Exploring the Association Between Frailty and Adverse Clinical Outcomes in Inflammatory Bowel Disease

by

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Abstract

Background and Rationale:

Chronological age does not always accurately reflect "biological age", or the extent of physiological reserve an individual possesses to endure stressors. The concept of physiological reserve is best represented by frailty; a multifaceted syndrome or state that encompasses both sarcopenia and malnutrition. In patients with inflammatory bowel disease (IBD), frailty has been reported to be independently associated with mortality and other adverse clinical outcomes and may act as an important risk-stratification tool in this population.

Purpose and Hypothesis:

The purpose of this study was to determine if frailty, measured through the Clinical Frailty Scale (CFS), handgrip strength (HGS), the Subjective Global Assessment (SGA), the abridged Patient-Generated Subjective Global Assessment (abPG-SGA), or the Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool (SaskIBD-NRT), is associated with a higher risk of adverse clinical outcomes in outpatients with IBD. It is hypothesized that these clinical frailty markers will predict the risk of IBD-related hospitalizations and surgeries, such as colectomies and small bowel resections.

Methods:

Consecutive IBD patients ≥18 years of age at two ambulatory care clinics in Alberta were prospectively enrolled in this study. IBD patients with a major medical comorbidity (chronic renal failure requiring dialysis, chronic pulmonary disease, or congestive heart failure with an ejection fraction <40%), previous colectomy, or those unable to provide informed consent were excluded. Patients who were pregnant or who had a disease duration under three months at the

time of enrollment were also excluded. Frailty was defined using the CFS, HGS, the SGA, the abPG-SGA, or the SaskIBD-NRT. Differences between baseline characteristics, frailty, sarcopenia, and malnutrition measurements or scores were determined using independent sample two-sided t-tests for continuous data or Pearson's chi-squared tests for categorical data. We constructed logarithm relative hazard graphs and Cox multivariable logistic regression models adjusting for the following confounders: age, sex, disease phenotype, clinical disease activity, exposure to biologics, exposure to steroids, previous IBD-related surgeries, and comorbidities (determined using the Charlson Comorbidity Index [CCI]; categorized into no comorbidities vs. ≥1 comorbidity). Multiple regression analyses were also completed, which also adjusted for the above listed confounders. A bivariate correlation test with a two-tailed test of significance was completed to analyze the possible correlation between the markers of frailty as well as with chronological age, where Spearman correlation coefficients were used to indicate the extent of the correlations. All statistical analyses were performed using SPSS statistical software (v28).

Results:

A total of 163 patients (35.6% Crohn's disease [CD] and 64.4% ulcerative colitis [UC]), with a mean age of 42.3 (±15.9) years, who were 50.9% female, had a mean Harvey Bradshaw index score of 3.7 (±3.9) and mean partial Mayo score of 1.3 (±1.8), were followed over a mean period of 43.9 (±10.1) months. Twenty-seven patients were hospitalized and 13 patients underwent IBD-related surgeries following baseline. It was determined that patients defined as frail through HGS (aHR 3.922, P=0.034), the abPG-SGA (ordinal form: aHR 1.071, P=0.030), or the SaskIBD-NRT (ordinal form: aHR 1.370, P=0.018; categorical form, high risk [score ≥5]: aHR 4.578, P=0.014) each had a significantly increased risk of IBD-related hospital admissions.

Finally, frailty defined using the abPG-SGA (β 0.001786, P=0.013) was associated with an increased proportion of time spent in hospital due to IBD-related reasons.

Conclusion:

HGS, a reflection of sarcopenia, and abPG-SGA as well as SaskIBD-NRT, both reflections of malnutrition, are frailty-defining entities that were all independently associated with an increased risk of IBD-related hospitalizations. The abPG-SGA was also independently associated with an increase in the proportion of time spent in hospital for IBD-related reasons. Future studies should aim to validate frailty, sarcopenia, and malnutrition tools in the IBD population in order to tailor care for all IBD patients.

Preface

This thesis is an original work by Katherine Bedard. The research project, of which this thesis is a part, received research ethics approval from the Health Research Ethics Board at the University of Alberta (Pro00073470) and at the University of Calgary (REB17-0890).

Dedication

I dedicate this thesis to my unparalleled supporters, my mother and father, who have always been my greatest source of advice, encouragement, and strength. Thank you both for motivating me to achieve my goals and for helping me to find humour in every situation.

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List of Abbreviations

5-ASA: 5-Aminosalicylates

abPG-SGA: Abridged Patient Generated Subjective Global Assessment

ACG: Adjusted Clinical Groups

aHR: Adjusted hazard ratio

aOR: Adjusted odds ratio

Anti-CBir1: Anti-flagellin

Anti-I2: Anti-*Pseudomonas fluorescens* antibodies

Anti-OmpC: Anti-*Escherichia coli* outer membrane porin C

Anti-TNF: Anti-tumor necrosis factor

CBC: Complete blood count

CCI: Charlson Comorbidity Index

CD: Crohn's disease

CDAI: Crohn's Disease Activity Index

CDM: Cumulative deficit model

CFS: Clinical Frailty Scale

CGA: Comprehensive Geriatric Assessment

CI: Confidence interval

CRP: C-reactive protein

CT: Computerized tomography

EFS: Edmonton Frail Scale

EMR: Electronic medical records

ESPEN: European Society for Parenteral and Enteral Nutrition

EWGSOP2: European Working Group on Sarcopenia in Older People 2

FCP: Fecal calprotectin

FI: Frailty index

GI: Gastrointestinal

GSS: Geriatric Status Scale

Hb: Hemoglobin

HBI: Harvey Bradshaw Index

HGS: Handgrip strength

HR: Hazard ratio

IBD: Inflammatory bowel disease

IBD-U: Inflammatory bowel disease type unclassified

ICD-9: International Classification of Diseases, Ninth Revision

ICD-10: International Classification of Diseases, Tenth Revision

IL: Interleukin

IPAA: Ileal pouch-anal anastomosis

IUS: Intestinal ultrasound

IVS: Intravenous corticosteroids

LOS: Length of stay

MAMC: Mid-arm muscle circumference

MRI: Magnetic resonance imaging

NSAID: Non-steroidal anti-inflammatory drug

pANCA: Perinuclear antineutrophil cytoplasmic antibodies

PD: Perianal disease

pMayo: Partial Mayo

SaskIBD-NRT: Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool

SCCAI: Simple Clinical Colitis Activity Index

TSF: Triceps skinfold

UC: Ulcerative colitis

WBC: White blood cell

Chapter 1: Introduction

1.1 Background

Inflammatory bowel disease (IBD), which includes the subtypes ulcerative colitis (UC), Crohn's disease (CD), and IBD type unclassified, is an autoimmune condition characterized by chronic inflammation that impacts the gastrointestinal (GI) system in a relapsing and remitting course.[1,2] An interplay between environmental influences and a genetic predisposition likely both contribute to the abnormal functioning of the enteric immune system and consequently the development of IBD.[2–4] In addition to these factors, the gut microbiota has been reported to play a role in the development and progression of IBD as well.[2,5] When comparing the subtypes of IBD, UC is characterized by continuous inflammation that affects the mucosa of the colon, whereas CD causes non-continuous transmural inflammation of the mucosa anywhere along the GI tract.[6] Recent estimates report the prevalence of IBD in Canada to be 0.7%, with this proportion projected to increase to 1.0% within the decade.[7]

The concept of frailty is difficult to encompass with a single definition, however, it can be described as the reduction of physiologic reserve due to the decline of multiple systems resulting in an increased vulnerability to stressors.[8,9] Similarly, the prevalence of frailty is difficult to determine due to the many assessment types and indices used to diagnose it.[10] It has been reported that frailty is associated with a reduction or alteration in diversity and the presence of certain bacteria types in the gut microbiome, which can result in the loss of muscle mass, or sarcopenia.[11–15] While the relationship between frailty, sarcopenia, and malnutrition will be discussed in greater detail later in this work, numerous assessment tools and models, such as the Fried phenotype model of frailty and the Hospital Frailty Risk Score, include sarcopenia and

malnutrition as frailty-defining diagnoses.[16,17] Similarly, the associations between frailty, sarcopenia, or malnutrition and adverse clinical outcomes in IBD patients will be discussed in Chapters 2 and 3, which demonstrates the importance of assessing frailty in addition to chronological age in this population.

1.2 Statement of the Problem and Purpose of the Thesis

While the interest in research surrounding the concepts of frailty and IBD has recently increased, a study focusing on the association between the Clinical Frailty Scale (CFS) and adverse clinical outcomes in the IBD population has yet to be completed. Similarly, though a study was very recently published that focused on the association between sarcopenia, as measured through handgrip strength (HGS), and adverse outcomes in the IBD population, this study included only inpatients from a single center and had a 90-day follow-up period. Further, although the relationships between frailty, sarcopenia, and malnutrition are well described in the existing literature, to our knowledge no studies have been completed that assess all of these concepts alongside an analysis of the associations between the assessments and adverse clinical outcomes in the IBD population.

The purpose of this research project, which includes both a systematic review of available literature as well as a prospective multicenter cohort study, was to summarize the current knowledge and evidence related to the association between frailty or sarcopenia and adverse non-surgical outcomes in the IBD population.[18] Following this consolidation of information, the project then focused on the investigation of the associations between markers of frailty (the CFS, HGS, Subjective Global Assessment [SGA], Abridged Patient-Generated Subjective Global Assessment [abPG-SGA], and Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool [SaskIBD-NRT]) and adverse clinical outcomes in an adult IBD population.

1.3 Study Objectives

In the present study, the following objectives were focused on:

1. To determine if an independent association existed between the presence of frailty, as determined through various assessments or screening tools (CFS, HGS, SGA, abPG-SGA, SaskIBD-NRT) and the risk of IBD-related hospitalizations or the occurrence of IBD-related surgeries in adult IBD outpatients.
2. To determine if the presence of frailty, as determined using the given frailty assessments and screening tools (CFS, HGS, SGA, abPG-SGA, SaskIBD-NRT), was associated with a significant increase in the proportion of time spent in hospital for IBD-related reasons.

1.4 Study Hypothesis

It is hypothesized that frail adult IBD outpatients, as defined through the CFS, HGS, SGA, abPG-SGA, or SaskIBD-NRT will have an independent increase in the risk of IBD-related hospital admissions and IBD-related surgeries in adult outpatients with IBD. It is further hypothesized that the presence of frailty, as determined through the above listed assessments and screening tools, will be associated with an independent increase in the proportion of time spent in hospital for IBD-related reasons.

1.5 Study Significance

This prospective study served to provide evidence as to whether frailty, including the facets of sarcopenia and malnutrition, should be taken into account when crafting the treatment plan and understanding the risk of adverse clinical outcomes of adult IBD outpatients. The results of this study would have a direct impact on how the physiologic reserve of adult IBD patients are

assessed, as these measurements of frailty would be used alongside chronological age to determine the overall vulnerability of each patient.

Chapter 2: Literature Review

The literature review in this chapter serves to provide an overview of the topics related to this thesis project. Specifically, the following subjects will be discussed: 1) the definition, epidemiology, diagnosis, and prognostic markers of IBD, 2) the definition, diagnosis, and prevalence of frailty, alongside its relationship with sarcopenia and malnutrition, and 3) available literature focusing on the association between frailty, sarcopenia, or malnutrition and adverse outcomes in the IBD population.

2.1 The Definition of Inflammatory Bowel Disease

As previously stated IBD, which includes UC, CD, and IBD type unclassified, is a chronic inflammatory disorder that impacts the mucosa of the GI tract. While the cause of IBD is unknown, current literature reports that genetic predispositions and environmental factors may result in atypical immune system functioning, resulting in the development of IBD.[2–4] This disease has a bimodal distribution of incidence, with the majority of cases being diagnosed in individuals 20 – 30 years of age and only 10-15% of diagnoses occurring after age 60.[19–22]

While similarities exist between UC and CD, these subtypes have distinct features related to both disease location and behavior. UC is defined as an inflammatory disease that affects the mucosa of the colon, whereas CD is a transmural inflammatory disease that affects the mucosa of any portion of the GI tract.[6]

In order to properly diagnose UC or CD, an endoscopy needs to be performed. Due to the visual aspect this procedure allows for, it is currently considered to be the gold-standard for diagnosing IBD, and further allows for the differentiation between UC and CD after histopathological assessment. This method also permits the gastroenterologist to determine the location and

severity of the inflammation through direct visualization, granting the opportunity for the most accurate diagnosis to be made and further for the correct treatment plan to be established.

