SYSTEMATIC REVIEW AND META-ANALYSIS

Association Between Frailty or Sarcopenia and Adverse Outcomes in Inflammatory Bowel Disease: A Systematic Review

Katherine Bedard,[1] Naheed Rajabali,[2] Puneeta Tandon,[3] Juan G. Abraldes,[3] and Farhad Peerani[3]

[1]Department of Medicine, Faculty of Graduate Studies and Research, University of Alberta, Edmonton, Alberta, Canada; [2]Division of Geriatric Medicine, University of Alberta, Edmonton, Alberta, Canada; and [3]Division of Gastroenterology, University of Alberta, Edmonton Alberta, Canada

BACKGROUND AND AIMS: Chronological age often guides the management of patients with inflammatory bowel disease (IBD). Frailty and sarcopenia, which are related but distinct entities that become increasingly prevalent with age, better predict nonsurgical and surgical outcomes in various chronic illnesses. We conducted a systematic review to assess the association between frailty or sarcopenia and adverse nonsurgical outcomes in adult patients with IBD. **METHODS:** Through a systematic literature review of 4 online databases (MEDLINE, EMBASE, Scopus, and CINAHL Plus), we identified 16 studies that focused on frailty or sarcopenia and nonsurgical outcomes in IBD. The Newcastle-Ottawa Scale was used to determine the quality of included studies. **RESULTS:** We identified 16 studies: 8 frailty-based and 8 sarcopenia-based studies (14 high-quality and 2 low-quality studies). All results were presented in a summarized narrative format. Frailty predicted all hospitalization-related outcomes (hospitalization, readmission, and length of stay) and mortality-related outcomes. The outcomes of therapeutic efficacy, need for therapy escalation, and infections had mixed results in relation to their association with frailty or sarcopenia. The data regarding sarcopenia and hospitalizations were also equivocal. **CONCLUSION:** This systematic review supports the use of frailty indices to predict hospitalization- and mortality-related outcomes in adult patients with IBD. Future research should focus on identifying and validating frailty and sarcopenia tools in IBD to better help predict adverse clinical outcomes and response to therapy.

Keywords: Crohn's Disease; Ulcerative Colitis; Myopenia; Reduced Function

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is an autoimmune condition of the gastrointestinal tract that likely results from an interplay between environmental triggers and an aberrant immune response in a genetically predisposed individual.[1] IBD has a bimodal distribution of incidence, with 10%–15% of new diagnoses occurring after the age of 60 years. Although older patients with IBD

generally have less complicated disease behavior, they have similar or even higher rates of surgery compared with younger-onset patients with IBD which may relate to decreased utilization of immunosuppression or even lower rates of response to antitumor necrosis factor (anti-TNF) therapies.[2] The management of IBD based on chronological age alone is inadvisable given that chronological age does not reflect "biological age" or the extent of physiological reserve an individual may have to endure stress from both the disease and various treatment strategies.[3] Emerging data suggest that measures reflecting biological age, such as frailty and sarcopenia, can act as prognosticating markers and provide nuanced information required for optimal clinical decision-making.[4]

Frailty is a term that represents a decline in multiple physiological systems that results in vulnerability after a stressor event,[5] whereas sarcopenia is defined by low muscle strength and low muscle quantity or quality.[6] Although frailty and sarcopenia are distinct concepts, sarcopenia represents the physical phenotype of frailty.[7] In the non-IBD patient population, frailty is associated with outcomes including falls, disability, hospitalizations, increased care requirements, and mortality.[5] Within the field of IBD, frailty and sarcopenia have primarily been evaluated in the context of surgery and postoperative complications.[8] In light of the increasing prevalence of elderly patients living with IBD,[9] there has been a recent interest in exploring the impact of frailty and sarcopenia on nonsurgical outcomes in
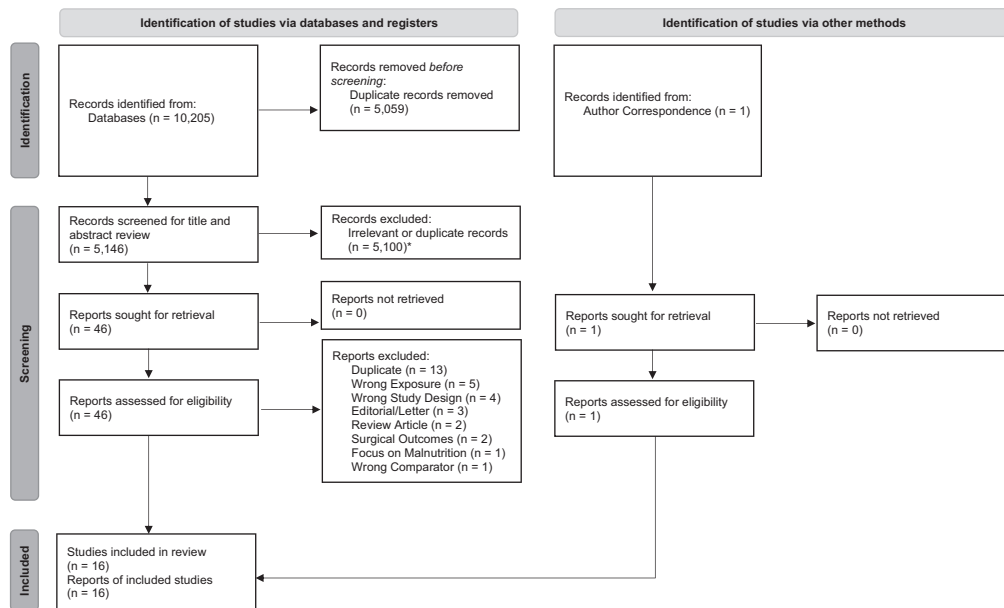
Figure. PRISMA flowchart demonstrating search results and the study selection process. *Focus on nutritional exposure (n = 12); focus on surgical outcomes (n = 16); focus on both nutritional exposure and surgical outcomes (n = 5). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

IBD.[10–13] Therefore, we aimed to summarize the existing literature to help inform the clinical care of all adult patients with IBD and guide future prospective studies in frailty and sarcopenia.

