The American Journal of Surgery	National surgical quality improvement program	Database-validated modified frailty index	Frailty is independently associated with serious morbidity, re-operation and mortality after colectomy for UC
Kochar *et al.*[94]	Alimentary Pharmacology and Therapeutics	Electronic health record	HFRS derived frailty related diagnosis code	Frailty is prevalent in IBD patients and associated with increased risk for mortality
Kochar *et al.*[95]	Gastroenterology	Electronic health record	HFRS derived frailty related diagnosis code	Frailty prior to treatment with anti-TNF agents or immunomodulators is associated with an increased risk of infections after treatment
Singh *et al.*[99]	Inflammatory Bowel Diseases	Optum labs claims data warehouse	HFRS	Frailty was associated with an increased risk of serious infections only in IBD patients treated with vedolizumab and not anti-TNF agents
Qian *et al.*[97]	Clinical Gastroenterology and Hepatology	US national readmissions database	HFRS	Frailty was associated with an increased risk of mortality, all-cause and IBD readmissions
Faye *et al.*[98]	Digestive Diseases and Sciences	US national readmissions database	Frailty defining clinical groups	Frailty predicts hospital re-admission while age did not
Kochar *et al.*[96]	Digestive Diseases and Sciences	Electronic health record	HFRS	Frail IBD patients who respond to anti-TNF therapy are more likely to have an improvement in frailty over time compared with IBD patients who do not respond to anti-TNF therapy

IBD, inflammatory bowel disease; HFRS, hospital frailty risk score; IPAA, ileal pouch anal anastomosis; TNF, tumor necrosis factor; UC, ulcerative colitis; US, United States.

for interventions to treat frailty. The field of interventions aimed to ameliorate frailty is expanding rapidly.[100,101] A majority of well-accepted interventions focus on exercise and nutritional supplementation. However, there have been no targeted studies of interventions to modulate frailty in patients with chronic immune mediated conditions. The applicability of frailty interventions studied in a general population of older adults is not known in the context of IBD. Attempting to ameliorate frailty provides a possible avenue to improve the health and care for older patients with IBD. As frailty is a multi-dimensional syndrome, early identification and characterization of frail patients with IBD presents an opportunity for true multi-disciplinary care with primary care providers, rehabilitation medication, nutritionists, and other health care professionals.

There is certainly no consensus in the literature, both in IBD and other fields, regarding the best assessment tool to measure frailty, monitor the trajectory of frailty, and mitigate frailty longitudinally. Many validated tools exist, including those that are tailored to perform quickly in a busy clinical setting. However, a tool must be tailored to its intended population and use. In the near future, there is a need for prospective studies that characterize frailty in IBD patients, understand the dynamic and longitudinal relationship between frailty and IBD disease activity, and, if pertinent, subsequently, design and test interventions to

ameliorate the burden of frailty in patients with IBD. There is also a great need for mechanistic research exploring the biologic relationship between IBD and the frailty syndrome to better elucidate the underlying mechanisms of the close associations demonstrated in a clinical context.