2.1.1 The Classification of Inflammatory Bowel Disease

Continuous inflammation of the colon characterizes UC, where the proximal extent of this inflammation determines the Montreal classification[23] disease location: proctitis if limited to the rectum, left-sided colitis if extending to the splenic flexure, and extensive colitis or pancolitis if extending beyond the splenic flexure. Conversely, discontinuous inflammation of structures in the GI tract characterizes CD, and one of the main clinical features differentiating UC from CD is the presence of fistulae.[6]

The disease phenotypes of UC and CD are examined differently using the Montreal classification system, where the former focuses on the severity of symptoms and disease location and the latter considers location, age at diagnosis, and disease behavior. Specifically, the location of UC is divided into three categories as mentioned previously, where extensive colitis, or pancolitis, (E3) is considered to be the most severe UC phenotype, as inflammation extends past the splenic flexure. Left-sided colitis (E2) is where disease activity extends until the splenic flexure and proctitis (E1) is where disease only affects the rectum. The severity of UC symptoms is categorized into four groups, with a lack of symptoms denoted as S0. If there is a presence of UC symptoms, the severity is then classified in the following way: mild (S1), moderate (S2), and severe (S3).[24] Switching focus to location in the phenotype of CD, the disease can affect the ileum (L1), the colon (L2), or both (L3); the involvement of the upper GI tract (L4) also impacts the severity of the disease. In terms of disease behavior, inflammatory activity (B1) is considered to be the mildest, whereas stricturing (B2) and penetrating or fistulizing behavior (B3) contribute to increasingly worse phenotypes. The presence of perianal disease (PD) is a second form of

disease behavior that is taken into account by the Montreal classification system for CD. The complete Montreal classification system for both UC and CD can be seen in Table 1.

Table 1. Montreal Classification for Ulcerative Colitis and Crohn's Disease

	Ulcerative Colitis	**Crohn's Disease**
Disease Severity	S0: Clinical remission S1: Mild activity S2: Moderate activity S3: Severe activity	
Disease Location/Extent	E1: Ulcerative proctitis E2: Left-sided colitis E3: Extensive colitis (pancolitis)	L1: Ileal L2: Colonic L3: Ileocolonic L4: Upper GI*
Age at Diagnosis		A1: <17 years of age A2: 17 – 40 years of age A3: >40 years of age
Disease Behavior		B1: Inflammatory B2: Stricturing B3: Penetrating P: Perianal disease modifier†

*Upper GI disease location can be added to L1 – L3 when present concurrently.

†When concurrent perianal disease is present, the P modifier is added to the disease behavior category.

2.2 The Epidemiology of Inflammatory Bowel Disease

2.2.1 Incidence of Inflammatory Bowel Disease

In general, the incidence of IBD in Western nations is currently relatively stable, which is in contrast to that of developing countries and newly industrialized nations, as a steady increase in IBD incidence is presently underway in those areas.[25] When stratified by global region, the incidence of IBD in Western regions has been reported to be significantly higher than Asian regions, with a family history of IBD also being less common in Asia.[26] Focusing on the incidence of IBD in Canadian provinces, the rate ranges from 18.7 – 51.8 cases per 100,000

Canadians. The incidence rate of UC between males and females in Canada is relatively equal, however females have a higher risk of developing CD, demonstrated by a ratio of 1.2 compared to Canadian males.[7]

2.2.2 Prevalence of Inflammatory Bowel Disease

Recent research has estimated that there are 6.9 million cases of IBD globally, with the prevalence in Canada estimated to be 0.7% of the population in 2018, with this number being projected to increase to 1.0% by 2030.[7] When comparing the prevalence of IBD between age groups, there was found to be a greater prevalence of IBD in those ≥45 as opposed to those <45 years of age.[27] Further, as noted by Kaplan & Windsor, and in agreement with previous reports, the prevalence of IBD is only continuing to increase, particularly in the Western World and newly industrialized countries. This increase is in opposition to that seen in developing countries, which are currently experiencing an increase in IBD incidence through the emergence of the disease but are not yet subject to the same sharp incline in prevalence that is impacting other nations.[25] Kaplan & Windsor also comment on the idea of a prevalence equilibrium in relation to IBD, where they project that within the next few decades Western nations will experience a plateau in prevalence. As explained by the authors, this future stabilization of prevalence will occur due to the mortality rate of elderly IBD patients approximating the incidence rate of IBD cases, where this incidence rate includes both novel environmental incidence and economic incidence, where the latter refers to previously undiagnosed cases of IBD being identified as a result of access to diagnostic tools such as endoscopies.[25]

2.2.3 Racial Disparities in Inflammatory Bowel Disease

Over identical 10-year periods, a significant difference can be seen in the adjusted IBD incidence rates of white adults and non-white adults. Specifically, white American adults had an incidence rate of 25 per 100,000 from 2000 – 2010, and non-white American adults had a rate of 15 per 100,000 over the same time period.[28] Further, it has been reported that those of South Asian and Ashkenazi Jewish descent in Canada are both high-risk populations for developing IBD.[7]

2.3 Diagnosis of Inflammatory Bowel Disease

As previously mentioned, endoscopies are required to diagnose IBD, however other confounding disease processes including non-steroidal anti-inflammatory drug (NSAID) enterocolopathy, infectious colitis, ischemic colitis and segmental colitis associated with diverticulosis need to be ruled out.[29] A variety of complementary investigations to endoscopy can be utilized to arrive at a diagnosis including biochemical testing and cross-sectional imaging.[30]

Patients that have developed IBD will often present with at least one of the following symptoms: abdominal pain, bloody stools, urgency, abnormal bowel patterns (commonly diarrhea), fatigue, and unintentional weight loss.[31] The Harvey-Bradshaw Index (HBI)[32] is an extremely useful and feasible tool to determine the current disease activity for CD patients. The index itself is composed of five components, of which the first three are scored by the patient in relation to the symptoms they experienced over the last 24-hour period: general well-being, abdominal pain, number of liquid stools, presence of an abdominal mass, and the presence of specific complications (anal fissure, novel fistula, aphthous ulcers, arthralgia, uveitis, erythema nodosum, abscess, and/or pyoderma gangrenosum).[33] A summed score of <5 has been reported as the cut-off to designate disease remission in CD patients, with a score of 5 – 7 denoting mild, 8 – 16

designating moderate, and >16 denoting severe disease activity.[34] The HBI has been reported as far less cumbersome than the Crohn's Disease Activity Index (CDAI), which is a weighted score that takes into account eight items, five of which are assessed in the HBI alongside an additional three: use of anti-diarrheal agents, hematocrit level, and body weight.[35] Similarly, the Mayo score also exists to determine disease activity in UC patients. The complete scoring system takes into account stool frequency, the presence and/or extent of rectal bleeding, endoscopy findings, and the Physician's Global Assessment, with scores ranging from 0 – 12.[36] A modified version of the Mayo scoring system also existed, known as the partial Mayo (pMayo) which excludes the requirement for endoscopic assessment, reducing the maximum total score from 12 to 9.[37] A pMayo score of <2 is the cut-off to signify disease remission in UC patients, and scores of 2 – 4, 5 – 6, and >6 denoting mild, moderate, and severe disease activity respectively.[38]

In addition to these symptoms, the presence of extraintestinal manifestations of IBD may also be identified, such as, but not limited to: ankylosing spondylitis, arthropathy, erythema nodosum, pyoderma gangrenosum, uveitis, iritis, aphthous stomatitis and primary sclerosing cholangitis.[39] At this time, factors such as family history, duration of related symptoms, extraintestinal symptoms, and pediatric growth failure will also be examined as they all strengthen the likelihood of IBD.[40]

If IBD is suspected, a biochemical assessment including a complete blood count (CBC) and a test for C-reactive protein (CRP) levels are conducted. CBC assessments incorporate measurements of hemoglobin (Hb), platelet, and white blood cell (WBC) concentrations which can be a reflection of blood loss and inflammatory processes. CRP, which is produced hepatically, increases in the body due to the marked increase in interleukin (IL) 6, IL-1β, and tumor necrosis factor-α (TNF-α).[41] This protein concentration then acts as an objective marker

which allows gauging of the degrees of disease activity and severity in those with IBD, as inflammation increases during the acute phase of IBD. However, it should be noted that there is evidence to suggest that CRP levels better predict disease activity in those with CD compared to UC, and not all IBD patients mount a CRP response when inflamed.[30]

In addition to CRP, fecal calprotectin (FCP) is another biochemical parameter that can be helpful in the diagnosis of IBD. In cases of intestinal inflammation, FCP levels rise and reflect this process, where a level ≥50mg/g has historically been designated as abnormal.[42] However, as noted by Ye et al., an FCP level of ≥100mg/g should instead be considered as the cut-off in order to avoid unnecessary endoscopies.[43]

Stool investigations to rule out infection are also necessary and test for *Clostridioides difficile*, Salmonella species, Shiga toxin-producing *Escherichia coli*, Campylobacter species, and Shigella species, as infections of the intestinal system may present similarly to IBD, or may be occurring concurrently with IBD.[30] Further, depending on recent travel history, the stool may also be tested for the presence of ova, parasites, and cysts.[30]

Lastly, the use of cross-sectional imaging tools such as magnetic resonance imaging (MRI) enterography, computerized tomography (CT) enterography, and intestinal ultrasound (IUS) are extremely useful for assisting in the diagnosis and management of CD, but are limited in that early detection of the disease is not always feasible using these cross-sectional imaging techniques.[44,45] These tools are not only non-invasive, but also allow for the visualization of the extramural and transmural extent of disease activity as well as for associated complications such as fistulae and abscesses.[46,47] Although not as well established in UC, imaging in the form of IUS is also helpful in assessing UC disease activity and severity.[48]

The gold standard for diagnosing IBD is endoscopy, which is a broad category that encompasses the following procedures: colonoscopy, balloon-assisted enteroscopy, flexible sigmoidoscopy, upper endoscopy (esophagogastroduodenoscopy) and video capsule endoscopy. Which endoscopic procedure is performed is typically based upon other historical, biochemical, and cross-sectional imaging findings, again highlighting the importance of these investigations in relation to IBD diagnoses.[49] In order to maximize the diagnostic capability of endoscopy and to differentiate between UC and CD, a minimum of two biopsies are obtained from each affected region of the GI tract.[50,51] The difference in disease location and the presence of granulomas can often help distinguish UC from CD.[51]

2.4 Prognostic Markers of Inflammatory Bowel Disease

2.4.1 Serological Markers

Serological markers serve as predictors of disease course and are extremely useful in regard to the prognosis of both UC and CD. When looking at UC patients, a robust immune response is seen against neutrophil antigens, which is demonstrated by an increased perinuclear antineutrophil cytoplasmic antibodies (pANCA) level.[52] An association between this increase in pANCA and a decreased probability of remission, and a heightened rate of relapses in UC patients has been reported. Antibodies more prevalent in CD include anti-*Saccharomyces cerevisiae* antibodies (ASCA), anti-*Escherichia coli* outer membrane porin C (anti-OmpC), anti-*Pseudomonas fluorescens* antibodies (anti-I2), and anti-flagellin antibodies (anti-CBir1). In particular, a direct relation exists between the increase of ASCA, anti-OmpC, anti-CBir1, and anti-I2 and the progression of complicated CD behavior.[52]

Aside from the aforementioned serological markers, CRP can also contribute to the determination of disease prognosis. Increased levels of CRP at the time of UC diagnosis are predictive of an increased risk of colectomies.[53] In relation to CD patients, FCP may be a more useful prognostic marker of disease recurrence. In a post-operative CD study, FCP was demonstrated to better in predicting disease recurrence compared to CRP.[54] Of note however, overall FCP appears to be less useful for determining disease activity in those with ileal CD as opposed to colonic and ileocolonic CD.[55]

2.4.2 Endoscopic Findings

When focusing on the endoscopic findings that aid in predicting the course of IBD, the main results that are considered informative are: the severity of mucosal lesions and the extent of mucosal healing.[52,56] It has been reported that IBD patients are more likely to have a poor disease prognosis if they possess severe mucosal lesions, as this is an indication of a more aggressive disease phenotype.[56] One aspect that contributes to the determination of lesion severity is the depth, where the presence of deep penetrating ulcerations acts as a predictive marker for the requirement of IBD-related surgeries in both CD and UC patients.[52] Next, current literature suggests that even in those with dormant UC, the existence of mild persistent inflammation is a predictor of recurring disease relapse in the future. This risk of relapse is further increased when paired with the presence of histological abnormalities in the intestinal epithelium, such as abnormal crypt architecture.[56] Patients who demonstrate mucosal healing on endoscopy have a lower requirement for colectomies and generally have a more positive prognosis.[52]

2.4.3 Genetic Markers

Genetic markers can also predict disease course, where loci such as *NOD2*, *CLEC7A*, and HLA-DRB1 have been demonstrated to have an association with either the development or prognosis of IBD.[56] First, current literature states that patients who carry at least one high-risk *NOD2* allele, have a heightened susceptibility for early-onset CD, disease involvement in the small intestine, stricturing CD behavior, and the need for intestinal resections.[52,57] It has been theorized that carrying at least one of these high-risk *NOD2* alleles results in two detrimental processes to occur in the individual: a reduction in antimicrobial peptide production and the loss of persistent activation of Nucleotide Oligomerization Domain (NOD) receptors, which typically function to provide tolerance to the GI microbiome.[58] Second, the *CLEC7A* gene encodes dectin-1, which is a receptor protein vital to the functioning of the innate immune system.[52,59] The inheritance of a *CLEC7A* haplotype was found to give rise to a form of UC that is relatively resistive to treatment, leading to a poorer UC prognosis. However, it should be noted that the *CLEC7A* genetic marker is not yet used in clinical practice.[43,56,60] Finally, the HLA-DRB1 locus has been shown to be associated with colonic inflammation in IBD patients, however these results have been inconsistent in comparison to those reported for the association between *NOD2* and the development of CD.[43,52] In addition to these genes, it has been stated that some non-coding single nucleotide polymorphisms (SNPs) may contribute to the course of CD without directly being associated with the initial development of the disease. One SNP in particular is the minor allele rs12212067 found within the *FOXO3A* gene. The possession of this variation results in a reduction of intestinal inflammation due to a direct increase in the production of transforming growth factor β1 (TGFβ1) and a subsequent decrease in tumor necrosis factor α (TNFα).[52,61] It should be stated that while the above genetic markers are associated with the onset or prognosis

of IBD, there are hundreds of other loci that possess the ability to contribute to the risk of developing UC and CD.[62] Further, it has been reported that the impact of genetic factors is not as significant in the development of CD in those with a late onset of the disease compared to those with an earlier onset, alluding to a possible difference in disease etiology and mechanisms.[63]