Materials and Methods

This systematic review adhered to the Meta-analyses of Observational Studies in Epidemiology reporting guidelines[14] when applicable and an a priori published protocol.[15] A Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart is provided in Figure, which demonstrates the manuscript selection process for this review.[16]

Search Strategy

We searched 4 online databases through to June 18, 2021 (MEDLINE [1946 Onward], EMBASE, Scopus, and CINAHL Plus [with Full Text]) using synonyms of IBD alongside search terms for both frailty and sarcopenia. While MEDLINE (1946 Onward) and EMBASE were accessed through Ovid, Scopus was accessed through Elsevier, and CINAHL Plus (with Full Text) was accessed through EBSCOhost. The following search terms were utilized: (IBD OR Crohn* OR inflammatory bowel disease* OR ulcerative colitis) AND (frail* OR sarcopenia OR comorbid* OR Karnofsky OR Charlson OR Edmonton Frailty OR Fried* OR accumulation of deficits OR comprehensive geriatric assessment) AND (infection* OR mortality OR morbidity OR hospital* OR readmission* OR complication* OR thromb* OR outcome* OR cancer OR malignan* OR death* OR fatal*). Comorbidities were included as a measurement of frailty if they were reported as a Charlson comorbidity index (CCI) score or were included as part of a validated frailty index. Furthermore, only studies in which the assessment of frailty or sarcopenia was specified as the primary aim of the study were included because the reported effect estimates of frailty and sarcopenia when these were not the primary exposure do not have a direct interpretation (i.e., the concept of "Table 2 fallacy").[28] No

restrictions were put on language or publication date, and both full articles and abstracts were included. Conference abstracts published between 2015 and 2020 from the European Crohn's and Colitis Organization, Advances in IBD, and Digestive Disease Week were searched for using the respective journals and conference archives. The references of systematic reviews on the topic published within the last 5 years and the references of included articles were also manually searched. Two reviewers (K.B. and F.P.) independently screened the title and abstract of studies identified in the primary search after duplicates were removed. The full texts of remaining manuscripts and abstracts were then assessed to determine if they met inclusion criteria. Any disagreement was resolved by consensus with a third reviewer (J.G.A.).

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) peer-reviewed observational case-controlled, retrospective, or prospective studies and randomized controlled trials including IBD participants and published in full manuscript or abstract form, (2) articles that assessed frailty or sarcopenia where frailty was defined by either an aspect of the Fried phenotype model[7] of frailty or the cumulative deficit model[5,29] of frailty and where sarcopenia was defined by low muscle quantity or quality,[6] (3) articles that focused on the impact of frailty or sarcopenia on nonsurgical outcomes, (4) articles where frailty or sarcopenia were identified as the primary aim of the study, and (5) articles that included a control cohort of patients with IBD without frailty or sarcopenia. We excluded studies that were (1) cross-sectional observational studies, (2) secondary articles, letters to the editor, or case reports, (3) studies that focused on pediatric (<18 years) patients with IBD or non-IBD patients, and (4) studies that primarily focused on the impact of malnutrition.

Outcomes

We analyzed adverse nonsurgical outcomes in this systematic review including infections, mortality rates,

Table 1. Characteristics of the Frailty-based Eligible Studies

Reference	Type of study	Number, type of participants	IBD type	Frailty tool	Outcome(s)	Follow-up duration (IQR)
Asscher et al, 2020[31]	Multicenter prospective cohort	410, outpatients	UC, CD, IBD-U	CCI[17]	Infections, hospitalizations, medication-related adverse events, discontinuation of IBD therapy, clinical effectiveness outcomes	Median of 102.40 wk (52–104 wk)
Bertani et al, 2020[33]	Multicenter prospective cohort	80, inpatients and outpatients	UC, CD	Reduced serum T3/T4 ratio[18]	Mucosal healing, clinical remission	54 wk
Faye et al, 2021[11]	Multicenter retrospective cohort	1,405,529, inpatients	UC, CD	Presence of at least 1 ICD-9-CM code derived from Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses[19]	30-d hospital readmission, 30-d readmission mortality, length of stay	30 d after index admission
Gondal et al, 2020[32]	Single-center retrospective cohort	2978, unknown	UC, CD, IBD-U	7-factor IBD frailty index >0.27 (derived from CSHA frailty index)[20]	Mortality, frequency of flares	Unknown
Kochar et al, 2020[34]	Multicenter retrospective cohort	3975, inpatients and outpatients	UC, CD	Adaptation of the Hospital Frailty Risk Score[21] (presence of at least 1 frailty-related ICD-9 code)	Infections, infection-related hospitalizations	Anti-TNF cohort: Median for frail 12 mo (7–17 mo), Median for fit 7 mo (4–14 mo); immunomodulator cohort: median for frail 11 mo (6–18 mo), Median for fit 8 mo (4–14 mo)
Kochar et al, 2020[36]	Multicenter retrospective cohort	11,001, inpatients and outpatients	UC, CD	Adaptation of the Hospital Frailty Risk Score[21] (presence of at least 1 frailty-related ICD-9 code)	Mortality	Median for frail 10.90 y (5.10–17.90 y), Median for fit 7.70 y (3.10–14.40 y)
Qian et al, 2020[35]	Multicenter retrospective cohort	47,402, inpatients	UC, CD	Hospital Frailty Risk Score[21] ≥5	Inpatient mortality, readmissions, unplanned hospitalizations	Median for frail 10 mo (8–11 mo), Median for fit 10 mo (7–11 mo)
Singh et al, 2020[13]	Multicenter retrospective cohort	5987, inpatients and outpatients	UC, CD	Hospital Frailty Risk Score[21] ≥5	Infections requiring hospitalization	Mean for frail 11.60 ± SD 10.20 mo, Mean for fit 16.30 ± SD 14.70 mo