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References

1. Alatab S, Sepanlou SG, Ikuta K, *et al*. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet Gastroenterol Hepatol* 2020; 5: 17–30.
2. Robertson DJ and Grimm IS. Inflammatory bowel disease in the elderly. *Gastroenterol Clin North Am* 2001; 30: 409–426.
3. Shivashankar R, Tremaine WJ, Harmsen WS, *et al*. Incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted county, Minnesota from 1970 through 2010. *Clin Gastroenterol Hepatol* 2017; 15: 857–863.
4. Shi HY, Chan FK, Leung WK, *et al*. Natural history of elderly-onset ulcerative colitis: results from a territory-wide inflammatory bowel disease registry. *J Crohns Colitis* 2016; 10: 176–185.
5. Ananthakrishnan AN, Donaldson T, Lasch K, *et al*. Management of inflammatory bowel disease in the elderly patient: challenges and opportunities. *Inflamm Bowel Dis* 2017; 23: 882–893.
6. Dahlhamer J, Zammitti E, Ward B, *et al*. Prevalence of inflammatory bowel disease among adults aged ⩾18 years - United States, 2015. *MMWR Morb Mortal Wkly Rep* 2016; 65: 1166–1169.
7. Coward S, Clement F, Benchimol EI, *et al*. Past and future burden of inflammatory bowel diseases based on modeling of population-based data. *Gastroenterology* 2019; 156: 1345–1353.e4.
8. Olshansky SJ. From lifespan to healthspan. *JAMA* 2018; 320: 1323.
9. Greuter T, Vavricka S, König AO, *et al*. Malignancies in inflammatory bowel disease. *Digestion* 2020; 101(Suppl. 1): 136–145.
10. Singh H, Nugent Z, Yu BN, *et al*. Higher incidence of clostridium difficile infection among individuals with inflammatory bowel disease. *Gastroenterology* 2017; 153: 430–438.e2.
11. Tinsley A, Navabi S, Williams ED, *et al*. Increased risk of influenza and influenza-related complications among 140,480 patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2019; 25: 369–376.
12. Bjarnason I, Macpherson A, Mackintosh C, *et al*. Reduced bone density in patients with inflammatory bowel disease. *Gut* 1997; 40: 228–233.
13. Card TW, Hubbard J, Logan R, *et al*. Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study. *Gut* 2004; 53: 251–255.
14. Wang J, Nakamura TI, Tuskey AG, *et al*. Polypharmacy is a risk factor for disease flare in adult patients with ulcerative colitis: a retrospective cohort study. *Intest Res* 2019; 17: 496–503.
15. Tadin Hadjina I, Zivkovic PM, Matetic A, *et al*. Impaired neurocognitive and psychomotor performance in patients with inflammatory bowel disease. *Sci Rep* 2019; 9: 13740.
16. Villumsen M, Aznar S, Pakkenberg B, *et al*. Inflammatory bowel disease increases the risk of Parkinson's disease: a Danish nationwide cohort study 1977–2014. *Gut* 2019; 68: 18–24.
17. Zhang B, Wang HE, Bai YM, *et al*. Inflammatory bowel disease is associated with higher dementia

risk: a nationwide longitudinal study. *Gut*. Epub ahead of print 23 June 2020. DOI: 10.1136/gutjnl-2020-320789.

18. Bollegala N, Jackson TD and Nguyen GC. Increased postoperative mortality and complications among elderly patients with inflammatory bowel diseases: an analysis of the national surgical quality improvement program cohort. *Clin Gastroenterol Hepatol* 2016; 14: 1274–1281.
19. Nguyen GC, Bernstein CN and Benchimol EI. Risk of surgery and mortality in elderly-onset inflammatory bowel disease: a population-based cohort study. *Inflamm Bowel Dis* 2017; 23: 218–223.
20. Dong C, Metzger M, Holsbø E, *et al*. Systematic review with meta-analysis: mortality in acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2020; 51: 8–33.
21. Rubin DT, Ananthakrishnan AN, Siegel CA, *et al*. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019; 114: 384–413.
22. Lichtenstein GR, Loftus EV, Isaacs KL, *et al*. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018; 113: 481–517.
23. Geisz M, Ha C, Kappelman MD, *et al*. Medication utilization and the impact of continued corticosteroid use on patient-reported outcomes in older patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016; 22: 1435–1441.
24. Rozich JJ, Dulai PS, Fumery M, *et al*. Progression of elderly-onset inflammatory bowel diseases: a systematic review and meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2020; 18: 2437–2447.e6.
25. Govani SM, Wiitala WL, Stidham RW, *et al*. Age disparities in the use of steroid-sparing therapy for inflammatory bowel disease. *Inflamm Bowel Dis* 2016; 22: 1923–1928.
26. Kochar B, Kalasapudi L, Ufere NN, *et al*. Systematic review of inclusion and analysis of older adults in randomized controlled trials of medications used to treat inflammatory bowel diseases. *Inflamm Bowel Dis*. Epub ahead of print 11 March 2021. DOI: 10.1093/ibd/izab052.
27. Lobaton T, Ferrante M, Rutgeerts P, *et al*. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; 42: 441–451.
28. Adar T, Faleck D, Sasidharan S, *et al*. Comparative safety and effectiveness of tumor necrosis factor alpha antagonists and vedolizumab in elderly IBD patients: a multicentre study. *Aliment Pharmacol Ther* 2019; 49: 873–879.
29. Parian A and Ha CY. Older age and steroid use are associated with increasing polypharmacy and potential medication interactions among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015; 21: 1392–1400.
30. Clegg A, Young J, Iliffe S, *et al*. Frailty in elderly people. *Lancet* 2013; 381: 752–762.
31. Orkaby AR, Nussbaum L, Ho Y-L, *et al*. The burden of frailty among U.S. veterans and its association with mortality, 2002–2012. *J Gerontol A Biol Sci Med Sci* 2019; 74: 1257–1264.
32. Fried LP, Ferrucci L, Darer J, *et al*. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59: M255–M263.
33. Vetrano DL, Palmer K, Marengoni A, *et al*. Frailty and multimorbidity: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci* 2019; 74: 659–666.
34. Oude Voshaar RC, Jeuring HW, Borges MK, *et al*. Course of frailty stratified by physical and mental multimorbidity patterns: a 5-year follow-up of 92,640 participants of the LifeLines cohort study. *BMC Med* 2021; 19: 29.
35. Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–M156.
36. Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173: 489–495.
37. Joseph B, Pandit V, Zangbar B, *et al*. Validating trauma-specific frailty index for geriatric trauma patients: a prospective analysis. *J Am Coll Surg* 2014; 219: 10–17.e1.
38. Legge A, Kirkland S, Rockwood K, *et al*. Construction of a frailty index as a novel health measure in systemic lupus erythematosus. *J Rheumatol* 2020; 47: 72–81.
39. Starkman R, Alibhai S, Wells RA, *et al*. An MDS-specific frailty index based on cumulative deficits adds independent prognostic information to clinical prognostic scoring. *Leukemia* 2020; 34: 1394–1406.
40. Yaksic E, Lecky V, Sharnprapai S, *et al*. Defining frailty in research abstracts: a systematic review and recommendations for standardization. *J Frailty Aging* 2019; 8: 67–71.