2.4.4 Clinical Characteristics

Disease phenotype and behavior, smoking status and age of onset are clinical characteristics that can predict how IBD patients fare with their disease. In terms of the location of inflammation in UC, a more extensive disease progression is indicative of a more severe disease course, and often predicts the need for colectomies[52]. PD, which is characterized by inflammation at or in close proximity to the anus and can manifest physically as fistulae, abscesses, fissures, stenosis, and tags, has been reported to be associated with an increased risk of a complicated disease phenotype and a significantly worse CD prognosis.[64,65] However, it should be noted that the definition of PD differs, where some consider all the above lesions as physical manifestations of PD, whereas others have a more limited definition on the lesions that are characterize the presence of this disease.[65] Next, patients with disease activity in the upper GI system (L4), and specifically in the jejunum of the small intestine, are at greater risk of developing stricturing disease behavior and a need for IBD-related surgery, such as a colectomy or a small bowel resection.[52] In terms of non-PD behavior, it is stated that those with a severe initial CD presentation that includes either stricturing or penetrating behavior are more likely to be subject to a more complicated disease phenotype.[60]

In relation to smoking status, it has been reported that UC patients that self-identify as current smokers experience a decreased number of relapses, reduced hospitalization rates, enhanced IBD regression, and decreased requirement for colectomies.[52] Further, it has also been stated that

active smokers have a lesser chance of developing UC in comparison to former and non-smokers.[66] However, contrary to these findings, the opposite has been demonstrated for CD, as those who actively smoke have both a greater risk of developing the disease and once diagnosed, often have more severe phenotypes than non-smokers.[67] While the nature of the differential effect of active smoking between UC and CD remains elusive, it has been theorized that the administration of nicotine likely plays a role.[66] This idea has been recently supported by a literature review, where it was determined that, when used in combination with traditional IBD treatment, transdermal nicotine patches have the capability of providing significant benefits in terms of disease severity in UC patients.[68]

Lastly, the age of disease onset is a valuable prognostic marker for both CD and UC, as the early onset of either of these IBD forms predicts a poor disease course, increased number of relapses, decreased response to administered treatments, greater need for IBD-related surgeries, and an increased risk of chronic morbidity.[40,52,60] In relation to CD cases that have a late onset, defined as an age at diagnosis of ≥55 years, these patients often present with UC-like characteristics such as heightened pANCA levels. Further, a reduction was reported in the proportion of new CD diagnoses for current smokers being made in this age category, which is a trend typically associated with novel UC diagnoses as a whole.[63] While older IBD patients generally have less complicated disease behavior, they have similar or even higher rates of surgery compared to younger-onset IBD patients which may relate to decreased utilization of immunosuppression or even lower rates of response to anti-tumor necrosis factor (anti-TNF) therapies.[3]

Although the majority of the literature focuses on chronological age, chronological age does not always reflect the extent of physiological reserve an individual may have to endure stress from both the disease and various treatment strategies.[69] Emerging data suggests that measures such as

frailty, sarcopenia, and malnutrition can act as prognosticating markers and provide nuanced information required for optimal clinical decision-making in the IBD patient population.

2.5 The Definition and Diagnosis of Frailty

A universally-accepted, all-encompassing clinical definition for the concept of frailty does not exist due to its instability and complexity, however it can be explained as a multifaceted syndrome or state resulting in the overall susceptibility of an individual, making them more vulnerable and less capable of enduring stressors.[70,71] In relation to the condition of specific patients, the term frailty can be defined in multiple different ways, where these operational definitions are reliant mainly on the index or score being utilized. In particular, three main routes for the definition of frailty have been defined previously: rules-based, summation of impairments, and clinical judgements.[70] Within each of these categories, there were multiple indices which were utilized in order to aid in the diagnosis of frailty, however there remains no current gold standard way to define or diagnose frailty due to its complexity. More recently, researchers have shifted the categorization of frailty, where the three aforementioned definition routes are instead classified as the syndrome or state of frailty. Specifically, the rules-based and clinical judgement routes of frailty are categorized as the syndrome of frailty, whereas the summation of impairments is categorized as the state of frailty.[72–75]

The Fried phenotype model of frailty[17] and the CFS[70] both assess frailty as a syndrome, whereas Rockwood and Mitnitski's frailty index (FI)[76], the Hospital Frailty Risk Score[77], the Johns Hopkins Adjusted Clinical Groups (ACG) Frailty Indicator[78], and the Canadian Study of Health and Aging (CSHA) Frailty Index are cumulative models that assess frailty as a state.[79] An overview of all listed frailty indices can be found in Table 2.

Table 2. Summary of Described Frailty Measurements

Frailty Measurement	Previous Route of Frailty Definition	Updated Categorization of Frailty Assessments	Cut-off to Determine Frailty
Fried Phenotype Model	Rules-based physical model	Frailty syndrome	≥3 listed manifestations
Clinical Frailty Scale	Subjective Clinical Judgement	Frailty syndrome	Total score of ≥4
Rockwood and Mitnitski's Frailty Index	Accumulation of Deficits/Summation of Impairments	Frailty state	Ratio of ≥0.25 from a total of 92 possible deficits
Hospital Frailty Risk Score	Accumulation of Deficits/Summation of Impairments	Frailty state	Ratio of ≥0.25 from a total of 109 possible ICD-10 codes
Johns Hopkins Adjusted Clinical Groups Frailty Indicator	Accumulation of Deficits/Summation of Impairments	Frailty state	≥1 listed frailty-defining diagnosis
Canadian Study of Health and Aging Frailty Index	Accumulation of Deficits/Summation of Impairments	Frailty state	Ratio of ≥0.25 from a total of 70 possible deficits

2.5.1 Assessment of Frailty as a Syndrome

The Fried phenotype model defines frailty in terms of the presence of a limited number of factors that all stem from a reduction in overall physical health. In particular, this model considers a reduction in handgrip strength, walking ability, body mass, endurance, and physical activity to be the five key signs that may indicate that an individual is frail.[17,79] The utilization of the Fried phenotype model allows for the determination of levels of frailty dependent on the number of above stated criteria that a person possesses, where a non-frail individual presents with zero, a pre-frail individual presents with between one and two, and a frail individual presents with at least three.[79] In order to gather the necessary information to utilize this model, physical tests that directly measure the identified criteria must be administered. When considering the Fried phenotype model of frailty as a whole, it is apparent that while it is a useful tool to evaluate the physical abilities of individuals, it fails to take into account such factors as cognitive decline and possible comorbidities. This disadvantage, alongside the need for physical testing, limits the use of this model in the clinical setting.[80]

The CFS, which again was a frailty measurement developed for those aged ≥65 based solely on clinical judgements, is an extremely useful tool due to its comprehensive scoring system, the relative ease of its administration, and the inclusion of multiple categories of frailty indicators.[70,81,82] The CFS incorporates possible comorbidities, disabilities, as well as cognitive and physical deficits into each given frailty score, which ranges from one, which denotes a very fit individual, to nine, which is given to those who are terminally ill.[70] An in-depth description of each score within the CFS is available in Appendix A1. When focusing directly on the administration ease of the CFS, it has been reported that compared to the other measurement tools, this scale has the greatest feasibility. This quality is of notable importance, as the scale allows for the determination of frailty level based on the Comprehensive Geriatric Assessment (CGA) as well as patient interviews, reducing the required time for test administration as well as eliminating the need for in-person physical testing.[83] This scale is also highly correlated with other validated frailty assessments, such as the Edmonton Frail Scale (EFS).[84] Further, between all frailty tools focused on in this section, the CFS was considered as the optimal predictor of post-operative mortality.[82] The CFS was again developed as an ordinal scale, with scores ranging from 1 – 9, however in the literature CFS scores are often grouped into dichotomous categories to indicate the presence or absence of frailty.[85] While a cut-off CFS score of four to designate is not the most commonly used, it does allow for all patients affected by frailty as defined by the CFS to be captured.[85,86] Looking at the CFS critically, one possible disadvantage of this scale would be the possibility of inter-rater variability. However, a study by Surkan et al. considered this limitation and reported that inter-rater reliability improves when those who score the CFS come from similarly trained backgrounds.[87]

2.5.2 Assessment of Frailty as a State

The FI developed by Rockwood and Mitnitski takes a different approach to the definition and determination of frailty, where a wide range of 92 deficits, including comorbidities, some geriatric syndromes, certain risk factors and both physical and cognitive impairments are considered.[76] However, it should be noted that in order to be included in the index, the deficits must have a prevalence that is greater than 1% that increase alongside chronological age, represent more than one organ system, and not be common prior to the age of 65.[79] These inclusion criteria present a possible limitation to this frailty instrument, as uncommon deficits or those restricted to a single organ may still impact the frailty of an individual but are not included in the index. Nevertheless, due to this measuring of a multitude of impairments, the FI is commonly referred to as the cumulative deficit model (CDM), where the necessary patient information can be taken from a CGA, which is completed through patient interviews.[76] Specifically, CDM scores are comprised of the number of deficits a person presents with divided by the number of impairments that were measured, where these scores then signify the degree of frailty present for the individual. The scores range between zero and one, with zero indicating no frailty and one signaling complete frailty, however the specific cut-offs indicating low, moderate, and high degrees of frailty have been disputed among the available literature. However, it is generally agreed upon that an FI score ≥ 0.25 is indicative of some degree of frailty.[79] It should be noted that this index was initially developed using a cohort of elderly patients, and therefore may not be accurate when scoring the frailty of younger individuals, especially given the above stated criteria for the included 92 deficits. A further limitation is that this tool implies an equality of the deficits in question and does not incorporate a weighted scale.

The Hospital Frailty Risk Score encompasses 109 frailty-defining International Classification of Diseases, Tenth Revision (ICD-10) codes, such as malnutrition, acute renal failure, and heart failure, and was initially used to predict 30-day mortality, prolonged hospital stays, and 30-day readmissions to hospital.[77] This tool is relatively useful, as patients can be administered a frailty score based solely on information previously input into an electronic database, and therefore no in-person testing needs to be conducted. Similar to Rockwood and Mitnitski's FI, this Risk Score was developed using elderly patients, and therefore its usability may be limited when concerned with other age groups. Further, similar to all other summation of impairment frailty tools, a major disadvantage of the Hospital Frailty Risk Score is the finite number of deficits that are considered, as if an individual possesses many impairments, but these are not reflected in the given index, the resulting score may not accurately reflect the true biologic reserve of that patient.

The Johns Hopkins ACG Frailty Indicator includes 10 frailty-defining diagnostic categories that each encompass multiple different International Classification of Diseases, Ninth Revision (ICD-9) identifying codes.[16,78] This specific tool was created specifically for use on administrative health data, making its feasibility of administration relatively high as it only relies on electronic codes. Table 3 displays the frailty-defining diagnoses alongside the relevant ICD-9 codes used in the Johns Hopkins ACG Frailty Indicator, where the presence of at least one diagnosis deems an individual as frail. However, the use of this tool in the IBD population may not be considered optimal, as one frailty-defining diagnosis is fecal incontinence which affects 41% of the IBD population and is diagnosed nearly eight times as often compared to those without IBD diagnoses.[88]

Table 3. Frailty-Defining Diagnoses and ICD-9 Codes in the Johns Hopkins ACG Frailty Indicator

Frailty-Defining Diagnosis	ICD-9 Codes*
Malnutrition	261, 262, 263.8, 263.9, V77.2
Dementia	290.20, 290.21, 290.3
Severe Vision Impairment	369.0, 369.00, 369.01, 369.03, 369.04, 369.06,369.07, 369.08
Decubitus Ulcer	707.0, 707.00,707.01, 707.02,707.03, 707.04,707.05, 707.06, 707.07, 707.09, 707.20, 707.21, 707.22, 707.23, 707.24, 707.25
Incontinence of Urine	788.34, 788.37
Weight Loss	783.2, 783.21, 783.22, 783.3
Fecal Incontinence	787.6
Social Support Needs	V60.0, V60.1, V60.2
Difficulty Walking	719.7, 781.2
Fall	E880, E880.0, E880.1, E880.9, E884.3

Table adapted from Goel et al., 2020.[16]

*The presence of at least one ICD-9 code denotes frailty.