CSHA, Canadian Study of Health and Aging; IBD-U, inflammatory bowel disease type unclassified; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

hospitalizations, hospital readmissions, length of hospital stays, frequency of flares, therapeutic response, clinical remission, mucosal healing, and addition or modification of IBD-related medications. For studies that reported on both nonsurgical and surgical outcomes, only nonsurgical outcomes were assessed.

Data Extraction and Quality Assessment

The following information was extracted: (1) study characteristics: publication date and journal, lead author contact details, funding sources, conflicts of interest for authors, location of study, period during which data were collected, aim of study, study design, follow-up duration; (2) patient characteristics: IBD subtype, mean age, sample size, inclusion and exclusion criteria, inpatient or outpatient; (3) exposure: method(s) used for frailty or sarcopenia detection; and (4) outcomes: measurement(s) and description of nonsurgical outcomes. A narrative synthesis method was used to summarize the results. The heterogeneity of the outcomes and the respective analyses performed prevented us from conducting a meta-analysis. The Newcastle-Ottawa Scale was utilized to assess study quality, with the results of these assessments displayed in Table A1.[30] Studies earning a score ≥6 were considered to be high quality. Both data extraction and quality assessment were completed by 2 reviewers (K.B. and F.P.) using a standardized data collection form. When data were unclear or missing, the reviewer (K.B.) contacted the primary study authors for clarification.

Results

We identified 16 studies: 8 frailty-based and 8 sarcopenia-based studies (Figure). Two were prospective and 14 were retrospective observational studies including 9 North American cohorts, 3 Asian cohorts, 3 European cohorts, and one Australian cohort. Additional characteristics of the studies are displayed in Tables 1 and 2, as well as Tables A2 and A3. Study sample sizes ranged between 23 and 1,405,529 patients with all but 2 studies being rated as high quality (Table A3). With respect to study selection, there were no disagreements between the primary 2 reviewers, which required consulting a third reviewer.

Frailty-based

Therapeutic Efficacy and Escalation. Asscher et al[31] conducted clinical efficacy analyses only on patients with active IBD at baseline defined by either a Harvey Bradshaw Index >4 or a Simple Clinical Colitis Activity Index >2. CCI scores were not associated with clinical remission, clinical response, corticosteroid-free clinical remission, combined biochemical and clinical remission, or biologic treatment persistence. Gondal et al[32] focused specifically on disease flares as an adverse outcome. Multivariable regression analysis revealed that frailty did not predict the risk of patients experiencing >5 IBD flares or relapses (odds ratio [OR] 1.20, 95% confidence interval [CI]

0.99–1.45, $P = .05$). In contrast to these findings, Bertani et al,[33] who defined frailty as a reduction in the triiodothyronine/thyroxine (T3/T4) ratio of individuals, demonstrated that a higher T3/T4 ratio was associated with a higher likelihood of mucosal healing (OR per unit increase: 6.4, 95% CI 2.9–14.3, $P < .0001$). Furthermore, the T3/T4 ratio was effective in predicting clinical remission, and for each unit increase from the baseline T3/T4 ratio, the OR was 8.80 (95% CI 3.5–22.0, $P < .0001$).

Infections. The risk of developing serious infections in patients on anti-TNF and vedolizumab was studied by Singh et al[13] who defined frailty using the Hospital Frailty Risk Score. Although frail patients were 1.9-times more likely to be at risk of serious infections (hazard ratio [HR] 1.90, 95% CI 1.60–2.27, $P < .01$), after adjusting for potential confounders, frailty was not independently associated with an increased risk of developing serious infections (adjusted HR [aHR] 1.12, 95% CI 0.93–1.36, $P = .23$). Age greater than 60 years was, however, independently associated with serious infections (aHR 2.24, 95% CI 1.72–2.90, $P < .01$). When patients were stratified by exposure to biologic medications, those with frailty on vedolizumab had a 1.7-times higher risk of developing serious infections (aHR 1.69, 95% CI 1.03–1.79, $P = .039$), whereas those with frailty on anti-TNF therapy were not at increased risk of serious infections (aHR 1.03, 95% CI 0.83–1.27, $P = .81$). Asscher et al had similar findings where CCI scores were not found to be associated with the occurrence of infections during treatment in the global series (OR 1.277, 95% CI 0.998–1.634, $P = .052$). However, in the subgroup of patients treated with vedolizumab (in comparison with ustekinumab), the CCI was found to be independently associated with the development of any infection during biologic treatment (OR 1.387, 95% CI 1.022–1.883, $P = .032$).[31] Furthermore, the CCI was not associated with adverse events (OR 1.228, 95% CI 0.963–1.567, $P = .098$) or treatment discontinuation (OR 1.444, 95% CI 0.920–2.267, $P = .110$).