41. Gill TM, Gahbauer EA, Allore HG, *et al*. Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006; 166: 418.

42. Gill TM, Gahbauer EA, Han L, *et al*. Trajectories of disability in the last year of life. *N Engl J Med* 2010; 362: 1173–1180.

43. Buckinx F, Rolland Y, Reginster JY, *et al*. Burden of frailty in the elderly population: perspectives for a public health challenge. *Arch Public Health* 2015; 73: 19.

44. Hubbard RE, O'Mahony MS, Savva GM, *et al*. Inflammation and frailty measures in older people. *J Cell Mol Med* 2009; 13: 3103–3109.

45. Collerton J, Martin-Ruiz C, Davies K, *et al*. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ study. *Mech Ageing Dev* 2012; 133: 456–466.

46. Harris TB, Ferrucci L, Tracy RP, *et al*. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999; 106: 506–512.

47. Yao X, Li H and Leng SX. Inflammation and immune system alterations in frailty. *Clin Geriatr Med* 2011; 27: 79–87.

48. Allen SC. Systemic inflammation in the genesis of frailty and sarcopenia: an overview of the preventative and therapeutic role of exercise and the potential for drug treatments. *Geriatrics (Basel)* 2017; 2: 6.

49. Montecino-Rodriguez E, Berent-Maoz B and Dorshkind K. Causes, consequences, and reversal of immune system aging. *J Clin Invest* 2013; 123: 958–965.

50. Leng SX, Xue QL, Tian J, *et al*. Inflammation and frailty in older women. *J Am Geriatr Soc* 2007; 55: 864–871.

51. Liu CK, Lyass A, Larson MG, *et al*. Biomarkers of oxidative stress are associated with frailty: the Framingham Offspring study. *Age (Dordr)* 2016; 38: 1.

52. López-Otín C, Blasco MA, Partridge L, *et al*. The hallmarks of aging. *Cell* 2013; 153: 1194–1217.

53. Ferrucci L and Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018; 15: 505–522.

54. Salaffi F, Di Carlo M, Farah S, *et al*. Prevalence of frailty and its associated factors in patients with rheumatoid arthritis: a cross-sectional analysis. *Clin Rheumatol* 2019; 38: 1823–1830.

55. Haider S, Grabovac I, Berner C, *et al*. Frailty in seropositive rheumatoid arthritis patients of working age: a cross-sectional study. *Clin Exp Rheumatol* 2019; 37: 585–592.