Finally, the CSHA Frailty Index is a 70-item measurement tool that is administered during a clinical examination, where such deficits as a history of Parkinson's disease, stroke, diabetes mellitus, and congestive heart failure are taken into account.[89] The CSHA Frailty Index factors the severity of each item into the total score of the patient, as each variable is administered a score of either 0, 0.33, 0.5, 0.67, or 1, where the presence of some variables were scored in a dichotomous fashion, and the remaining in a trichotomous one. Though this frailty tool was not initially crafted to categorize individuals into fit or frail, a cut-off point of ≥0.25, or a total score of 17.5/70 deficits, has been given by the original authors of the index.[89] Even though this index includes some variables common in the general IBD population, such as GI, abdominal, rectal, and toileting issues, the cut-off score of 17.5 ensures that IBD patients that are affected by those four listed deficits will not be considered frail without possessing at least 14 further deficits. For this reason, the CHSA Frailty Index should be considered appropriate for use in an IBD population, which is in contrast to the Johns Hopkins ACG Frailty Indicator.[78,89]

2.6 The Prevalence of Frailty

Current literature reports different rates of frailty prevalence dependent on multiple factors, one of which is the frailty tool or index that is used. Specifically, O'Caoimh et al. state that while the Fried phenotype model of frailty estimated prevalence at approximately 12% of individuals, the summation of impairments model estimated frailty to be much higher at 24%.[10] Further, these researchers also reported that when accumulation of deficits indices were used, females have a higher risk of frailty, with the prevalence being 29% compared to 20% for males.[10]

2.7 Sarcopenia in the Context of Frailty

2.7.1 Definition of Sarcopenia

Sarcopenia, which the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) defines as a disorder of the skeletal muscles that is characterized by an enhanced reduction in both the mass and function of these muscles, is associated with multiple chronic inflammatory diseases including IBD. Alongside these associations, this skeletal muscle disorder has also been linked to a multitude of negative manifestations such as frailty, mortality, and a general decline in function.[90] Although frailty and sarcopenia are indeed distinct concepts, sarcopenia is considered to be a widely recognized physical manifestation of frailty.[13,17] Further, HGS is named as one of the tools alongside the CFS that facilitates an appropriate assessment of frailty in clinical practice.[91]

2.7.2 Mechanisms of Sarcopenia

The relationship between sarcopenia and disorders of inflammation in general has been reported to be due to two main mechanisms, where both stem from the systemic increase of inflammatory

factors such as IL-1, IL-6, tumor necrosis factor α (TNFα), and CRP.[90] The first proposed pathway that describes the consequence of sarcopenia following the establishment of a chronic inflammatory disorder is based around the increase in both IL-6 and TNFα, which both accelerate the breakdown of skeletal muscle proteins when at higher levels than normal. Further, there may also be a simultaneous decrease in the synthesis of novel proteins, where there is then a reduction in existing skeletal muscle proteins alongside a reduced production of replacement proteins.[90] Second, current literature has suggested another possible mechanism that focuses directly on the integrity of the endothelium. Specifically, the above stated increase in markers of chronic inflammation cause a reduction in this integrity, resulting in the loss of coordinated vasodilation through impaired gap junction communication, especially affecting the vasodilator response. This relative vasoconstriction directly causes a decrease in the available oxygen and nutrients being supplied to the skeletal muscle cells, impacting the adequacy at which the skeletal muscles can function.[90] In both mechanisms, this increase in chronic inflammatory markers is ultimately associated with a reduction in muscle mass, a decrease in strength, and disability.

2.7.3 Relationship with Malnutrition

Alongside these given physiological explanations for the development of sarcopenia following chronic inflammation, an accelerated course for this skeletal muscle disease has been reported in those who suffer from undernutrition. In particular, individuals with IBD experience malnutrition due primarily to the chronic inflammation of the mucosa, and the subsequent impairment in nutrient absorption. Further, an increased level of intestinal protein and a disturbance in metabolism both possess the capacity to impact the nutrition level of those with IBD, however these factors are secondary to the decreased absorption of nutrients.[92]

2.7.2 Diagnostic Methods of Sarcopenia

The mid-arm muscle circumference (MAMC) measurement is a tool used in order to obtain data pertaining to the muscle mass or protein reserve of a patient, where the values are attained through the physical measurement of the circumference of the mid-arm region of an individual, as well as the triceps skinfold (TSF) thickness, using a standard MAMC tape measure.[92] Once the values are obtained for an individual, the product of (3.14 x TSF thickness) is subtracted from the mid-arm circumference value, giving the complete MAMC measurement. This value is then referenced against standardized values in order to determine the muscle mass and relative nutrition status of the patient. However, it should be noted that numerous different cut-off points are utilized to diagnose sarcopenia using MAMC values, such as values that fall below the 10^{th} percentile or those in the bottom tertile, and that the EWGSOP2 does not recommend the use of MAMC measurements to diagnose sarcopenia.[90,93,94]

HGS is a useful tool used as a surrogate measurement of the total functional muscle capacity of an individual, which is quantified using a mechanism such as the Jamar® Hydraulic Hand Dynamometer.[95] Similar to MAMC, HGS can also categorized by standardized cut-off values, where cut-off values exist dependent on such factors as sex, age, and hand dominance. The most widely accepted cut-off is that of the EWGSOP2, which defines sarcopenia in HGS as <16 kg for females and <27 kg for males.[90]

For the quantification of skeletal muscle index (SMI) in individuals, MRI and CT imaging are reported as being the gold-standard due to their inter-observer reliability and agreement between radiological assessment methods.[96] Specifically, cross-sectional imaging at the third lumbar level has been demonstrated to be an ideal area to quantify overall muscle mass, as it does not rely on

the SMI of a single muscle, such as with the measuring of the psoas muscle as a surrogate marker of sarcopenia.[97]

2.8 Malnutrition in the Context of Frailty

2.8.1 Definition of Malnutrition

The concept of malnutrition, similar to frailty, does not have one universally accepted definition. In general, malnutrition describes an excess, deprivation, or imbalance of essential nutrients that results in adverse effects on functional capacity, body composition, and clinical outcomes.[98,99] Depending on the individual case, malnutrition can be either a cause or consequence of chronic disease, where the former can be associated with such factors as compromised immune function and reduced muscle mass/function, and the latter with reduced dietary intake and reduced absorption of nutrients.[98] Along the same lines, the recognized phenotype of malnutrition is described as the loss of body mass with an increase of general weakness.[100]

2.8.2 Diagnostic Methods of Malnutrition

While a wide array of malnutrition assessments and screening tools exist, the SGA, PG-SGA, abPG-SGA, and SaskIBD-NRT will be focused on in this project. It should be noted that body mass index (BMI) is not being considered as a valid method of determining malnutrition risk in this study, and similarly malnutrition risk tools that include BMI as a form of nutritional assessment will not be included. This exclusion is due to current literature that states the BMI should not be utilized in order to determine malnutrition in the IBD population.[101–103]

The SGA, which is administered by a trained professional such as a physician or registered dietician, can be considered the current gold-standard for the diagnosis of malnutrition in the general population, including those with IBD.[104] This assessment categorizes individuals as well-

nourished (A), moderately malnourished (B), or severely malnourished (C). The SGA is similar to the CFS in that it relies on clinical judgements in order to develop a coordinated treatment plan. Within this assessment, the nutrition status, and by extension frailty, of each patient is determined and factored into the decision when looking at the most favorable therapy route. In order to administer an accurate assessment, the SGA takes into account weight changes, dietary intake, GI symptoms, functional capacity, disease state and/or comorbidities, and an in-person physical exam.[104] An in-depth description of the scoring system of the SGA is available in Appendix A2-1.

While both the PG-SGA and the abPG-SGA assign scores to patients that range between 0 and 35, with higher scores denoting a greater risk of malnutrition, the abPG-SGA foregoes the physical assessment that is completed by a trained clinician as part of both the SGA and PG-SGA.[105] Therefore, the PG-SGA assigns both a numerical score to each patient alongside a categorization akin to that of the SGA that determines malnutrition based on a physical assessment (PG-SGA A, B, or C).[106] While the abPG-SGA, which is entirely completed by the patient, was developed as an ordinal score with scores ranging from 0 – 35, it has also been implemented in a categorical fashion, which may categorize scores in a dichotomous form to indicate the risk of malnutrition (0 – 5: no risk of malnutrition; ≥6: risk of malnutrition).[105,107] An overview of the entire abPG-SGA scoring system is available in Appendix A2-2.

Finally, the SaskIBD-NRT is a patient self-reported questionnaire that was designed specifically for those with IBD in order to accurately gauge the level of nutrition for the patient.[108] This screening tool utilizes questions related to GI symptoms, unintentional weight loss, poor food intake and food restrictions in order to administer the individual a total score from 0 – 9 indicating their level of nutritional risk. These scores are then categorized into the following

groups to determine the risk of malnutrition: low risk (0 – 2), medium risk (3 – 4), and high risk (≥5).[108] The complete scoring system of the SaskIBD-NRT is shown in Appendix A2-3.

2.9 Association Between Frailty, Sarcopenia, and Malnutrition and Inflammatory Bowel Disease

2.9.1 Review of Studies Related to the Association Between Frailty and Inflammatory Bowel Disease

2.9.1.1 Observational Studies Related to Frailty and Non-Surgical Outcomes in Inflammatory Bowel Disease

This section explores a subset of available literature related to the association between frailty and non-surgical outcomes, such as hospitalization, infections, and mortality, in IBD patients. A comprehensive systematic review was conducted that focused on the relationship between frailty and sarcopenia and adverse non-surgical clinical outcomes.[18] While some of the included studies are outlined below, a complete overview of the review is available in Chapter 3.

Kochar et al. conducted a retrospective cohort study that examined the association between frailty and the increased risk of infection following the administration of immunosuppressive agents, where a modified version of the Hospital Frailty Risk Score was used to quantify frailty.[109] This tool was adapted to include only 10 ICD-9 codes for frailty in this study, and those who possessed at least one relevant ICD-9 code for frailty, such as wheelchair dependence and urinary incontinence, in the two years prior to immunosuppressive treatment were placed within the frail cohorts. The full list of ICD-9 codes utilized in the study can be seen in Table 4. As previously mentioned, the primary outcome tracked in this study was the occurrence of an infection in the 1-year period following the administration of either anti-tumor necrosis factor (anti-TNF) medications or immunomodulators, and the secondary outcome looked at was

infection-related hospitalizations that occurred during the same period.[109] In general, it was found that frailty is independently associated with both an increase in infections as well as infection-related hospitalizations, where in the case of both anti-TNF and immunomodulator administration the infection rate increased by 10% for frail participants. When considering possible limitations, it should be noted that the Hospital Frailty Risk Score was developed to determine frailty in an older population, so it is possible that the frailty of younger participants went undetected in this study.[77,109] However, along those same lines, due to only one frailty code being required to designate a participant as frail, the given cohort of frail individuals may include those who would typically be deemed fit by tools such as the CFS. A second possible limitation is the reduction in ICD-9 codes that the researchers used to determine the presence of frailty, as this adapted score again only took into account 10 codes. This adaptation both increases the risk of misclassifying participants within the cohorts, and further heightens the probability of some frailty cases going undetected.

Table 4. ICD-9 Codes Used by Kochar et al. to Identify Frailty

Frailty Defining Diagnosis	**ICD-9 Code**
Other protein calorie malnutrition	263.8
Unspecified protein calorie malnutrition	263.9
Subacute delirium	293.1
Persistent mental disorders due to conditions classified elsewhere	294
Difficulty in walking	719.7
Urinary incontinence	788.3
Senility without psychosis	797
Other ill-defined conditions Wheelchair dependence	799.89 v46.3
Unspecified problem related to lifestyle	V69.9

Table adapted from Kochar et al., 2020.[109]

*The presence of at least one ICD-9 code denotes frailty.

A second, similar study was conducted by Kochar et al. which focused mainly on the possible association between frailty and increased mortality rates in IBD patients. Participants were recruited and separated in the same fashion as the previously described study, and the cohort design was retrospective as well.[109,110] Again, similar to their previous study, these researchers used an adapted Hospital Frailty Risk Score to determine the presence of frailty in the IBD patients, where the occurrence of at least one ICD-9 code shown in Table 4 resulted in the placement of the participant into the frail cohort. Through this study, it was determined that frailty was independently associated with the following outcome variables: longer follow-up periods, increased comorbidity scores, and increased mortality rates.[110] In particular, the frail cohort had mean comorbidity scores five points greater than that of the fit cohort, their mortality rate was 15% greater, and their follow-up periods were on average three years longer. However, it should be noted that the causes of death were not determined for any of the given participants, which is a substantial limiting factor, alongside the limiting factors from the previous study by Kochar et al. that are also applicable here, for this study and may infringe on the accuracy of the reported mortality results.

Next, a study conducted by Qian et al. investigated if frailty was an independent predictor of increased mortality and hospital readmission rates utilized similar techniques as Kochar et al., and produced comparable results.[109,111] Specifically, this was a retrospective cohort study that utilized the Hospital Frailty Risk Score to detect frailty in the adult IBD participants who had all been admitted to the hospital for reasons related to their IBD diagnoses. It should be noted that unlike the previously described studies, Qian et al. opted to utilize the un-adapted version of the Hospital Frailty Risk Score, thus taking into account 109 ICD-9 codes.[111] Again, similar to the associations reported by Kochar et al., frailty was found to be independently associated with a

significantly increased risk of both post-discharge mortality and hospital readmissions, where the latter was found to be due mainly to infections. Specifically, participants who were deemed to be frail experienced a 57% increase in post-discharge mortality risk and a 21% greater risk of readmission.[111] Possible limitations of this study include the grouping of medium- and high-risk frailty participants together in the same cohort and a lack of data pertaining to out-of-hospital participant mortalities. Qian et al. describe that the progression of IBD may be associated with adverse health outcomes, where this topic serves as a possible area for future research. This possibility for research is supported by Kochar et al., as it was stated that the trajectories of frailty should be looked at in those who are afflicted by such chronic disorders as IBD.[109,111]

2.9.1.2 Observational Studies Related to Frailty and Surgical Outcomes in Inflammatory Bowel Disease

The impact of frailty on adverse surgical outcomes in IBD patients is now focused on, where four manuscripts are summarized to determine the relationship between frailty and the specific listed outcomes.