Finally, Kochar et al[34] explored the development of infections in relation to the presence of frailty as measured by the Hospital Frailty Risk Score. Contrary to the results published by Asscher et al and Singh et al, those who were frail before the initiation of anti-TNF therapy had a higher risk of infection (adjusted OR [aOR] 2.05, 95% CI 1.07–3.93). The presence of at least one comorbidity was also found to be an independent predictor of infections in the frail population before initiating anti-TNF medication (aOR 3.21, 95% CI 1.79–5.76). There were too few patients in the anti-TNF cohort to perform a sound analysis; however, a difference was still reported between the infection-related hospitalization rates of frail and fit patients (9% vs 5%, aOR 1.51, 95% CI 0.62–3.66, $P = .19$). Similarly, patients with IBD who were frail before immunomodulator initiation had an increased risk of infection (aOR 1.81, 95% CI 1.22–2.70) with the presence of

Table 2. Characteristics of the Sarcopenia-based Eligible Studies

Reference	Type of study	Number, type of participants	IBD type	Sarcopenia tool	Outcome(s)	Follow-up duration
Adams et al, 2017[38]	Single-center retrospective cohort	90, unknown	UC, CD	CT image at L3 (cutoff points <38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men[22]; skeletal muscle tissue density of −29 to +150 HU)	Hospital admissions, need for new biologics	24 wk
Bamba et al, 2020[12]	Single-center retrospective cohort	187, inpatients	UC, CD	CT image at L3 (cutoff points <38 cm^2/m^2 for women and <42 cm^2/m^2 for men; skeletal muscle tissue density of −29 to +150 HU)[23]	Prolonged LOS (≥30 d)	61–1503 d
Campbell et al, 2020[40]	Single-center retrospective cohort	98, inpatients and outpatients	UC, CD, IBD-U	CT or MRI scans at L3 (cutoff points <38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men)	Infections, hospitalizations, clinical response	Unknown (within 1 y of biologic initiation)
Cushing et al, 2018[39]	Single-center retrospective cohort	89, inpatients	UC	CT images at L3 (cutoff points <39 cm^2/m^2 for women and <55 cm^2/m^2 for men[24]; skeletal muscle tissue density of −30 to +150 HU)	Failure to respond to IVS	Unknown (however, based on outcome likely 3–7 d from time of index hospitalization)
Ge et al, 2021[10]	Single-center retrospective cohort	23, unknown	UC	CT images at L3 (cutoff point SMI < the lowest sex-specific quartile)[25]	Failure to respond to IVS	5 d
Grillot et al, 2020[41]	Single-center retrospective cohort	88, inpatients	CD	CT images at L3 (cutoff points <38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men)[26]	Recurrent hospitalizations, abscess(es), use of anti-TNFα therapy, change or dose optimization of anti-TNFα therapy	Median for sarcopenic, 25.20 ± SD 21.60 mo; Median for nonsarcopenic, 18.00 ± SD 17.20 mo
Holt et al, 2017[37]	Single-center retrospective cohort	68, unknown	UC, CD	CT or MRI images at L3 (cutoff point < gender-specific median skeletal muscle area)	Treatment failure (postinduction hospital admission for IBD, escalation of anti-TNFα dose or immunosuppressants, emergence of a new fistula, rising CDAI >150)	Mean 809.80 ± SD 664.30 d
Lee et al, 2020[42]	Single-center retrospective cohort	79, unknown	CD	CT images at L3 (cutoff points <31 cm^2/m^2 for women and <49 cm^2/m^2 for men)[27]	Hospitalizations, first prescription of biologics, immunomodulators, or corticosteroids	Median 34.80 mo

CDAI, Crohn's Disease Activity Index; HU, Hounsfield unit; IBD-U, inflammatory bowel disease unclassified; IVS, intravenous corticosteroids; L3, third lumbar spine vertebra; SD, standard deviation.

comorbidity also independently predicting infection risk (aOR 7.26, 95% CI 3.79–13.91). Infection-related hospitalization rates after immunomodulator initiation were found to be significantly higher in frail patients than those in fit patients (13% vs 5%, aOR 2.08, 95% CI 1.33–3.26, $P < .01$).

Hospitalizations. Asscher et al[31] determined that CCI scores were independently associated with an increased risk of at least one hospitalization during treatment in both the vedolizumab (aOR 1.586, 95% CI 1.127–2.231, $P = .008$) and ustekinumab groups (aOR 1.623, 95% CI 1.035–2.546, $P = .035$). Conversely, age at baseline was not associated with hospitalizations in either vedolizumab- (aOR 0.986, 95% CI 0.958–1.014, $P = .313$) or ustekinumab-treated patients (aOR 0.986, 95% CI 0.951–1.021, $P = .418$). A subgroup analysis revealed that although the CCI was associated with IBD, infection, or malignancy-related hospitalizations in the ustekinumab group (aOR 1.625, 95% CI 1.002–2.634, $P = .049$), there was no association in the vedolizumab group (aOR 1.388, 95% CI 0.933–2.066, $P = .105$).

Qian et al[35] found that frailty, as defined by the Hospital Frailty Risk Score, remained an independent predictor of both 6-month readmissions (aHR 1.21, 95% CI 1.17–1.25, $P < .01$) and 6-month severe IBD-related hospitalizations (aHR 1.22, 95% CI 1.16–1.29). Annually, frail patients also spent more time in the hospital than nonfrail patients (9 days [interquartile range {IQR} 4–18 days] vs 5 days [IQR 3–10 days], $P < .01$). Similarly, Faye et al[11] found an association between frailty and an increased risk of 30-day hospital readmissions (adjusted risk ratio [aRR] 1.16, 95% CI 1.14–1.17, $P < .01$). After malnutrition, weight loss, and fecal incontinence were removed from the frailty-defining International Classification of Disease (ICD) 9 codes, frailty remained an independent predictor of hospital readmissions (aRR 1.07, 95% CI 1.04–1.10). Finally, the presence of any number of comorbidities was found to be independently associated with an increase in the 30-day readmission risk (aRR 1.10, 95% CI 1.09–1.12, $P < .01$).