56. Tada M, Yamada Y, Mandai K, *et al*. Correlation between frailty and disease activity in patients with rheumatoid arthritis: data from the CHIKARA study. *Geriatr Gerontol Int* 2019; 19: 1220–1225.

57. Salaffi F, Di Carlo M, Farah S, *et al*. The Comprehensive Rheumatologic Assessment of Frailty (CRAF): development and validation of a multidimensional frailty screening tool in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2020; 38: 488–499.

58. Salaffi F, Farah S and Di Carlo M. Frailty syndrome in musculoskeletal disorders: an emerging concept in rheumatology. *Acta Biomed* 2020; 91: 274–296.

59. Rockwood MR, Macdonald E, Sutton E, *et al*. Frailty index to measure health status in people with systemic sclerosis. *J Rheumatol* 2014; 41: 698–705.

60. Andrews JS, Trupin L, Wysham KD, *et al*. The impact of frailty on changes in physical function and disease activity among adults with rheumatoid arthritis. *ACR Open Rheumatol* 2019; 1: 366–372.

61. Legge A, Kirkland S, Rockwood K, *et al*. Evaluating the properties of a frailty index and its association with mortality risk among patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2019; 71: 1297–1307.

62. McGovern D, Williams SP, Parsons K, *et al*. Long-term outcomes in elderly patients with ANCA-associated vasculitis. *Rheumatology* 2020; 59: 1076–1083.

63. Motta F, Sica A and Selmi C. Frailty in rheumatic diseases. *Front Immunol* 2020; 11: 576134.

64. Makary MA, Segev DL, Pronovost PJ, *et al*. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; 210: 901–908.

65. Birkelbach O, Mörgeli R, Spies C, *et al*. Routine frailty assessment predicts postoperative complications in elderly patients across surgical disciplines – a retrospective observational study. *BMC Anesthesiol* 2019; 19: 204.

66. Shinall MC, Arya S, Youk A, *et al*. Association of preoperative patient frailty and operative stress with postoperative mortality. *JAMA Surg* 2020; 155: e194620.

67. Chow WB, Ko CY, Rosenthal RA, *et al. ACS NSQIP®/AGS best practice guidelines: optimal preoperative assessment of the geriatric surgical patient*. Chicago: American College of Surgeons, 2012.
68. Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5: 649–655.
69. Karnofksy DA and Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM (ed.) *Evaluation of chemotherapeutic agents*. New York: Columbia University Press, 1949, p.196.
70. Kumar Pal S, Katheria V and Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. *CA Cancer J Clin* 2010; 60: 120–132.
71. Cohen HJ, Smith D, Sun C-L, *et al.* Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. *Cancer* 2016; 122: 3865–3872.
72. Sakatoku K, Takeoka Y, Miura A, *et al.* Combination of frailty status and comorbidity score improves the stratification of survival in patients with myelodysplastic syndrome owing to good predictive capability for infection-related mortality. *Clin Lymphoma Myeloma Leuk* 2019; 19: 799–805.
73. Ommundsen N, Wyller TB, Nesbakken A, *et al.* Frailty is an independent predictor of survival in older patients with colorectal cancer. *Oncologist* 2014; 19: 1268–1275.
74. Aaldriks AA, van der Geest LG, Giltay EJ, *et al.* Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol* 2013; 4: 218–226.
75. Aaldriks AA, Maartense E, le Cessie S, *et al.* Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Crit Rev Oncol Hematol* 2011; 79: 205–212.
76. Puts MT, Monette J, Girre V, *et al.* Are frailty markers useful for predicting treatment toxicity and mortality in older newly diagnosed cancer patients? Results from a prospective pilot study. *Crit Rev Oncol Hematol* 2011; 78: 138–149.
77. Denkinger MD, Hasch M, Gerstmayer A, *et al.* Predicting fatigue in older breast cancer patients receiving radiotherapy. *Z Gerontol Geriatr* 2015; 48: 128–134.
78. Farcet A, De Decker L, Pauly V, *et al.* Frailty markers and treatment decisions in patients seen in oncogeriatric clinics: results from the ASRO pilot study. *PLoS One* 2016; 11: e0149732.
79. Lai JC, Covinsky KE, Dodge JL, *et al.* Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017; 66: 564–574.
80. Lai JC, Rahimi RS, Verna EC, *et al.* Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. *Gastroenterology* 2019; 156: 1675–1682.
81. Lai JC, Sonnenday CJ, Tapper EB, *et al.* Frailty in liver transplantation: an expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. *Am J Transplant* 2019; 19: 1896–1906.
82. Abraham C and Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; 361: 2066–2078.
83. Casati M, Ferri E, Azzolino D, *et al.* Gut microbiota and physical frailty through the mediation of sarcopenia. *Exp Gerontol* 2019; 124: 110639.
84. Haran JP and McCormick BA. Aging, frailty, and the microbiome-how dysbiosis influences human aging and disease. *Gastroenterology* 2021; 160: 507–523.
85. Jackson MA, Jeffery IB, Beaumont M, *et al.* Signatures of early frailty in the gut microbiota. *Genome Med* 2016; 8: 8.
86. Picca A, Ponziani FR, Calvani R, *et al.* Gut microbial, inflammatory and metabolic signatures in older people with physical frailty and sarcopenia: results from the BIOSPHERE study. *Nutrients* 2019; 12: 65.
87. Ticinesi A, Mancabelli L, Tagliaferri S, *et al.* The gut-muscle axis in older subjects with low muscle mass and performance: a proof of concept study exploring fecal microbiota composition and function with shotgun metagenomics sequencing. *Int J Mol Sci* 2020; 21: 8946.
88. Picca A, Fanelli F, Calvani R, *et al.* Gut dysbiosis and muscle aging: searching for novel targets against sarcopenia. *Mediators Inflamm* 2018; 2018: 7026198.
89. Borren NZ, Plichta D, Joshi AD, *et al.* Alterations in fecal microbiomes and serum metabolomes of fatigued patients with quiescent inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2021; 19: 519–527.