First, Obeid et al. looked at frailty as a possible predictor of post-operative complications following colectomies in a retrospective cohort study, where participants were separated into frail and fit groups.[112] To measure frailty, the researchers used a modified version of the CSHA Frailty Index that consisted of 11 variables which may indicate the presence of frailty, such as functional status, diabetes mellitus, and a history of pneumonia. A frailty score was then determined, on a scale from 0 – 1 for each patient based on the proportion of given frailty variables present within their medical history.[112] Obeid et al. primarily tracked the occurrence of Clavien class IV and V complications in participants following their colectomies, which can be defined as complications requiring intensive care unit-level care and mortality, respectively.[112]

The given results of this study support an independent association between frailty and adverse post-operative complications, as the prevalence of either Clavien class IV or V complications was reported to be 59.3% for those in the frail cohort, compared to 3.2% for those deemed to be fit. One major limitation of this study is that outside of the given deficits outlined in the frailty tool, no comorbidities were recorded for the participating subjects, which may have contributed to the frailty present as well as to the adverse outcomes of the patients.[113] Obeid et al. does assert that the future study of frailty in the long-term is necessary to evaluate how this chronic affliction may impact the outcomes of patients.[112]

Telemi et al. conducted a similar study in relationship to adverse outcomes following colectomies, however these researchers only included patients with UC in this study. Again, similar to the previously described study, patients with UC were identified through the use of ICD-9 codes in this retrospective cohort study, and frailty was scored using a frailty index based on the CSHA Frailty Index.[114] The specific outcomes tracked by Telemi et al. included 30-day post-operative morbidity rates, and Clavien class IV and V complications. The researchers reported that as frailty scores increased from 0 to 0.18 or greater, which corresponds to the presence of at least two specified frailty variables, the morbidity rate significantly increased from 25.4% to 52.1%, providing evidence that frailty may be a predictor of adverse post-operative outcomes.[114] Further, frailty was reported to be independently associated with occurrences such as septic complications, serious morbidities, and subsequent surgeries. A possible limitation of this study, which extends to the other studies discussed that rely on a modified tool to quantify frailty, is that the physical phenotype of frailty is not considered. This means that participants that are afflicted by such aspects as slow walking speed and significant unintentional weight loss would not be categorized as frail.

Next, a retrospective cohort study conducted by Cohan et al. was reviewed, which looked at the possible association between frailty and post-operative outcomes following ileal pouch-anal anastomoses (IPAAs) in UC patients, where ICD-9 codes were again used to identify these individuals.[115] A frailty trait count was utilized to determine the presence of frailty in participants, where six aspects are considered, such as diabetes mellitus, congestive heart failure and dependent functional status. Cohan et al. focused on two main outcome variables: the number of major complications that occur in the 30-day post-operative period and the hospital stay length. However, contrary to other published literature, these researchers found no significant association between the presence of frailty and either of the listed outcome variables, which was reported to be evidence to support that IPAAs can be performed safely in frail UC patients.[115] The utilization of the frailty trait count should be considered alongside these results, as this tool may have let many frail participants go undetected due to the relatively low number of frailty aspects considered.

The final article looked at in relation to frailty and surgical outcomes was published by Robinson et al., which took a broad look at the impact of frailty on post-operative outcomes. This prospective cohort study included elderly participants who had undergone colorectal or cardiac operations, however only the colorectal surgeries will be focused on.[116] This study utilized a comprehensive measurement of frailty, where seven different measurements were combined to give composite scores for each participant, including the Charlson Comorbidity Index (CCI), the Katz Score, and the Timed Up and Go test. Again, the outcome variables focused on in this study were post-operative complications and hospital stay length, and it was determined that these outcomes both increased alongside the summative frailty scores. Specifically, in relation to those who had undergone colorectal surgeries, those participants who were deemed to be frail were 13

times as likely to be afflicted by adverse post-operative outcomes as compared to the fit participant group.[116] It should be noted that the population of this study was almost entirely men, so one limitation is that these results are not generalizable to the overall frail or IBD population. Further, each participant submitted a self-report on their fall history, which may not have been accurate if they were simultaneously afflicted by a cognitive deficit such as dementia.

As outlined above, and as stated in additional published articles, frailty has been reported to have a significant association with adverse surgical outcomes, such as post-operative complications, 30-day post-operative morbidity rates and subsequent surgeries.

2.9.2 Review of Studies Related to the Association Between Sarcopenia and Inflammatory Bowel Disease

2.9.2.1 Observational Studies Related to Sarcopenia and Non-Surgical Outcomes in Inflammatory Bowel Disease

Similar to the above section related to frailty and non-surgical outcomes in IBD patients, the relationship between sarcopenia and adverse clinical outcomes in this same population was also investigated. The conducted systematic review looked at this topic and found eight related articles, however none of the given literature unanimously supported an association between the presence of sarcopenia and non-surgical outcomes in IBD patients. Specifically, the findings related to therapeutic efficacy, infections, need for therapy escalation, and hospitalizations were equivocal.[18] The following three article summaries are a subset of those included in the review, and serve to illustrate the conflicting evidence on this topic.

Campbell et al. utilized radiological imaging, namely abdominal MRI and CT images, in order to quantify sarcopenia in a cohort of adult IBD patients to investigate if an association between the presence of sarcopenia and infections, hospitalizations, or response to therapy exist.[117] The given

cut-off values given were <38.5cm^2/m^2 for women and <52.4cm^2/m^2 for men, meaning that any participant with a value less than the appropriate value for their sex would be deemed to be sarcopenic. However, in this study, an association was only found between sarcopenia and infection rates in those ≥50 years old, where no significant relationship was found in participants of younger ages, or between sarcopenia and hospitalizations or clinical response to therapy.[117]

Next, a retrospective study was conducted by Grillot et al. that looked at the possible association between sarcopenia and hospitalizations in CD patients.[118] Similar to the methods of Campbell et al., these researchers utilized CT imaging in order to quantify sarcopenia, where the same cut-off points were used to designate which participants were deemed to have a normal SMI and those who were deemed sarcopenic. However, in this study, contrary to the findings of the previous article, sarcopenic participants were found to have a significantly greater hospitalization rate compared to the control cohort, although this association did not stand when multivariable analysis was completed.[118]

The third retrospective study, conducted by Holt et al., looked at the relationship between sarcopenia and early treatment failure related to anti-TNF medication in patients with IBD.[119] Similar to both Campbell et al. and Grillot et al., Holt et al. utilized radiological abdominal imaging to measure muscle quantity, where sarcopenia was defined as less than the gender-median skeletal muscle area. Following analysis, sarcopenic patients were found to have a significantly shorter time to anti-TNF treatment failure compared to the control cohort.[119]

2.9.2.2 Observational Studies Related to Sarcopenia and Surgical Outcomes in Inflammatory Bowel Disease

The relationship between sarcopenia and surgical outcomes in IBD patients is heavily researched relative to that of non-surgical clinical outcomes.[120] Similar to the previous three sections, due to

the number of relevant articles only a subset will be summarized. In general, similar to studies that focus on the association between sarcopenia and non-surgical outcomes, those that concentrate on surgical outcomes, such as need for IBD-related surgeries, post-operative complications, and surgical site infections, often utilize cross-sectional radiological imaging as the main method of quantifying skeletal muscle.

First, Berger et al. conducted a retrospective cohort study that concentrated on the relationship between low SMI, quantified using abdominal CT imaging, and the risk of 30-day post-operative infectious complications in IBD patients.[121] Interestingly, and dissimilar to other sarcopenia articles discussed previously, these researchers used cut-offs relative to both sex and BMI for male participants, increasing the validity of SMI quantification in this cohort. Specifically, the cut-off values used were the following: $\leq 43 cm^2/m^2$ for males with a BMI <25, $\leq 53 cm^2/m^2$ for males with a BMI ≥25, and $\leq 41 cm^2/m^2$ for females no matter their BMI value.[121] Following multivariable analysis, where BMI was controlled for, it was determined that an association existed between sarcopenia and post-operative infectious complications in IBD patients.[121]

Next, Fujikawa et al. conducted a retrospective cohort study in order to investigate the association between sarcopenia, as quantified through CT imaging at the level of the psoas muscle, and surgical site infections in IBD patients.[122] Again, dissimilar to the other sarcopenia-focused articles discussed previously, these researchers focused on the level of the psoas muscle in order to quantify low SMI, where the utilized cut-offs designating sarcopenia were the bottom quartile for males and females separately. After multivariable analysis was completed, Fujikawa et al. determined that sarcopenia was independently associated with post-operative IBD surgical site infections in the given IBD patient population.[122]

Finally, Zhang et al. proposed that an association existed between sarcopenia and major post-operative complications, such as renal failure, stoma stenosis, and anastomotic leakage, in a population of patients with CD undergoing bowel resections.[123] Again, similar to most other sarcopenia-based articles described, these researchers utilized CT imaging at the abdominal level to quantify sarcopenia, where the given SMI cut-offs were <55 cm^2/m^2 for male participants and <39 cm^2/m^2 for female participants.[123] Following multivariable analysis, sarcopenia, alongside pre-operative enteral nutrition status, was found to be an independent predictor of severe post-operative complications.

2.9.3 Review of Studies Related to the Association Between Malnutrition and Inflammatory Bowel Disease

2.9.3.1 Observational Studies Related to Malnutrition and Non-Surgical Outcomes in Inflammatory Bowel Disease

Articles with a primary aim of determining associations between malnutrition and adverse non-surgical outcomes were then researched. Similar to the previous sections, only a subset of the returned articles will be outlined due to the amount of literature published on this topic.

First, a cross-sectional study was conducted that focused on the association between malnutrition, as defined using the PG-SGA, and the occurrence of active disease or the number of 12-month hospital admissions.[124] In this study population, 16.3% were found to be moderately malnourished or suspected of being malnourished, which was defined as a PG-SGA of B, as no severely malnourished (PG-SGA C) were identified. Using independent sample t-tests, this study reports there were significant associations between a malnourished state (PG-SGA B) and both clinical outcomes (active IBD: P=0.002; 12-month hospital admission: P=0.028).[124]

Next, Nguyen et al. proposed that an association existed between protein-calorie malnutrition and health outcomes, such as mortality and mean hospital LOS, in IBD patients.[125] In this study, malnutrition was defined using relevant ICD-9 codes, where micronutrient deficiencies were excluded. Compared to those not affected by malnutrition, those patients deemed to be malnourished had a significantly higher risk of in-hospital mortality ($P<0.0001$). Similarly, the mean hospital LOS for malnourished patients was over double that of patients not deemed to be malnourished ($P<0.00001$).[125]

Finally, a study was published by Gajendran et al. that looked at the significant risk factors for emergency department visits in IBD patients.[126] Malnutrition was identified by the presence of a relevant IBD-9 malnutrition-defining code, which was found to be significantly associated with the risk of hospitalization at the time of emergency department visit (odds ratio [OR] 6.29, $P<0.001$).[126]

2.9.3.1 Observational Studies Related to Malnutrition and Surgical Outcomes in Inflammatory Bowel Disease

The impact of malnutrition of the occurrence of surgical outcomes in IBD patients will now be focused on, where both post-operative infectious risk and post-operative complications were researched.

Yamamoto et al. conducted a case-control study in which malnutrition was defined using the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines, where the presence of at least one of the following designated patients as malnourished: 10-15% 6-month weight loss, BMI $<18.5 kg/m^2$, SGA categorization of C, or serum albumin $<30 g/L$.[127] The focus of this study was to investigate the association between pre-operative nutrition status and various surgical outcomes. In patients who had received biologic therapy in the 8-week period prior to

surgery, poor nutrition as defined above significantly increased the risk of post-operative infections (P=0.03).[127]

Next, a retrospective cohort study published by Ayoub et al. assessed the association between malnutrition and post-operative GI surgery complications, where malnutrition was defined using ESPEN guidelines.[128] The presence of >10% 6-month weight loss was found to be significantly associated with post-operative non-infectious complications (adjusted odds ratio [aOR] 15.55, P<0.01). Further, patients who received pre-operative total parenteral nutrition for at least 60 days had a significantly lower risk of these complications (aOR 0.07, P=0.03).[128]

Lastly, a study conducted by Schiesser et al. focused on the association between malnutrition and post-operative complications following elective GI surgeries.[129] Although three different assessments were used to diagnose frailty, only the nutrition risk score was found to be significantly associated with post-operative complications following multiple regression analysis (aOR 4.20, P=0.024).