Mortality. Gondal et al[32] reported that frail patients possessed a higher risk of mortality than nonfrail patients (OR 1.52, 95% CI 1.07–2.16, $P = .01$). Similarly, Qian et al[35] demonstrated that frailty, as defined by the Hospital Frailty Risk Score, remained an independent predictor of inpatient mortality (aHR 1.57, 95% CI 1.34–1.83, $P < .01$). Next, Kochar et al[36] reported that the mortality rate of frail patients was nearly 3 times higher than nonfrail patients (aOR 2.90, 95% CI 2.29–3.68).

Finally, the results by Faye et al[11] supported the findings from the abovementioned studies, where frailty was found to be associated with the 30-day readmission mortality rate of patients (aRR 1.12, 95% CI 1.02–1.23, $P = .02$). Interestingly, when stratified by IBD subtype, this association remained for frail patients with UC (aRR 1.32, 95% CI 1.13–1.55, $P < .01$), but not frail patients with CD (aRR 1.09, 95% CI 0.97–1.22, $P = .14$). On multivariable analysis (aRR 1.26, 95% CI 1.07–1.49, $P < .01$), the presence of at least 2 comorbidities was also an independent predictor of the 30-day readmission mortality rate of all patients.

Sarcopenia-based

Therapeutic Efficacy and Escalation. Holt et al[37] found that sarcopenic patients, defined as those with skeletal muscle areas less than the gender-specific median, had a shorter median time to therapy failure (520 ± standard deviation 135 days) than nonsarcopenic patients (1100 ± standard deviation 151 days), HR 2.062, 95% CI 1.068–3.980, $P = .031$. This trend extended to 24 months where 61.7% of sarcopenic patients lost response compared with 27.6% of nonsarcopenic patients (OR 0.25, 95% CI 0.09–0.70, $P = .014$). Failure of therapy was defined by a composite outcome including postinduction hospitalization or surgery for IBD, escalation of the anti-TNF dose or immunomodulator for clinical loss of response, presence of a new fistula, or a CD Activity Index >150. Similarly, Adams et al[38] determined that the cohort of patients without sarcopenia saw a reduction in Harvey Bradshaw Index scores (−2.3, $P = .004$), whereas the sarcopenic cohort did not experience this reduction (+0.4, $P = .80$). In the study conducted by Ge et al,[10] an independent association was reported between the presence of sarcopenia, as determined through the use of previously defined muscle mass cutoff points specific to the level of the third lumbar spine vertebra (L3), and the failure of intravenous corticosteroid therapy for the hospitalized patients with acute severe UC (OR 3.130, 95% CI 1.609–6.087, $P = .001$). Similarly Cushing et al[39] demonstrated that sarcopenia independently predicted failure of intravenous corticosteroid therapy for hospitalized patients with acute severe UC (OR 3.98, 95% CI 1.12–14.1, $P = .033$). In contrast to these findings, Campbell et al[40] failed to find any association between sarcopenia and the clinical response to therapy in those over 50 years of age.

With respect to therapy escalation, Grillot et al[41] also failed to find any difference between sarcopenic and nonsarcopenic patients in relation to the need to start (54% vs 41.7%, $P = .259$), switch (16.3% vs 33.3%, $P = .067$), or optimize (45.8% vs 38.9%, $P = .524$) anti-TNF medications. Similarly, Lee et al[42] determined that there was no association between sarcopenia, defined using Korean-specific skeletal muscle index (SMI) cutoff values, and the first prescription of biologics (infliximab or adalimumab, $P = .481$), immunomodulators ($P = .370$), or corticosteroids ($P = .842$). Finally, univariable analysis in the study by Adams et al[38] failed to reveal an association between sarcopenia and the need for new biologic medication after anti-TNF initiation.

Infections. Two studies focused specifically on the relationship between sarcopenia and the presence of infections. Grillot et al[41] determined through univariable

analysis that sarcopenic patients more frequently developed abscesses than nonsarcopenic patients (51.0% vs 16.7%, $P = .001$); however, this was not significant after multivariable analysis. In contrast, although Campbell et al[40] did not find an association between the presence of sarcopenia in the entire cohort and an increased risk of developing infections (HR 1.42, 95% CI 0.75–2.68, $P = .278$), when patients were stratified by age, those ≥ 50 years with sarcopenia were 6 times more likely to have infections (HR 5.78, 95% CI 1.27–26.37, $P = .023$). This association remained when disease duration and concomitant steroid use were controlled for (HR 6.90, 95% CI 1.34–35.54, $P = .021$).

Hospitalizations. Bamba et al[12] explored prolonged hospital length of stay (LOS) in relation to sarcopenia, where multivariable analysis showed that a low psoas muscle index (PMI) on admission to the hospital was found to be associated with a prolonged LOS (HR 0.662, 95% CI 0.480–0.883, $P = .004$). When stratified by IBD subtype in univariable analysis, both a low SMI and a low PMI were associated with an increased LOS in patients with CD (SMI: HR 0.942, 95% CI 0.894–0.992, $P = .020$; PMI: HR 0.648, 95% CI 0.489–0.858, $P < .001$), whereas only a low PMI was predictive of a prolonged LOS in patients with UC (HR 0.707, 95% CI 0.505–0.989, $P = .028$). Although Grillot et al[41] demonstrated that sarcopenic patients experienced a higher number of hospitalizations than those without sarcopenia (61.2% vs 36.1%, $P = .022$), this association was not significant on multivariable analysis.

Similarly, Adams et al[38] used univariable analysis and found no significant difference between the hospitalization rates of sarcopenic and nonsarcopenic patients ($P = .60$). Finally, Lee et al[42] replicated these findings, as no association was found between sarcopenia and cumulative hospitalization-free survival ($P = .772$).

