

# Frailty in Patients With Inflammatory Bowel Disease

Ashwin N. Ananthakrishnan, MD, MPH

Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Corresponding author:

Dr Ashwin N. Ananthakrishnan  
Massachusetts General Hospital  
165 Cambridge Street, 9th floor  
Boston, MA 02114  
Tel: (617) 724-9953  
E-mail: [aananthakrishnan@mgh.harvard.edu](mailto:aananthakrishnan@mgh.harvard.edu)

**Abstract:** Older individuals comprise a growing proportion of patients with inflammatory bowel disease (IBD). Assessing older patients for frailty, defined as an age-related decline in multiple physiologic systems, is increasingly recognized as important for risk-stratifying patients with IBD. Mechanistically, both persistent chronic inflammation and common microbial perturbations may predispose patients with IBD to the development of frailty. In those with IBD, frailty is associated with an increased risk for mortality that is independent of age and comorbidity. Among hospitalized patients, frailty is associated with a higher risk for readmission and postoperative complications. In patients starting on immunomodulator or tumor necrosis factor–alpha antagonist therapy, frailty is also associated with an increased risk for infectious complications, including serious infections. For a beneficial effect on patient outcomes, it is important that clinicians familiarize themselves with the tools for assessing frailty and implement interventions aimed at mitigating the individual components of the frailty phenotype. This article examines the proposed mechanisms for an association between frailty and IBD, tools for assessment of frailty, and data involving the impact of frailty on outcomes in patients with IBD.

By 2040, nearly 1 in 5 Americans will be 65 years of age or older. Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), affects an estimated 3 million individuals in the United States.<sup>1</sup> Although IBD is traditionally considered to be a disease of young persons, up to 20% of new diagnoses of IBD may be in patients older than 60 years. Because the life expectancy of individuals with this disease is now for the most part preserved with more effective treatment of inflammation and comorbidity, a growing proportion of the adult population with IBD consists of persons older than 60 years.<sup>2-4</sup> Although therapeutic advances, including drugs with various mechanisms of action and the use of treat-to-target strategies, have improved overall outcomes in patients with IBD, the pace of these

## Keywords

Frail, inflammation, microbiome, biologic, sarcopenia

**Table.** Components of the Fried Frailty Phenotype

Involuntary weight loss of 10 lb or more in the last 6 months
Reduced grip strength
Difficulty initiating movements
Reduced walking speed
Fatigue or exhaustion

Fit, 0 abnormalities; prefrail, 1 to 2 abnormalities; frail, 3 or more abnormalities.

scientific developments has been relatively slow in older patients, who are underrepresented in treatment trials. Of particular importance in older patients is the concept of risk stratification. This principle is well recognized in younger patients, in whom severity of clinical and endoscopic disease and prognostic factors are used to inform the best therapeutic strategy. However, the choice of therapeutic strategy is of particular importance in older patients because of their increased vulnerability to the physical, psychological, and functional limitations of undertreated inflammation as well as their heightened susceptibility to the adverse effects of therapy, in particular immunosuppression.<sup>2-4</sup> Frailty is an important concept that has emerged to aid in the risk stratification of older patients.