Chapter 3: A Systematic Review of the Association Between Frailty or Sarcopenia and Adverse Outcomes in Inflammatory Bowel Disease

3.1 Introduction

IBD, which includes UC, CD, and IBD type unclassified, is a chronic autoimmune condition that impacts the GI system, where genetic predispositions, environmental influences, and improper immune responses each likely contribute to the development of this disease.[2] The incidence of IBD is distributed in a bimodal fashion, where most novel cases are diagnosed between the ages of 20 and 30, and only 10-15% diagnosed at or following age 60.[20,21,130] However, the management of IBD based on chronological age alone is not advised, as this characteristic does not always accurately reflect the true physiologic reserve an individual possesses to endure stressor events.[69] In contrast, the concepts of frailty and sarcopenia have been reported to act as appropriate measures of physiologic reserve, which can serve to provide information allowing for proper clinical decision-making to occur.[131]

Frailty, which again demonstrates the physiologic reserve of an individual, can be characterized by the decline of multiple physiological systems.[71] Even though frailty and sarcopenia can be considered as distinct concepts, sarcopenia is defined as the reduction of both muscle mass and function, which represents the Fried phenotype of frailty.[17,90] While frailty has been well documented to act as a prognostic marker of adverse non-surgical outcomes such as hospitalizations and mortality in other populations, the evaluation of frailty in the IBD population has mainly centered around the occurrence of surgical complications and outcomes.[132] However, a recent increase in research related to the association between frailty and non-surgical outcomes in the IBD population has emerged.[133–136] This systematic review aimed to summarize the available literature related to frailty and sarcopenia and adverse non-surgical

outcomes in an adult IBD population in order to identify associations and gaps in knowledge, as well as to guide future studies in this area.

3.2 Methods

3.2.1 Search Strategy

Four online databases were searched (MEDLINE [1946 Onward], EMBASE, Scopus, and CINAHL Plus [with Full Text]) through to June 18, 2021, using synonyms of IBD, frailty, and sarcopenia. Ovid was utilized to access MEDLINE (1946 Onward) and EMBASE, while Elsevier and EBSCOhost were used to retrieve articles from Scopus and CINAHL Plus (with Full Text) respectively. The following terms were used to search the four aforementioned databases: (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 CCI score or were included as part of a validated frailty index, as the CDM is considered a valid way of diagnosing frailty.[137] In order to avoid the consequences of "Table 2 Fallacy", only studies that focused on the association between frailty or sarcopenia and adverse clinical outcomes as the primary aim of the study were included in this review.[138,139] Independent screening of the titles and abstracts of articles was completed by two reviewers following the removal of duplicate studies. The full text of all remaining articles following the initial screening phase were then assessed by these two reviewers.

3.2.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria used for this systematic review are displayed in Table 5.

Table 5. Inclusion and Exclusion Criteria for the Given Systematic Review Studies

Inclusion Criteria	Exclusion Criteria
1) Published peer-reviewed observational retrospective, prospective, or case-controlled studies focusing on adult IBD patients, either in full manuscript or abstract form	1) Cross-sectional observational studies
2) Studies that had a primary focus on frailty or sarcopenia	2) Secondary articles, letters to the editor, case reports
3) Studies that assessed the association between frailty or sarcopenia and adverse non-surgical outcomes	3) Studies that focused on a pediatric (<18 years of age) or non-IBD population
4) Studies that included a control cohort of fit participants with IBD	4) Studies that focused on the association between malnutrition and outcomes

3.2.3 Outcomes

Non-surgical adverse outcomes were analyzed in this review, which included the following: infections, hospitalizations, mortality rates, clinical remission, mucosal healing, therapeutic response, frequency of IBD flares, length of hospital stays, hospital readmissions, and the addition or modification of IBD-related medications.

3.3 Results:

A total of 16 studies were included in this systematic review, with eight focused on frailty and the remaining eight focused on sarcopenia. Characteristics of each of the frailty- and sarcopenia-centered eligible studies are shown in Tables 6 and 7, respectively.

Table 6. 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[140]	Multicenter prospective cohort	410, outpatients	UC, CD, IBD-U	CCI[141]	Infections, hospitalizations, medication-related adverse events, discontinuation of IBD therapy, clinical effectiveness outcomes	Median of 102.40 weeks (52-104 weeks)
Bertani et *al*., 2020[142]	Multicenter prospective cohort	80, inpatients and outpatients	UC, CD	Reduced serum T3/T4 ratio[143]	Mucosal healing, clinical remission	54 weeks
Faye et *al*., 2021[133]	Multicenter retrospective cohort	1,405,529, inpatients	UC, CD	Presence of at least 1 ICD-9-CM code derived from Johns Hopkins ACG frailty-defining diagnoses[78]	30-day hospital readmission, 30-day readmission mortality, length of stay	30 days following index admission
Gondal et *al*., 2020[144]	Single center retrospective cohort	2,978, unknown	UC, CD, IBD-U	7-factor IBD frailty index >0.27 (derived from CSHA frailty index)[145]	Mortality, frequency of flares	Unknown
Kochar et *al*., 2020[109]	Multicenter retrospective cohort	3,975, inpatients and outpatients	UC, CD	Adaptation of the Hospital Frailty Risk Score (presence of at least 1 frailty-related ICD-9 code)[77]	Infections, infection-related hospitalizations	Anti-TNF cohort: Median for frail 12 months (7-17 months); Median for fit 7 months (4-14 months) Immunomodulator cohort: Median for frail 11 months (6-18 months); Median for fit 8 months (4-14 months)
Kochar et *al*., 2020[110]	Multicenter retrospective cohort	11,001, inpatients and outpatients	UC, CD	Adaptation of the Hospital Frailty Risk Score (presence of at least 1 frailty-related ICD-9 code)[77]	Mortality	Median for frail 10.90 years (5.10-17.90 years) Median for fit 7.70 years (3.10-14.40 years)
Qian et *al*., 2020[111]	Multicenter retrospective cohort	47,402, inpatients	UC, CD	Hospital Frailty Risk Score ≥5[77]	Inpatient mortality, readmissions, unplanned hospitalizations	Median for frail 10 months (8-11 months) Median for fit 10 months (7-11 months)
Singh et *al*., 2020	Multicenter retrospective cohort	5,987, inpatients and outpatients	UC, CD	Hospital Frailty Risk Score ≥5[77]	Infections requiring hospitalization	Mean for frail 11.60 ± SD 10.20 months Mean for fit 16.30 ± SD 14.70 months

ACG, Adjusted Clinical Groups; CCI, Charlson Comorbidity Index; CD, Crohn's disease; CSHA, Canadian Study of Health and Aging; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease type unclassified; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; T3, triiodothyronine; T4, tetraiodothyronine; TNF, tumor necrosis factor; UC, ulcerative colitis.

Table 7. 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[146]	Single center retrospective cohort	90, unknown	UC, CD	CT image at L3 (cut-off points <38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men)[123]	Hospital admissions, need for new biologic	24 weeks
Bamba et *al*., 2020[135]	Single center retrospective cohort	187, inpatients	UC, CD	CT image at L3 (cut-off points <38 cm^2/m^2 for women and <42 cm^2/m^2 for men)[147]	Prolonged LOS (≥30 days)	61-1,503 days
Campbell et *al*., 2020[117]	Single center retrospective cohort	98, inpatients and outpatients	UC, CD, IBD-U	CT/MRI scans at L3 (cut-off 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 year of biologic initiation)
Cushing et *al*., 2018[148]	Single center retrospective cohort	89, inpatients	UC	CT images at L3 (cut-off points <39 cm^2/m^2 for women and <55 cm^2/m^2 for men)[123]	Failure to respond to IVS	Unknown (however, based on outcome likely 3-7 days from time of index hospitalization)
Ge et *al*., 2021[136]	Single center retrospective cohort	23, unknown	UC	CT images at L3 (cut-off point SMI < the lowest sex-specific quartile)[149]	Failure to respond to IVS	5 days
Grillot et *al*., 2020[118]	Single center retrospective cohort	88, inpatients	CD	CT images at L3 (cut-off points <38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men)[150]	Recurrent hospitalizations, abscess(es), use of anti-TNFα therapy, change/dose optimization of anti-TNFα therapy	Median for sarcopenic 25.20 ± SD 21.60 months Median for non-sarcopenic 18.00 ± SD 17.20 months
Holt et *al*., 2017[119]	Single center retrospective cohort	68, unknown	UC, CD	CT/MRI images at L3 (cut-off point <gender-specific median skeletal muscle area)	Treatment failure (post-induction 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 days
Lee et *al*., 2020[151]	Single center retrospective cohort	79, unknown	CD	CT images at L3 (cut-off points <31 cm^2/m^2 for women and <49 cm^2/m^2 for men)[152]	Hospitalizations, first prescription of biologic, immunomodulator, or corticosteroid	Median 34.80 months

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CT, computerized tomography; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease type unclassified; IVS, intravenous corticosteroids; L3, third lumbar level; LOS, length of stay; MRI, magnetic resonance imaging; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.

3.2.1 Results of the Frailty-Based Studies

The findings regarding associations between frailty and adverse non-surgical outcomes were mixed. First, all hospitalization- (admissions, readmissions, and LOS) and mortality-related outcomes were found to be significantly associated with the presence of frailty, as determined using the assessment methods outlined in Table 6. In contrast, the outcomes of infections or therapeutic efficacy/escalation returned mixed results in relation to their association with frailty.

3.2.2 Results of the Sarcopenia-Based Studies

As a whole, the associations between sarcopenia and each of the given adverse outcomes (hospitalizations, prolonged LOS, infections, impaired therapeutic response, addition/modification of IBD-related medications) were found to be equivocal. While some of the studies returned significant results in relation to the association between sarcopenia and the stated outcomes, these were not consistent between different studies.

3.4 Discussion

Through the summarization of available literature related to the association between frailty or sarcopenia and adverse non-surgical outcomes in the IBD population, it was determined that frailty is independently associated with the occurrence of hospitalization- (admissions, readmissions, and prolonged LOS) and mortality-related outcomes in the adult IBD population. However, most of the frailty-based studies utilized modified frailty assessments have not been validated for use in the IBD population.[109–111,134,144]

Chapter 4: Frailty as Defined by Handgrip Strength, the Abridged Patient-Generated Subjective Global Assessment, and the Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool is Independently Associated with Hospitalizations in Adults with Inflammatory Bowel Disease

4.1 Introduction:

IBD is an autoimmune condition influenced by environmental factors and genetic predispositions that impacts the GI system and gives rise to both local and systemic manifestations.[2–4] While a bimodal distribution of incidence exists for IBD, with the majority of novel cases being diagnosed between the ages of 20 and 30, and only 10-15% of new diagnoses occurring after the sixth decade of life,[19,20] a greater prevalence of IBD is present in those ≥45 as opposed to <45 years of age.[27] Advanced age in IBD patients has been reported to be associated with increased inpatient mortality, thrombotic complications, and high health resource utilization.[153–155] However, chronological age does not always accurately reflect "biological age", or the extent of physiological reserve an individual possesses to endure stressors.[156] More recently, frailty has been independently associated with all-cause hospitalizations, all-cause mortality, and increased mean hospital LOS, demonstrating the prognostic ability of frailty in a variety of chronic disease states.[157–159]

This idea of physiological reserve is best demonstrated by the concepts of frailty, sarcopenia, and malnutrition, where the presence of any of these deficits results in an increased degree of susceptibility and vulnerability. Though frailty, sarcopenia and malnutrition are distinct concepts, due to the multifaceted nature of frailty and the contribution of sarcopenia and malnutrition to the overall degree of vulnerability, all three of these concepts were considered to be valid determinants of frailty.

While the majority of literature surrounding frailty and IBD focuses on population-based administrative health data, the purpose of this study was to determine if frailty, measured through the CFS, HGS, SGA, abPG-SGA, or SaskIBD-NRT, is associated with an independent increased risk of adverse clinical outcomes in outpatients with IBD. It is hypothesized that frailty defined using these parameters will be associated with a heightened risk of IBD-related hospitalizations and surgeries, such as colectomies and small bowel resections.

4.2 Methods:

4.2.1 Study Population Selection

Patients with a confirmed diagnosis of IBD, either UC or CD, followed by a gastroenterologist at one of two IBD specialty ambulatory care clinics in Alberta, Canada (at the University of Alberta and Calgary) were prospectively enrolled between May 2017 and March 2018. The Health Research Ethics Boards at the University of Alberta (Pro00073470) and the University of Calgary (REB17-0890) both provided approval for this study. Patient data was collected from the prospectively collected database of a previously published study by Taylor et al., as well as through electronic medical record (EMR) chart reviews conducted on Alberta Netcare and Connect Care.[160] IBD patients ≥18 years of age and with an IBD disease duration ≥3 months at the time of enrolment were included in this study. All included patients provided written informed consent prior to the initiation of the study.

The exclusion criteria for patients were as follows: 1) presence of a major medical comorbidity (chronic renal failure, chronic pulmonary disease, or congestive heart failure [ejection fraction <40%]), 2) previous colectomy, 3) current pregnancy, 4) inability to provide informed consent, and 5) had English language difficulties.

4.2.2 Frailty, Sarcopenia, and Malnutrition Assessment

Assessment of frailty, sarcopenia, and malnutrition was completed at the enrolment of each patient into this study, which again occurred from May 2017 to March 2018. The CFS scoring system is available in Appendix 1, and the breakdown of the SGA, abPG-SGA, and SaskIBD-NRT systems can be found in Appendix 2.