Discussion

In this systematic review, we summarized the findings from 16 studies that explored the impact of frailty or sarcopenia on nonsurgical outcomes in patients with IBD. Although the frailty and sarcopenia tools were diverse and the clinical outcomes varied, some meaningful observations were made. Although frailty was measured by the Canadian Study of Health and Aging Frailty Index,[20] the Hospital Frailty Risk Score,[21] the CCI,[17] the Johns Hopkins Adjusted Clinical Groups Frailty Indicator,[19] and the T3/T4 ratio,[18] sarcopenia was primarily defined by SMI cutoffs at the L3 vertebral level on CT or MRI.[22,27,43] Frailty predicted hospitalization, readmission, LOS, and mortality, whereas the data regarding sarcopenia and hospitalizations were equivocal. Moreover, the outcomes of therapeutic efficacy, need for therapy escalation, and infections had mixed results in relation to their association with frailty or sarcopenia. Summarizing the current knowledge makes it evident that frailty and sarcopenia are important yet understudied

prognostic tools within IBD that have thus far been primarily investigated to predict surgical outcomes.[8]

Although there exist 2 main conceptual models for frailty—the phenotype model and cumulative deficit model—there is no gold standard to define frailty. The current available literature concerning frailty in IBD and nonsurgical outcomes utilizes frailty tools that most closely resemble the cumulative deficit model either directly or indirectly (ie, the T3/T4 ratio correlates with the Multidimensional Geriatric Assessment and Multi Prognostic Index)[18] as well as sarcopenia measurements that reflect the physical phenotype of frailty. Other facets of frailty including malnutrition, mental health, and cognitive impairments were not specifically explored in this systematic review unless they were included in a frailty tool that incorporated the cumulative deficit model. Two recent systematic reviews have explored components of the comprehensive geriatric assessment[44] and malnutrition[45] on IBD outcomes, and both call for further research given the heterogeneity of the studies. Finally, although the CCI was not originally developed as a frailty index, we included the CCI as a frailty tool as other validated frailty indices incorporate comorbidities as a major component of their score.[5]

Most frailty-based articles used a modified version of frailty indices originally developed using elderly participants, and none have been validated for the patient population with IBD.[13,32,34–36] While the Hospital Frailty Risk Score was developed based on ICD-10 codes in hospitalized patients aged 75 years or older,[21] the John Hopkins Adjusted Clinical Groups Frailty Indicator used ICD-10 codes to predict health care utilization and costs,[19] and the Canadian Study of Health and Aging Frailty Index was derived from a prospective cohort of patients aged 65 years or older focusing on 70 frailty items.[20] Unfortunately, Gondal et al[32] did not clarify how they modified the Canadian Study of Health and Aging Frailty Index. Furthermore, the Hospital Frailty Risk Score was the most commonly included frailty tool; however, its use was not standardized across the studies. For example, it was adapted by all 3 authors using ICD-9 codes instead of ICD-10 codes used in the original score. While 2 studies by Kochar et al classified frailty based on the presence of any ICD defining the frailty code,[34,36] Qian et al and Singh et al both modified the score and assigned patients a designation of being fit (frailty risk score <5) or frail (frailty risk score ≥ 5).[13,35] Furthermore, the most common ICD frailty codes captured across the studies include diagnoses that may more accurately reflect manifestations of active IBD rather than frailty ("malnutrition", "weight loss", "hypokalemia", "dehydration", "joint pain", "disorders of fluid electrolyte and acid-base balance", "other and unspecified anemias", "acute renal failure", "protein energy malnutrition"). While Faye et al and Kochar et al conducted sensitivity analyses to control for this, Singh et al and Qian et al did not.[11,13,34–36]

Similar to the frailty tools, there are limitations to the sarcopenia measurements used as they do not truly reflect

the definition of sarcopenia as espoused by the European Working Group on Sarcopenia in Older People 2. European Working Group on Sarcopenia in Older People 2 defines sarcopenia as low muscle quantity or quality along with a measure of muscle function or strength, whereas all sarcopenia studies lacked a component of muscle function or strength. The most readily available screening tool to assess for sarcopenia in patients with IBD was derived from analyzing the lumbar muscle cross-sectional area at L3 by CT. Only one study utilized the cross-sectional area at L3 by MRI, and another study adopted the PMI. Moreover, the cutoffs used to define sarcopenia also varied among studies. Although 4 articles reported either identical or very similar definitions for sarcopenia (<38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men[38,40,41] or <39 cm^2/m^2 for women and <55 cm^2/m^2 for men),[39] the remaining 4 articles used quite variable definitions. One article cited <38 cm^2/m^2 for women and <42 cm^2/m^2 for men,[12] another specified <31 cm^2/m^2 for women and <49 cm^2/m^2 for men,[42] a third determined the appendicular SMI of each individual comparing them to the gender-specific SMI medians,[37] and a fourth stated an SMI less than that of the lowest sex-specific quartile, with no values given.[10] These definitions were based on SMI values from multiple different populations; however, none were specific to patients with IBD. Finally, there was a lack of standardized protocols for scan acquisition with 6 different software types being utilized,[10,12,37,39,41,42] and one study failed to disclose which software was used.[40]