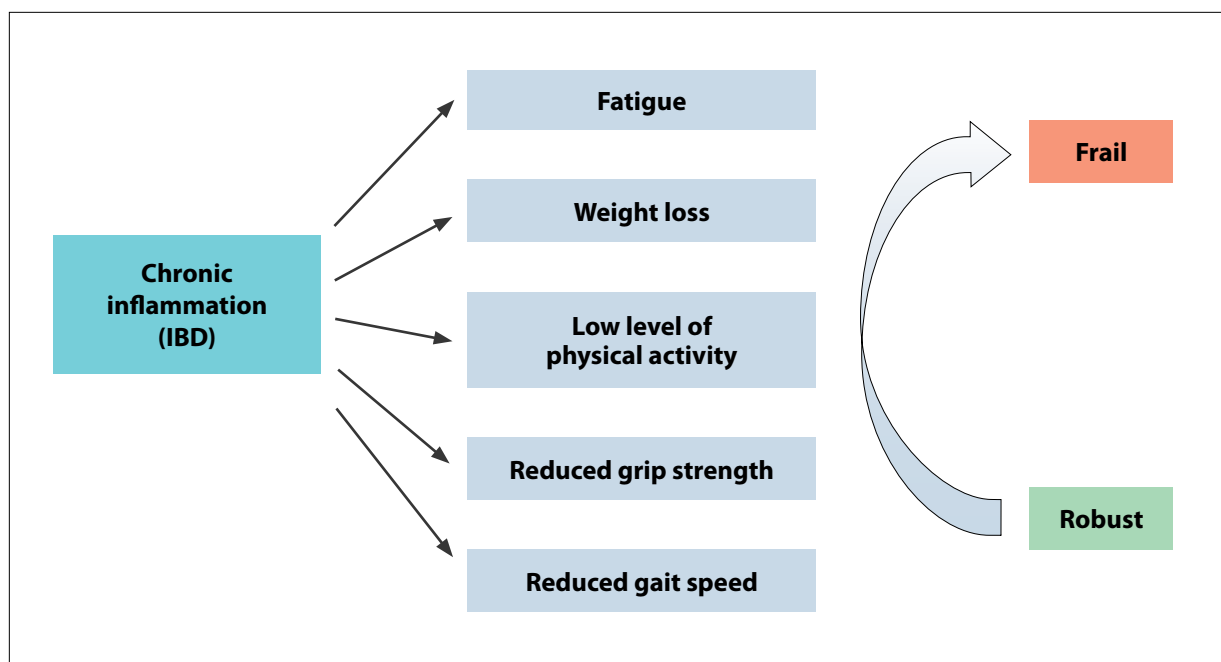
Frailty is defined as an aging-associated decline in reserve and function across multiple physiologic systems that confers an increased vulnerability to adverse health outcomes.<sup>5-8</sup> One of the earliest definitions of frailty was that of Fried and colleagues, who proposed a phenotype based on an amalgam of 5 clinical features: weight loss, low level of physical activity, impaired grip strength, slow gait, and exhaustion (Table).<sup>6</sup> The presence of at least 3 of these features is necessary to label an individual as frail, whereas the presence of 1 to 2 features confers a label of prefrail. A second model for quantifying frailty was proposed by Rockwood and Mitnitski.<sup>7</sup> Their model of cumulative deficits defines frailty as an accumulation of multiple impairments.<sup>7</sup> Emerging data suggest that an assessment of frailty is important in patients with IBD and may help identify those at higher risk for either disease- or treatment-related complications.<sup>9-12</sup> Closely related to frailty is the concept of sarcopenia, which is defined as a syndrome characterized by reduced skeletal muscle mass and strength; sarcopenia therefore contributes to 2 of the factors comprising the Fried frailty phenotype. Together with the emerging data on frailty in IBD, a growing body

of literature highlights a potential association between inflammation and the proinflammatory microbial changes that occur in sarcopenia, and consequently the adverse effect of sarcopenia on outcomes in patients with IBD.<sup>13-17</sup> This article examines possible mechanisms for the relationship between IBD and frailty through the effects of chronic inflammation and microbial alterations (Figure). In addition, the article reviews the clinical literature regarding the effect of frailty on patients with IBD and provides suggestions for how to assess these patients for frailty and incorporate the findings into decisions regarding their treatment.

## Inflammation and Frailty

Several lines of evidence support a link between frailty and systemic inflammation in the general population and in persons with chronic diseases.<sup>5,18,19</sup> Although the support for this hypothesis is stronger in cross-sectional studies, longitudinal studies have also suggested that chronic systemic inflammation may lead to an increased risk for frailty. Among 117 individuals 62 to 95 years of age, the levels of serum interleukin (IL)-6, tumor necrosis factor receptor (TNFR)-1, and TNFR-2 were higher in frail and prefrail than in nonfrail individuals.<sup>20</sup> In a Spanish cohort of adults aged 65 years and older, frailty was associated with increases in IL-6 and soluble TNFR-2 levels.<sup>21</sup> A meta-analysis summarized 32 cross-sectional studies comparing serum inflammatory markers in 3232 frail and 11,483 prefrail individuals with the markers in individuals who were robust.<sup>22</sup> Both the frail and prefrail patients had significant elevations in serum C-reactive protein (CRP) and IL-6 levels when compared with robust controls. Cross-sectionally, among participants in the Women's Health and Aging studies whose serum IL-6 levels were in the highest quartile, the likelihood of being frail was increased 2-fold.<sup>23</sup> Independently, elevated IL-6 levels have been associated with decreased muscle strength, sarcopenia, and reduced gait speed, all of which are components of the frailty syndrome.<sup>24</sup>