90. Cohan JN, Bacchetti P, Varma MG, *et al*. Outcomes after ileoanal pouch surgery in frail and older adults. *J Surg Res* 2015; 198: 327–333.

91. Telemi E, Trofymenko O, Venkat R, *et al*. Frailty predicts morbidity after colectomy for ulcerative colitis. *Am Surg* 2018; 84: 225–229.

92. Asscher VER, Lee-Kong FVY, Kort ED, *et al*. Systematic review: components of a comprehensive geriatric assessment in inflammatory bowel disease – a potentially promising but often neglected risk stratification. *J Crohns Colitis* 2019; 13: 1418–1432.

93. Gilbert T, Neuburger J, Kraindler J, *et al*. Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; 391: 1775–1782.

94. Kochar B, Cai W, Cagan A, *et al*. Frailty is independently associated with mortality in 11,001 patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2020; 52: 311–318.

95. Kochar B, Cai W, Cagan A, *et al*. Pretreatment frailty is independently associated with increased risk of infections after immunosuppression in patients with inflammatory bowel diseases. *Gastroenterology* 2020; 158: 2104–2111.e2.

96. Kochar B, Cai W and Ananthakrishnan A. Inflammatory bowel disease patients who respond to treatment with anti-tumor necrosis factor agents demonstrate improvement in pre-treatment frailty. *Dig Dis Sci*. Epub ahead of print 1 May 2021. DOI: 10.1007/s10620-021-06990-8.

97. Qian AS, Nguyen NH, Elia J, *et al*. Frailty is independently associated with mortality and readmission in hospitalized patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. Epub ahead of print 12 August 2020. DOI: 10.1016/j.cgh.2020.08.010.

98. Faye AS, Wen T, Soroush A, *et al*. Increasing prevalence of frailty and its association with readmission and mortality among hospitalized patients with IBD. *Dig Dis Sci*. Epub ahead of print 1 January 2021. DOI: 10.1007/s10620-020-06746-w.

99. Singh S, Heien HC, Sangaralingham L, *et al*. Frailty and risk of serious infections in biologic-treated patients with inflammatory bowel diseases. *Inflamm Bowel Dis*. Epub ahead of print 16 December 2020. DOI: 10.1093/ibd/izaa327.

100. Marcucci M, Damanti S, Germini F, *et al*. Interventions to prevent, delay or reverse frailty in older people: a journey towards clinical guidelines. *BMC Med* 2019; 17: 193.

101. Puts MTE, Toubasi S, Andrew MK, *et al*. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. *Age Ageing* 2017; 46: 383–392.

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