In spite of the limitations in the current literature, our systematic review identified knowledge gaps that can be addressed in the future. First, most studies that evaluated sarcopenia or frailty in the context of immunosuppression focused on anti-TNF therapy: 5 with anti-TNF,[13,33,34,37,38] 3 with vedolizumab,[13,31,33] and 1 with ustekinumab.[31] Clinical outcomes in patients on biologic and small-molecule therapies may be differentially affected by sarcopenia or frailty. For example, Asscher et al[31] demonstrated that the CCI was significantly associated with any infection during treatment in vedolizumab-treated patients (OR 1.387, 95% CI 1.022–1.883, $P = .036$) but not with ustekinumab-treated patients (OR 1.134, 95% CI 0.720–1.788, $P = .587$). Similarly, Singh et al[13] showed that frailty was associated with a 1.7-fold increased rate of serious infections in vedolizumab-treated patients (HR 1.69, 95% CI 1.03–1.79, $P = .039$), but not with anti-TNF–treated patients (HR 1.03, 95% CI 0.83–1.27, $P = .81$). The authors postulate that this association may relate to selection bias in terms of which patients are preferentially placed on vedolizumab. Second, the effect of sarcopenia or frailty on nonsurgical IBD outcomes may differ depending on the IBD subtype. Bamba et al[12] reported that although a low SMI was associated with prolonged LOS in patients with CD (HR 0.942, 95% CI 0.894–0.992, $P = .02$), it was not associated with prolonged LOS in patient with UC (HR 0.958, 95% CI 0.905–1.015, $P = .121$). Furthermore, Faye et al[11] illustrated that frailty increased

the risk of readmission mortality in patients with UC (aRR 1.32, 95% CI 1.13–1.55, $P < .01$) but not in patients with CD (aRR 1.09, 95% CI 0.97–1.22, $P = .14$). Third, no study adequately controlled for disease severity or phenotype, but rather surrogate markers of disease activity were used such as the need for endoscopy. It is evident that disease severity and phenotype affect the natural history of IBD as well as response to therapy,[46,47] and this can only be captured in prospective cohorts with well-defined phenotypes.

In summary, although the effect of sarcopenia and frailty on most adverse nonsurgical outcomes in patients with IBD is equivocal, frailty predicts hospitalizations and mortality mirroring other chronic disease states.[48–50] Building on the clinical review published recently by Faye and Colombel[51] as well as the systematic review by Asscher et al,[44] our systematic review summarizes the outcomes on therapeutic efficacy, contrasts and compares in greater detail the frailty measures utilized, and describes the impact of sarcopenia on IBD outcomes. Admittedly, frailty and sarcopenia are challenging concepts to study as they overlap with various entities including immunosenescence, malnutrition, comorbidities, social determinants of health, cognition, and mental health. Furthermore, retrospective studies of frailty based on administrative health databases are potentially limited by misclassification bias as well the fact that diagnostic coding does not take into account how a clinician weighs the various aspects of frailty for an individual patient.[52,53] Prospective studies utilizing standardized definitions of frailty and sarcopenia are needed with well-defined clinical outcomes such as response to therapy, adverse events, and hospitalizations. Future prospective studies could consider incorporating the Clinical Frailty Scale as it is easy to administer and relies on clinical judgment, potentially increasing its usability.[54,55] Furthermore, sarcopenia studies would benefit from including not only a measure of muscle quantity or quality but also a measure of muscle strength or function such as handgrip strength or gait speed assessments.[56,57] The ultimate goal is to identify complete measures or markers of biological age or physiological reserve, while validating existing measures such as frailty and sarcopenia tools in the patient population with IBD to tailor care not only for the elderly, but for all patients with IBD.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2021.11.009.

References

1. Abraham C, Cho J. Inflammatory bowel disease. N Engl J Med 2009;361:2066–2078.
2. Ananthakrishnan AN, Shi HY, Tang W, et al. Systematic review and meta-analysis: phenotype and clinical outcomes of older-onset inflammatory bowel disease. J Crohns Colitis 2016;10:1224–1236.

3. Sturm A, Maaser C, Mendall M, et al. European Crohn's and Colitis Organisation topical review on IBD in the elderly. J Crohns Colitis 2017;11:263–273.

4. Bellone F, Sardella A, Muscianisi M, et al. Fatigue, sarcopenia, and frailty in older adults with inflammatory bowel disease. Minerva Gastroenterol (Torino) 2021.

5. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013;381:752–762.

6. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:601.

7. 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–M157.

8. Lightner AL, Regueiro M, Click B. Special considerations for colorectal surgery in the elderly IBD patient. Curr Treat Options Gastroenterol 2019;17:449–456.

9. 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.

10. Ge X, Jiang L, Yu W, et al. The importance of sarcopenia as a prognostic predictor of the clinical course in acute severe ulcerative colitis patients. Dig Liver Dis 2021;53:965–971.

11. 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 2021;66:4178–4190.

12. Bamba S, Inatomi O, Takahashi K, et al. Assessment of body composition from CT images at the level of the third lumbar vertebra in inflammatory bowel disease. Inflamm Bowel Dis 2021;27:1435–1442.

13. 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 2021;27:1626–1633.

14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology A proposal for reporting. JAMA 2000;283:2008–2012.

15. Bedard K, Tandon P, Rajabali N, et al. The association between frailty/sarcopenia and adverse non-surgical outcomes in adults with inflammatory bowel disease: a systematic review. PROSPERO: international prospective register of systematic reviews. 2021. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234969. Accessed March 5, 2021.

16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

17. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–1251.

18. Pasqualetti G, Calsolaro V, Bernardini S, et al. Degree of peripheral thyroxin deiodination, frailty, and long-term survival in hospitalized older patients. J Clin Endocrinol Metab 2018;103:1867–1876.

19. Abrams C, Lieberman R, Weiner JP. Development and evaluation of the Johns Hopkins University risk adjustment models for Medicare+ choice plan payment. The Johns Hopkins University, 2003. https://www.hopkinsacg.org/document/development-and-evaluation-of-the-johns-hopkins-university-risk-adjustment-models-for-medicare-choice-plan-payment/. Accessed March 15, 2021.