The CFS[70] was utilized in order to quantify frailty in included patients, where research assistants completed the subjective assessment and administered the appropriate scores. In order to ensure consistency of the scores, each research assistant was trained on how to properly administer the CFS assessment and how to translate findings into a score from 1 – 9. Any patient with a CFS score of <4 was considered fit, while any patient with a score of ≥4 was considered frail in the categorized form of this scale.

Sarcopenia was assessed using HGS, which again was obtained by trained research assistants through the use of a Jamar® Hydraulic Hand Dynamometer. The presence of sarcopenia was determined using the cut-offs of <16 kg and <27 kg, for female and male patients respectively.[90] While MAMC information was collected by a registered dietician, these values were not used to determine the presence of sarcopenia as recommended by the EWGSOP2.[90]

Finally, malnutrition information was collected using the SGA, the abPG-SGA and the SaskIBD-NRT, where the SGA groupings were determined by a registered dietician and the abPG-SGA scores and SaskIBD-NRT groupings were self-reports completed by the patients themselves. Those deemed as Moderate (B) or Severe (C) on the SGA were considered to be malnourished, whereas abPG-SGA and SaskIBD-NRT scores are presented as both ordinal variables, from 0 – 35 and 0 – 9 respectively, and categorical groupings, where the cut-off designating risk of

malnutrition was ≥6 for the abPG-SGA and either 3 – 4 (medium risk) or ≥5 (high risk) for the SaskIBD-NRT.[105,108,160]

4.2.3 Baseline Characteristics and Outcomes

In addition to frailty, sarcopenia, and malnutrition information collected at enrolment, the following baseline characteristics were also collected for patients when available: age, sex, location of IBD care clinic, IBD subtype (UC or CD), disease duration, follow-up length, number of IBD-related hospitalizations in the 12-month period prior to baseline, information regarding the disease phenotype of UC or CD using the Montreal Classification[23] system, pMayo[37] or HBI[32] scores, IBD-related surgeries at any point prior to baseline (small bowel resection/stricturoplasty, ileocecal resections, or segmental colonic resections), relevant laboratory tests (albumin, hemoglobin, c-reactive protein, and fecal calprotectin), BMI, smoking status, exposure to biologic medications (Remicade [infliximab], Renflexis [infliximab-abda], Inflectra [infliximab-dyyb], Simponi [golimumab], Humira [adalimumab], Entyvio [vedolizumab], or Stelara [ustekinumab]), exposure to 5-ASA medications (Sulfasalazine, Salofalk [mesalamine], Asacol [mesalamine], Mezavant [mesalamine], or Pentasa [mesalamine]), exposure to steroids (prednisone, Entocort [budesonide], Cortiment [budesonide multi-matrix], intravenous [IV] Solu-medrol [methylprednisolone], or IV Solu-cortef [hydrocortisone]), and exposure to immunomodulators (methotrexate, Imuran [azathioprine], or 6-mercaptopurine).

The outcomes of interest for this study are IBD-related hospitalizations and IBD-related surgeries at any point following baseline. The following reasons for hospitalizations were included: disease flares requiring medical management, infections (excluding abscesses related to perforating disease), complications of previous IBD-related surgeries, colorectal dysplasia,

colorectal cancer, and IBD drug intolerances. Similarly, the following reasons for IBD-related surgical procedures were included: disease activity, colorectal dysplasia, and colorectal cancer.

The following data was collected in relation to the outcome of IBD-related hospitalizations: time-to-first hospitalization and the LOS of all IBD-related hospitalizations. In contrast, only the type and time-to-first IBD-related surgery was collected, with the following types of surgical procedures being included: colectomy (with pouch or ileostomy), small bowel resection/stricturoplasty, ileocecal resection, segmental colonic resection, and post-operative complications arising from a previous IBD-related surgery. Perianal fistulotomies and incision and drainage of perianal abscesses were not included as a surgical procedure if they were performed alone.

4.2.4 Statistical Analysis

Logarithm relative hazard graphs and both Cox univariable and multivariable logistic regression models were constructed, with the logarithm relative hazard graphs and Cox multivariable logistic regression models adjusting for the following confounders: age, sex, disease phenotype (mild: proctitis/left-sided colitis [UC] or inflammatory behavior [CD]; severe: pancolitis [UC] or stricturing/penetrating behavior [CD]), disease activity (remission or level of disease activity determined by pMayo[37] [UC] or HBI score[32] [CD]), exposure to biologics, exposure to steroids, previous IBD-related surgeries, and present comorbidities (determined using the CCI; categorized into no comorbidities and ≥1 comorbidity). Appendix 3 displays the associations between all confounding variables and frailty as defined by each of the frailty assessments and screening tools. Multiple regression models were also constructed in order to analyze the outcome of proportion of time spent in hospital due to IBD-related reasons, where the total summed LOS of each patient was divided by the follow-up period to yield the proportion of time

spent in hospital. Differences between baseline characteristics, frailty, sarcopenia, and malnutrition measurements or scores were determined using independent sample two-sided t-tests for continuous data or Pearson's chi-squared tests for categorical data. A bivariate correlation test with a two-tailed test of significance was completed to analyze the possible correlation between the markers of frailty, where Spearman correlation coefficients were used to indicate the extent of the correlations. All statistical analyses were performed using SPSS statistical software (v28).

4.3 Results:

4.3.1 Baseline Characteristics

Table 8 displays the baseline characteristics of all 163 included patients (35.6% CD and 64.4% UC), who had a mean age 42.3 (±15.9) years, were 50.9% female, and had a mean HBI score of 3.7 (±3.9) and mean pMayo score of 1.3 (±1.8). These patients were followed over a mean period of 43.9 (±10.1) months. Additional columns in Table 8 serve to demonstrate all baseline characteristics according to IBD subtype (UC and CD). As demonstrated by Table 8, the mean age (38.7 years [UC]; 44.2 years [CD], P=0.035) and disease duration (118.3 months [UC]; 169.8 [CD], P=0.009) of CD patients were significantly higher than those of UC patients. Regarding medication exposure, UC patients had a significantly increased current exposure to 5-ASA medications (50.0% [UC]; 12.4% [CD], P<0.001), whereas the proportion of current exposure to immunomodulators was significantly higher in CD patients (36.2% [UC]; 48.6% [CD], P=0.008).

It should be noted that even though a significant difference appears to exist between UC and CD patients in relation to IBD-related surgeries prior to baseline, all patients with prior colectomies

were excluded from the study. Therefore, no included UC patients had experienced any previous IBD-related surgeries.

Table 8. Baseline Characteristics of Patients

Variable	Total Patients (n=163)	Ulcerative Colitis Patients (n=58)	Crohn's Disease Patients (n=105)	P-value*
Age				
Mean age, years (SD)	42.3 (15.9)	38.7 (15.8)	44.2 (15.7)	**0.035**
<60 years	139 (85.3%)	52 (89.7%)	87 (82.3%)	
≥60 years	24 (14.7%)	6 (10.3%)	18 (17.1%)	
Sex				0.88
Male	80 (49.1%)	28 (48.3%)	52 (49.5%)	
Female	83 (50.9%)	30 (51.7%)	53 (50.5%)	
Disease Duration				
Mean duration, months (SD)	151.5 (137.3)	118.3 (96.9)	169.8 (152.5)	**0.009**
≤24 months	19 (11.7%)	7 (12.2%)	12 (11.4%)	
>24 months	144 (88.3%)	51 (87.9%)	93 (88.6%)	
Follow-Up Length				
Mean length, months (SD)	43.9 (10.1)	42.2 (9.6)	44.9 (10.2)	0.10
Previous IBD-Related Hospitalizations				0.89
0, in previous 12 months	134 (82.2%)	48 (82.8%)	86 (81.9%)	
≥1, in previous 12 months	29 (17.8%)	10 (17.2%)	19 (18.1%)	
Montreal Classification				
MCUC (n=58)				-
1	1 (1.7%)	1 (1.7%)	-	
2	15 (25.9%)	15 (25.9%)	-	
3	42 (72.4%)	42 (72.4%)	-	
MCCD (n=105)				
Age at Diagnosis				-
≤16 years	22 (21.0%)	-	22 (21.0%)	
17 – 40 years	65 (61.9%)	-	65 (61.9%)	
>40 years	18 (17.1%)	-	18 (17.1%)	
Disease Location				-
Terminal Ileum	26 (24.8%)	-	26 (24.8%)	
Colonic	21 (20.0%)	-	21 (20.0%)	
Ileocolonic	58 (55.2%)	-	58 (55.2%)	
Upper GI Involvement				-
Yes	14 (13.3%)	-	14 (13.3%)	
No	91 (86.7%)	-	91 (86.7%)	
Disease Behavior				-
Inflammatory	48 (45.7%)	-	48 (45.7%)	
Stricturing	32 (30.5%)	-	32 (30.5%)	
Penetrating	25 (23.8%)	-	25 (23.8%)	
Perianal Fistula(e)				-
Present	23 (21.9%)	-	23 (21.9%)	
Absent	82 (78.1%)	-	82 (78.1%)	
Disease Activity				
pMayo Score (n=58)				
Mean score (SD)	1.3 (1.8)	1.3 (1.8)	-	-
<2	38 (65.5%)	38 (65.5%)	-	
2 – 4	14 (24.1%)	14 (24.1%)	-	
≥5	6 (10.3%)	6 (10.3%)	-	
HBI Score (n=105)				
Mean score (SD)	3.7 (3.9)	-	3.7 (3.9)	-
<5	73 (69.5%)	-	73 (69.5%)	

5 – 7	17 (16.2%)	-	17 (16.2%)	
8 – 16	13 (12.4%)	-	13 (12.4%)	
>16	2 (1.9%)	-	2 (1.9%)	
Overall Disease Activity (n=163)				0.46
Remission	111 (68.1%	38 (65.5%)	73 (69.5%)	
Mild	31 (19.0%	14 (24.1%)	17 (16.2%)	
Moderate	19 (11.7%	6 (10.3%)	13 (12.4%)	
Severe	2 (1.2%	0 (0.0%)	2 (1.9%)	
Previous IBD-Related Surgeries				**<0.001**
None	123 (75.5%)	58 (100.0%)	65 (61.9%)	
Small Bowel Resection / Stricturoplasty	20 (12.3%)	0 (0.0%)	20 (19.0%)	
Ileocecal Resection	15 (9.2%)	0 (0.0%)	15 (14.3%)	
Segmental Colonic Resection	5 (3.1%)	0 (0.0%)	5 (4.8%)	
Laboratory Tests				
Albumin (n=68)				
Mean albumin, g/L (SD)	42.1 (3.8)	43.2 (3.1)	41.6 (4.0)	0.07
<35g/L	3 (4.4%)	0 (0.0%)	3 (6.5%)	
≥35g/L	65 (95.6%)	22 (100.0%)	43 (93.5%)	
Hemoglobin (n=123)				
Mean hemoglobin, g/L (SD)	138.6 (16.7)	138.4 (21.0)	138.6 (14.5)	0.95
<120g/L	13 (10.6%)	7 (18.4%)	6 (7.1%)	
120 – 160g/L	102 (82.9%)	27 (71.1%)	75 (88.2%)	
>160g/L	8 (6.5%)	4 (10.5%)	4 (4.7%)	
C-Reactive Protein (n=122)				
Mean c-reactive protein, mg/L (SD)	4.7 (7.5)	4.3 (7.0)	4.9 (7.7)	0.64
<8.0mg/L	97 (79.5%)	33 (82.5%)	64 (78.0%)	
≥8.0mg/L	25 (20.5%)	7 (17.5%)	18 (22.0%)	
BMI				
Mean BMI, kg/m^2 (SD)	26.7 (5.6)	26.6 (6.1)	26.8 (5.3)	0.80
<25kg/m^2	67 (41.1%)	26 (44.8%)	41 (39.0%)	
25 – 29.9kg/m^2	63 (38.7%)	19 (32.8%)	44 (41.9%)	
≥30kg/m^2	33 (20.2%)	13 (22.4%)	20 (19.0%)	
Smoking Status				**0.048**
Non-Smoker	86 (52.8%)	34 (58.6%)	52 (49.5%)	
Previous Smoker	27 (16.6%)	4 (6.9%)	23 (21.9%)	
Current Smoker	50 (30.7%)	20 (34.5%)	30 (28.6%)	
Biologic Medication				0.07
None	38 (23.3%)	19 (32.8%)	19 (18.1%)	
Previous	6 (3.7%)	3 (5.2%)	3 (2.9%)	
Current	119 (73.0%)	36 (62.1%)	83 (79.0%)	
5-ASA Medication				**<0.001**
None	59 (36.2%)	7 (12.1%)	52 (49.5%)	
Previous	62 (38.0%)	22 (37.9%)	40 (38.1%)	
Current	42 (25.8%)	29 (50.0%)	13 (12.4%)	
Steroids				0.08
None	45 (27.6%)	12 (20.7%)	33 (31.4%)	
Previous	96 (58.9%)	34 (58.6%)	62 (59.0%)	
Current	22 (13.5%)	12 (20.7%)	10 (9.5%)	
Immunomodulators				**0.008**
None	39 (23.9%)	22 (37.9%)	17 (16.2%)	
Previous	52 (31.9%)	15 (25.9%)	37 (35.2%)	
Current	72 (44.2%)	21 (36.2%)	51 (48.6%)	

5-ASA, 5-aminosalicylic acid; BMI, body mass index; CD, Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; pMayo, Partial Mayo; SD, standard deviation; UC, ulcerative colitis.