In contrast to supportive experimental studies and cross-sectional data regarding the association between inflammation and frailty, longitudinal studies have yielded more mixed results. In the English Longitudinal Study of Ageing, baseline CRP level was only modestly correlated with incident frailty. For each standard deviation increase in CRP, the odds of incident frailty were numerically but not statistically significantly increased in women (odds ratio [OR], 1.27; 95% CI, 0.96-1.69), with no effect noted in men.<sup>25</sup> Similarly, in a study by Reiner and colleagues, no association was found between IL-6 and CRP levels and incident frailty.<sup>26</sup> In contrast, among 620 women in a study by Ferrucci and colleagues, high



**Figure.** Effect of inflammation in inflammatory bowel disease (IBD) on the frailty phenotype.

baseline IL-6 levels were associated with increased risks for incident limited mobility, limited walking, and decline in walking speed, effects that were partially mediated by a decline in muscle strength.<sup>24</sup>

The exact mechanism by which such inflammatory mediators may cause frailty, and whether their effect is peripherally or centrally mediated, remains to be defined. An emerging body of evidence demonstrates a prevalence of altered innate and adaptive immune responses in frailty. In older adults, the rate of lipopolysaccharide-induced peripheral blood mononuclear cell production of IL-6 is higher in frail than in nonfrail patients.<sup>27</sup> Levels of CD8+ and CD8+CD28+ T cells are higher in frail women than in nonfrail women.<sup>28</sup> Counts of T cells expressing CCR5+ are also higher in frail than in nonfrail older patients.<sup>29</sup> Additionally, alterations in the B-cell compartment, including a decreased B-cell repertoire, are observed in frail older adults, and this has been hypothesized to explain the lower rates of response to influenza and pneumococcal vaccination in the setting of frailty. In a small cohort of 16 paired frailty-, age-, and sex-matched controls, frailty was associated with upregulation of expression of the *CXCL10* gene, which encodes a proinflammatory cytokine.<sup>30</sup> Neopterin, a marker of monocyte/macrophage-mediated activation, was also elevated in frail community-dwelling individuals in comparison with those who were robust.<sup>18</sup> A study of 6 patients who underwent proteomic analysis revealed elevated levels of angiotensinogen, kininogen-1, and

antithrombin III in comparisons of frail and nonfrail individuals.<sup>31</sup>

### Role of the Microbiome in Frailty

Intriguing emerging data suggest that microbial alterations in the gut may be linked to the development of frailty. This may be a mechanism by which systemic inflammation mediates its effect on frailty. Jackson and colleagues profiled the microbiome from 728 female twins and found an inverse association between frailty and  $\alpha$ -diversity of the microbiome.<sup>32</sup> *Eggerthella lenta* and *Eubacterium dolichum* were more abundant in frail individuals, whereas *Faecalibacterium prausnitzii*, a common producer of butyrate, was less abundant in frail individuals.<sup>32</sup> Similar trends were observed in patients with chronic kidney disease, in whom frailty was associated with a higher abundance of *Citrobacter* and *Coprobacillus* but a lower abundance of saccharolytic and butyrate-producing bacteria, including *F prausnitzii* and *Roseburia*.<sup>33</sup> A frail microbial pattern correlated with the presence of serum markers of inflammation.<sup>33</sup> However, of note, the association between microbial alterations and frailty is not restricted to very elderly individuals; findings have been similar in cohorts recruiting younger patients. Verdi and colleagues examined the gut microbiome in 1551 individuals older than 40 years.<sup>34</sup> A statistically significant inverse association was observed between frailty measured with the Fried Frailty Index and choice reaction time or verbal

fluency. Also noted was an inverse association between  $\alpha$ -diversity of the microbiome and the Deary-Liewald reaction time (DLRT) task. On a species level, an inverse association was found between an abundance of Burkholderiales and the DLRT task that remained robust after adjustment for frailty, suggesting both a frailty-dependent and a frailty-independent association of the microbiome with cognition.