20. Rockwood K, Stadnyk K, MacKnight C, et al. A brief clinical instrument to classify frailty in elderly people. Lancet 1999;353:205–206.

21. 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.

22. Zhang T, Cao L, Cao T, et al. Prevalence of sarcopenia and its impact on postoperative outcome in patients with Crohn's disease undergoing bowel resection. JPEN J Parenter Enteral Nutr 2017;41:592–600.

23. Nishikawa H, Shiraki M, Hiramatsu A, et al. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res 2016;46:951–963.

24. Zhang T, Ding C, Xie T, et al. Skeletal muscle depletion correlates with disease activity in ulcerative colitis and is reversed after colectomy. Clin Nutr 2016;36:1586–1592.

25. Dedhia PH, White Y, Dillman JR, et al. Reduced paraspinous muscle area is associated with post-colectomy complications in children with ulcerative colitis. J Pediatr Surg 2018;53:477–482.

26. Prado CMM, Lieff JR, Mccargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–635.

27. Mourtzakis M, Prado CMM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33:997–1006.

28. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. Ann Am Thorac Soc 2019;16:22–28.

29. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001;1:323–336.

30. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. Canada: Ottawa Hospital Research Institute, 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 20, 2021.

31. Asscher VE, Biemans VB, Pierik MJ, et al. Comorbidity, not patient age, is associated with impaired safety outcomes in vedolizumab- and ustekinumab-treated patients with inflammatory bowel disease—a prospective multicentre cohort study. Aliment Pharmacol Ther 2020;52:1366–1376.

32. Gondal A, Rehman M, Farooq U, et al. The association of frailty with mortality and relapse frequency in inflammatory bowel disease. Am J Gastroenterol 2020;115:S337–S338.

33. Bertani L, Tricò D, Pugliese D, et al. Serum triiodothyronine-to-thyroxine (T3/T4) ratio predicts therapeutic outcome to biological therapies in elderly IBD patients. Aliment Pharmacol Ther 2021;53:273–280.

34. 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.

35. 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 2020;20:1–10.

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

37. Holt DQ, Varma P, Strauss BJG, et al. Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis. Eur J Clin Nutr 2017;71:773–777.

38. Adams DW, Gurwara S, Silver HJ, et al. Sarcopenia is common in overweight patients with inflammatory bowel disease and may predict need for surgery. Inflamm Bowel Dis 2017;23:1182–1186.

39. Cushing KC, Kordbacheh H, Gee MS, et al. Sarcopenia is a novel predictor of the need for rescue therapy in hospitalized ulcerative colitis patients. J Crohns Colitis 2018;12:1036–1041.

40. Campbell JP, Teigen L, Feussom G, et al. Sarcopenia predicts infection in patients with inflammatory bowel disease (IBD) older than 50 years starting biologic medications. AGA Abstr 2020;158:S672–S673.

41. Grillot J, Engremont C, Parmentier A, et al. Sarcopenia and visceral obesity assessed by computed tomography are associated with adverse outcomes in patients with Crohn's disease. Clin Nutr 2020;39:3024–3030.

42. Lee CH, Yoon H, Oh DJ, et al. The prevalence of sarcopenia and its effect on prognosis in patients with Crohn's disease. Intest Res 2020;18:79–84.

43. Raff S, Rome I, Baracos VE, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–495.

44. 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.

45. Li S, Ney M, Eslamparast T, et al. Systematic review of nutrition screening and assessment in inflammatory bowel disease. World J Gastroenterol 2019; 25:3823–3837.

46. Gisbert JP, Chaparro M. Predictors of primary response to biologic treatment [anti-TNF, vedolizumab, and ustekinumab] in patients with inflammatory bowel disease: from basic science to clinical practice. J Crohns Colitis 2020;14:694–709.

47. Koliani-Pace JL, Siegel CA. Prognosticating the course of inflammatory bowel disease. Gastrointest Endosc Clin N Am 2019;29:395–404.

48. Mei F, Gao Q, Chen F, et al. Frailty as a predictor of negative health outcomes in chronic kidney disease: a systematic review and meta-analysis. J Am Med Dir Assoc 2021;22:535–543.

49. Kennedy CC, Novotny PJ, Lebrasseur NK, et al. Frailty and clinical outcomes in chronic obstructive pulmonary disease. Ann Am Thorac Soc 2019;16:217.

50. Nguyen TN, Cumming RG, Hilmer SN. The impact of frailty on mortality, length of stay and re-hospitalisation in older patients with atrial fibrillation. Heart Lung Circ 2016;25:551–557.

51. Faye AS, Colombel J. Aging and IBD: a new challenge for clinicians and researchers. Inflamm Bowel Dis 2021;izab039.

52. Song X, Mitnitski A, MacKnight C, et al. Assessment of individual risk of death using self-report data: an artificial neural network compared with a frailty index. J Am Geriatr Soc 2004;52:1180–1184.

53. Charlson ME, Hollenberg JP, Hou J, et al. Realizing the potential of clinical judgment: a real-time strategy for predicting outcomes and cost for medical inpatients. Am J Med 2000;109:189–195.

54. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. Can Med Assoc J 2005;173:489–495.

55. Sze S, Pellicori P, Zhang J, et al. Identification of frailty in chronic heart failure. JACC Heart Fail 2019;7:291–302.

56. Bahat G, Kilic C, Altinkaynak M, et al. Comparison of standard versus population-specific handgrip strength cut-off points in the detection of probable sarcopenia after launch of EWGSOP2. Aging Male 2020; 23:1564–1569.

57. Bahat G, Tufan A, Tufan F, et al. Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. Clin Nutr 2016;35:1557–1563.