Indirect support for the potentially causal role of the microbiome in frailty is derived from intervention studies demonstrating a beneficial effect of dietary or other therapies that modify the flora. In a clinical trial, Ghosh and colleagues used 16s rRNA methods to profile the fecal microbiome in 612 nonfrail or prefrail patients who received a 12-month-long Mediterranean diet intervention.<sup>35</sup> Adherence to the diet was associated with an attenuated loss of microbial diversity and an increase in anti-inflammatory organisms, such as *F. prausnitzii* and *Roseburia*. In contrast, levels of proinflammatory organisms, such as *Ruminococcus torques*, *Dorea formicigenerans*, and *Collinsella*, were inversely correlated with dietary adherence. Importantly, taxa that were positively correlated with the diet were more abundant in nonfrail individuals. Diet-responsive taxa were associated with serum high-sensitivity CRP, IL-18, sgp130, and adiponectin, illustrating that there was a correlation between the microbiome and these cytokines. Diet-responsive taxa were also inversely associated with reduced gait speed, higher Fried Frailty Index scores, reduced cognitive function, and frailty measured with handgrip strength. In a mouse model of aging, elevated serum levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and increased intestinal permeability were less striking in germ-free mice than in conventional mice.<sup>36</sup> In other research, prebiotic interventions decreased serum levels of CXCL11 and increased the abundance of Ruminococcaceae, *Parabacteroides*, and *Phascolarctobacterium* in frail older patients.<sup>37</sup>

### Frailty in Other Immune-Mediated Diseases

Most studies of inflammation and frailty have been conducted in the general population. Yet, by virtue of their protracted remitting-relapsing course and the often-young age of patients at onset, chronic immune-mediated diseases (IMDs) offer an attractive model of the time-varying, longitudinal effects of inflammation on frailty. Few studies have examined these effects; however, existing data suggest both a higher prevalence of frailty in patients with IMDs and occurrence at a younger age. In a cross-sectional analysis of 210 patients with rheumatoid arthritis, 17% were frail and 32% were prefrail.<sup>38</sup> Importantly, these percentages were higher than the 8% and 17% prevalence of frailty and prefrailty, respectively, in healthy controls.

The higher prevalence was observed in younger as well as older individuals. Among 100 patients with rheumatoid arthritis 18 to 65 years of age, only 55% were noted to be robust; 15% were frail and 30% were prefrail, rates strikingly similar to those in older patients with rheumatoid arthritis.<sup>39</sup> Specifically, a study of 60 patients with IBD (mean age, 40 years) matched with similar controls demonstrated significant levels of neurocognitive decline and impaired psychomotor function; these findings correlated with elevated CRP and reduced hemoglobin levels, both markers of inflammation.<sup>40</sup> Functional magnetic resonance imaging studies of patients with IBD, particularly those with active disease, revealed altered signaling in cingulate and parahippocampal regions that correlated with cognitive impairment.<sup>41</sup> Epidemiologic studies comparing patients with IBD and controls also suggested a 3-fold elevation in risk for dementia and onset 7 years earlier in patients with IBD.<sup>42</sup> Taken together, these studies highlight both the prevalence and effects of frailty in individuals with chronic IMDs.

### Clinical Studies of Frailty and Inflammatory Bowel Disease

One of the initial studies examining frailty in IBD was by Kochar and colleagues, who used the validated hospital frailty scale to define frailty in a cohort of 11,001 patients with IBD.<sup>9</sup> The prevalence of frailty increased from 4% among those aged 20 to 29 years to 25% in those 90 years of age and older. Importantly, frailty was independently associated with a nearly 3-fold increase in risk for death (OR, 2.90; 95% CI, 2.29-3.68) after adjustment for age, comorbidity, and disease severity. Separately, the authors also examined the effect of frailty on infections in the first year after anti-TNF- $\alpha$  or immunomodulator therapy.<sup>10</sup> In this study, 1299 patients were treated with an anti-TNF- $\alpha$  agent (5% of them frail in the 2 years prior) and 2676 patients were treated with an immunomodulator (7% of them frail in the 2 years prior). At follow-up, the presence of frailty before treatment independently increased the risk for posttreatment infection with an anti-TNF- $\alpha$  agent (OR, 2.05; 95% CI, 1.07-3.93) or immunomodulator (OR, 1.81; 95% CI, 1.22-2.70).

Faye and colleagues used the Nationwide Readmissions Database to examine the effect of frailty on rates of hospital admission and mortality.<sup>11</sup> Their study, comprising the years from 2010 to 2014, included 1,405,529 index admissions; of the admitted patients, 11% were considered frail according to the presence of relevant International Classification of Diseases-9 codes. Frailty was independently associated with both readmission (relative risk [RR], 1.16; 95% CI, 1.14-1.17) and readmission mortality (RR, 1.12; 95% CI, 1.02-1.23).<sup>11</sup> Using

the same database for the year 2013, Qian and colleagues similarly established that frailty conferred a 57% increase in the risk for mortality and a 22% increase in the risk for readmission in patients with severe IBD (adjusted hazard ratio, 1.22; 95% CI, 1.16-1.29).<sup>12</sup> The median duration of hospitalization was longer in frail than in nonfrail patients (9 vs 5 days), and the mean hospitalization costs of frail patients were almost \$7000 higher.<sup>12</sup>

The effect of frailty on postoperative outcomes has also been explored. Among all patients undergoing elective surgery, not just those with IBD, frailty doubled the risk for unplanned readmission after the procedure.<sup>43</sup> Frailty was also associated with an increased risk for complications (RR, 2.6). Specifically, Telemi and colleagues used data from the National Surgical Quality Improvement Program on 943 patients with UC who underwent colectomy.<sup>44</sup> Higher scores on the modified frailty index were associated with increased morbidity, septic complications, and cardiopulmonary complications. Frailty was also associated with significant increases in overall morbidity, Clavien class IV complications, and mortality.<sup>44</sup>

### Modifiability of Frailty in Inflammatory Bowel Disease and Other Immune-Mediated Diseases

Few studies have examined the effect of treating inflammation on frailty. Indirect evidence for such an effect can be derived from studies demonstrating an association between disease activity and frailty. Among 100 patients with rheumatoid arthritis in a prospective cohort, only 6.7% of those in remission were frail, compared with 46.7% of those with a moderate or high level of disease activity.<sup>38</sup> In a cohort of 1200 patients with IBD initiating anti-TNF- $\alpha$  therapy, frailty in the year before and the year following treatment was assessed by using a claims-based frailty model (unpublished data). Strikingly, the response to treatment was strongly correlated with posttreatment frailty. Patients who were nonresponders were 3 times more likely than responders to be frail in the year following treatment. Nearly 25% of those who had been frail in the year before treatment experienced a decrease in frailty of 50% or more, and 15% experienced a decrease of more than 100%. This effect was similar in younger and older patients, and in those with or without significant comorbidity. In an animal model, Thevaranjan and colleagues found elevated serum levels of IL-6 and TNF- $\alpha$  in old vs younger mice.<sup>36</sup> Elevated serum levels of TNF- $\alpha$  were associated with increased intestinal permeability and reduced killing of *Streptococcus pneumoniae* bacteria by macrophages. Age-related changes in the microbiome can be reversed by reducing serum TNF- $\alpha$  with TNF- $\alpha$  antagonist therapy.

Separately, indirect evidence suggests that treatment of IBD may have a beneficial effect on components closely related to frailty, including poor nutritional status, sarcopenia, and fatigue. In a cohort of patients with moderate-to-severe CD, up to one-third were undernourished before treatment.<sup>45</sup> Treatment with infliximab resulted in weight gain, with more than 90% of patients achieving a normal body mass index. Attainment of clinical remission was the strongest determinant of improvement in nutritional status. In randomized, controlled trials, treatment with infliximab and other TNF- $\alpha$  antagonists was associated with improved levels of serum albumin, another important marker of nutritional status. Both randomized, controlled trials and observational studies of cohorts have shown that in addition to restoration of normal weight, effective treatment is associated with an improved sense of well-being and reduced fatigue, both important correlates of frailty. In a small cohort of 19 individuals starting treatment with infliximab, reversal of sarcopenia with increases in muscle mass and muscle strength correlated with a decrease in serum IL-6.<sup>46</sup>

### Conclusion

The management of older patients with IBD requires an assessment of their functional status in addition to the characteristics of their disease to allow appropriate risk stratification. Frailty is an important measure of age-related decline, and its presence helps identify patients who may be more vulnerable to adverse health outcomes. It is important that clinicians caring for older patients with IBD familiarize themselves with the concept of frailty and the measures that facilitate an assessment of frailty in clinical practice. These include simple tools such as the clinical frailty scale as well as assessments of grip strength and gait speed. Whenever possible, efforts should be made to reduce frailty, such as by improving nutritional status and controlling inflammation, both of which contribute to several components of the frailty phenotype. Frailty should also be taken into consideration during selection of the appropriate therapeutic strategy. Frail patients in particular may benefit from more targeted immunosuppressive therapy to reduce the risk for infectious complications. The choice of a therapeutic strategy must also factor in the time to response because protracted inflammation itself can contribute to frailty. The multidisciplinary management of older patients with IBD is essential to ensure optimal patient outcomes.

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