*Significant differences between subgroups (UC and CD) at P<0.05. Bold values indicate statistically significant differences between groups.

In addition to the baseline variables displayed in Table 8, Table 9 displays the characteristics of frailty through the variables of CFS, HGS, SGA, abPG-SGA, and SaskIBD-NRT. Similar to the previous table, the characteristics of Table 9 are displayed for all IBD patients alongside additional columns for UC and CD patients separately.

As demonstrated by Table 9, the only marker of frailty that reflects a significant difference between the IBD subtypes is abPG-SGA, where the mean abPG-SGA of CD patients is significantly increased compared to that of UC patients (2.3 [UC]; 4.1 [CD], P=0.02).

Table 9. Baseline Frailty, Sarcopenia, and Malnutrition Characteristics of Patients

Characteristic	Total Patients (n=163)	Ulcerative Colitis Patients (n=58)	Crohn's Disease Patients (n=105)	P-value*
CFS				
Mean score (SD)	2.2 (1.1)	2.1 (1.0)	2.3 (1.1)	0.53
<4	146 (89.6%)	55 (94.8%)	91 (86.7%)	
≥4	17 (10.4%)	3 (5.2%)	14 (13.3%)	
HGS				0.08
Non-sarcopenic	149 (91.4%)	50 (86.2%)	99 (94.3%)	
Sarcopenic	14 (8.6%)	8 (13.8%)	6 (5.7%)	
SGA				0.29
Well (A)	136 (83.4%)	46 (79.3%)	90 (85.7%)	
Moderate (B)	27 (16.6%)	12 (20.7%)	15 (14.3%)	
Severe (C)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
abPG-SGA				
Mean score (SD)	3.5 (5.5)	2.3 (4.1)	4.1 (6.1)	**0.02**
<6	126 (77.3%)	47 (81.0%)	79 (75.2%)	
≥6	37 (22.7%)	11 (19.0%)	26 (24.8%)	
SaskIBD-NRT				
Mean score (SD)	1.61 (1.6)	1.29 (1.6)	1.78 (1.7)	0.494
Low Risk (0 – 2)	121 (74.2%)	47 (81.0%)	74 (70.5%)	
Medium Risk (3 – 4)	28 (17.2%)	7 (12.1%)	21 (20.0%)	
High Risk (≥5)	14 (8.6%)	4 (6.9%)	10 (9.5%)	

abPG-SGA, abridged patient-generated Subjective Global Assessment; CFS, Clinical Frailty Scale; HGS, handgrip strength; SaskIBD-NRT, Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool; SD, standard deviation; SGA, Subjective Global Assessment.

*Significant differences between subgroups (UC and CD) at P<0.05. Bold values indicate statistically significant differences between groups.

4.3.2 Effect of Frailty-Defining Measurement Tools on IBD-Related Hospitalizations and Surgeries

In total, 27 patients experienced at least one IBD-related hospitalization and 13 of those patients underwent IBD-related surgery. For all frailty-defining measurement tools (CFS, HGS, abPG-SGA, SGA, and SaskIBD-NRT) both Cox univariable and multivariable logistic regression models were constructed. Alongside these analyses, logarithm relative hazard graphs were crafted for each tool in relation to both stated outcomes. A summary of all calculated hazard ratios (HRs) and adjusted hazard ratios (aHRs) alongside 95% confidence intervals (CIs) and P-values are displayed in Table 10. It should be noted that all ordinal scales (CFS, abPG-SGA, and SaskIBD-NRT) are displayed as both their entire ordinal scores as well as the cut-offs to designate the presence of frailty or malnutrition. For the calculated HRs and aHRs of ordinal variables, the values do not correspond to an increased or decreased risk of IBD-related hospitalization outcomes and surgeries between fit and frail groups, but rather indicate a heightened or reduced risk of the outcomes alongside each unit increase of the scales.

Table 10. Cox Univariable HR and Multivariable aHR for IBD-Related Hospitalizations and Surgeries for all Frailty, Sarcopenia, and Malnutrition Assessments and Screening Tools

Measurement	Outcome	Univariable HR (95% CI)	P-value*	Multivariable aHR (95% CI)	P-value*
CFS Ordinal CFS Score (1 – 9)	IBD-Related Hospitalizations	0.981 (0.685 – 1.405)	0.916	0.969 (0.657 – 1.431)	0.875
	IBD-Related Surgeries	1.032 (0.632 – 1.685)	0.901	0.955 (0.555 – 1.642)	0.868
CFS Score ≥4	IBD-Related Hospitalizations	1.635 (0.565 – 4.728)	0.364	1.366 (0.449 – 4.156)	0.583
	IBD-Related Surgeries	1.599 (0.354 – 7.215)	0.541	1.019 (0.203 – 5.125)	0.982
HGS: Sarcopenia (HGS: females <16 kg, males <27 kg)	IBD-Related Hospitalizations	1.975 (0.683 – 5.715)	0.209	3.922 (1.111 – 13.849)	**0.034**
	IBD-Related Surgeries	1.898 (0.420 – 8.566)	0.405	3.341 (0.449 – 24.838)	0.239
SGA: Moderate Malnutrition (B)	IBD-Related Hospitalizations	1.224 (0.464 – 3.234)	0.683	0.822 (0.283 – 2.393)	0.720
	IBD-Related Surgeries	0.941 (0.208 – 4.244)	0.936	0.433 (0.090 – 2.086)	0.297
abPG-SGA Ordinal abPG-SGA Score (0 – 35)	IBD-Related Hospitalizations	1.084 (1.030 – 1.140)	**0.002**	1.071 (1.007 – 1.139)	**0.030**
	IBD-Related Surgeries	1.077 (1.007 – 1.152)	**0.030**	1.042 (0.960 – 1.131)	0.327
abPG-SGA Score ≥6	IBD-Related Hospitalizations	2.343 (1.072 – 5.122)	**0.033**	2.025 (0.802 – 5.114)	0.136
	IBD-Related Surgeries	3.282 (1.102 – 9.773)	**0.033**	2.080 (0.600 – 7.209)	0.248
SaskIBD-NRT Ordinal SaskIBD-NRT Score (0 – 9)	IBD-Related Hospitalizations	1.373 (1.117 – 1.686)	**0.003**	1.370 (1.055 – 1.780)	**0.018**
	IBD-Related Surgeries	1.482 (1.115 – 1.970)	**0.007**	1.349 (0.931 – 1.955)	0.114
SaskIBD-NRT: Medium Risk (Scores 3 – 4)	IBD-Related Hospitalizations	2.793 (1.171 – 6.663)	**0.021**	1.602 (0.512 – 5.014)	0.418
	IBD-Related Surgeries	4.876 (1.410 – 16.859)	**0.012**	2.707 (0.389 – 18.823)	0.314
SaskIBD-NRT: High Risk (Scores ≥5)	IBD-Related Hospitalizations	4.090 (1.471 – 11.370)	**0.007**	4.578 (1.362 – 15.389)	**0.014**
	IBD-Related Surgeries	6.204 (1.482 – 25.980)	**0.012**	4.398 (0.787 – 24.585)	0.092

abPG-SGA, abridged patient-generated Subjective Global Assessment; aHR, adjusted hazard ratio; CFS, Clinical Frailty Scale; CI, confidence interval; HGS, handgrip strength; HR, hazard ratio; IBD, inflammatory bowel disease, SaskIBD-NRT, Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool; SGA; Subjective Global Assessment.

*Significant HRs and aHRs at P<0.05. Bold values indicate statistically significant HRs and aHRs.

4.3.3 Effect of Frailty on IBD-Related Hospital Admissions and Surgeries

In regard to the frailty defined using CFS as a categorical variable, neither of the HRs related to the outcomes of IBD-related hospitalizations or surgeries were found to be statistically significant under univariable analysis. These findings were mirrored when the CFS was treated as an ordinal variable, as again neither HR was found to be statistically significant.

Similarly, when multivariable analysis was completed for the CFS, frailty as defined using either the categorical or ordinal form of the assessment was not found to be significantly associated with an altered risk of IBD-related hospitalizations or surgeries. All HR and aHR values, alongside 95% CIs and relevant p-values, can be found in Table 10.

Logarithm relative hazard graphs were constructed in order to illustrate the risk of IBD-related hospitalizations between the fit (CFS <4) and frail (CFS ≥4) patients (Figure 1A), as well as for the complete range of ordinal CFS scores (Figure 1B).

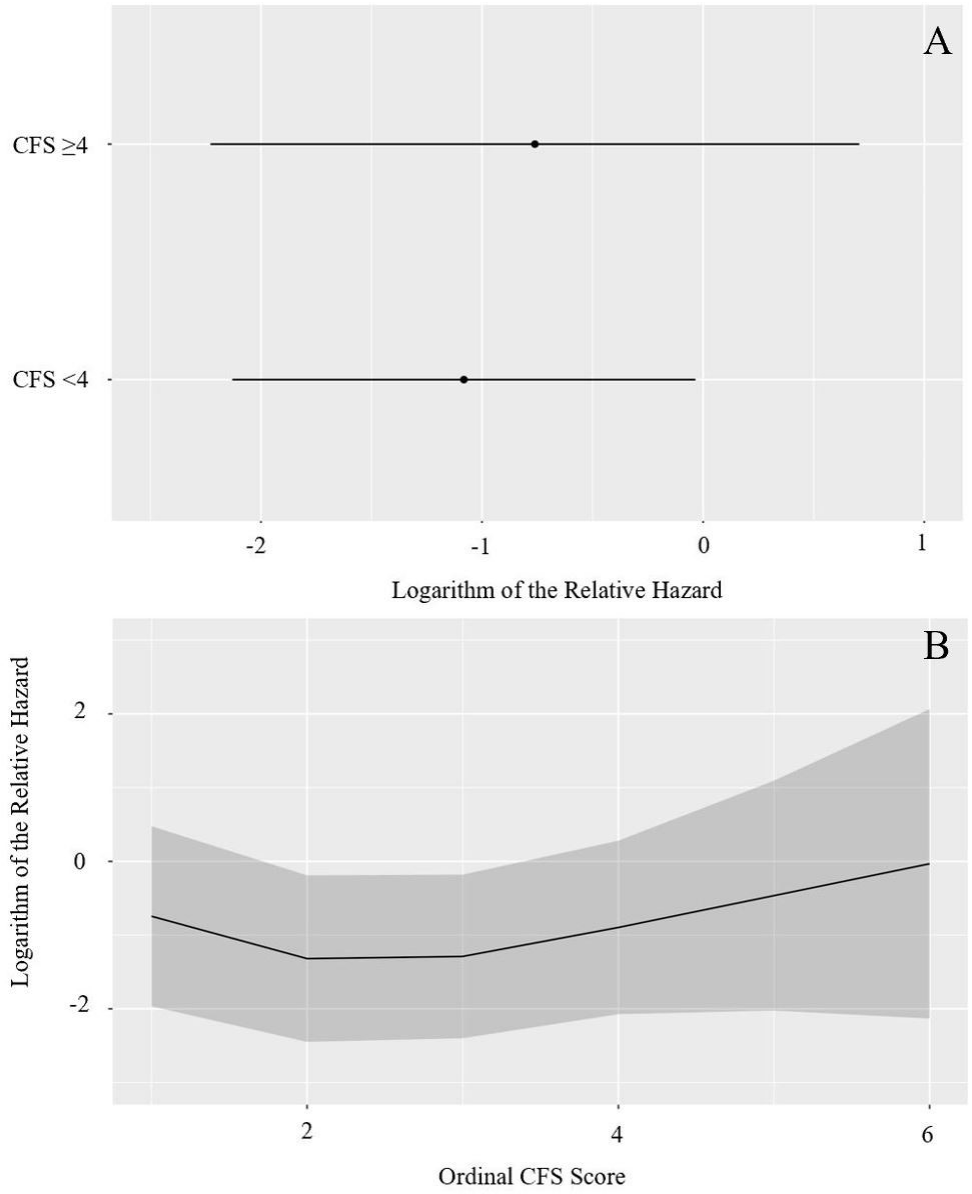

Figure 1. (A) Logarithm of the relative hazard graph demonstrating the risk of IBD-related hospitalizations between fit (CFS <4) and frail (CFS ≥4), (B) logarithm of the relative hazard graph demonstrating the risk of IBD-related hospitalizations as ordinal CFS score increases.

4.3.4 Effect of Sarcopenia on IBD-Related Hospital Admissions and Surgeries

Upon univariable analysis, the calculated HR for sarcopenic patients was 1.975 for the risk of IBD-related hospitalizations and 1.898 for the risk of IBD-related surgeries. However, as demonstrated by the stated p-values in Table 10, neither of the given HR values calculated using univariable analysis were statistically significant.

However, in contrast to that of the CFS, this multivariable regression analysis produced an aHR of 3.922 for the risk of IBD-related hospitalizations in sarcopenic patients, which was found to be statistically significant (P=0.034). Though the aHR produced for the risk of IBD-related surgeries in sarcopenic patients was 3.341, this value was not found to be statistically significant (P=0.239).

Figure 2 demonstrates the logarithm of the relative hazard of IBD-related hospitalizations between those patients deemed to be sarcopenia by HGS (females <16 kg, males <27 kg) and those deemed to be non-sarcopenic (females ≥16 kg, males ≥27 kg) by the same tool.

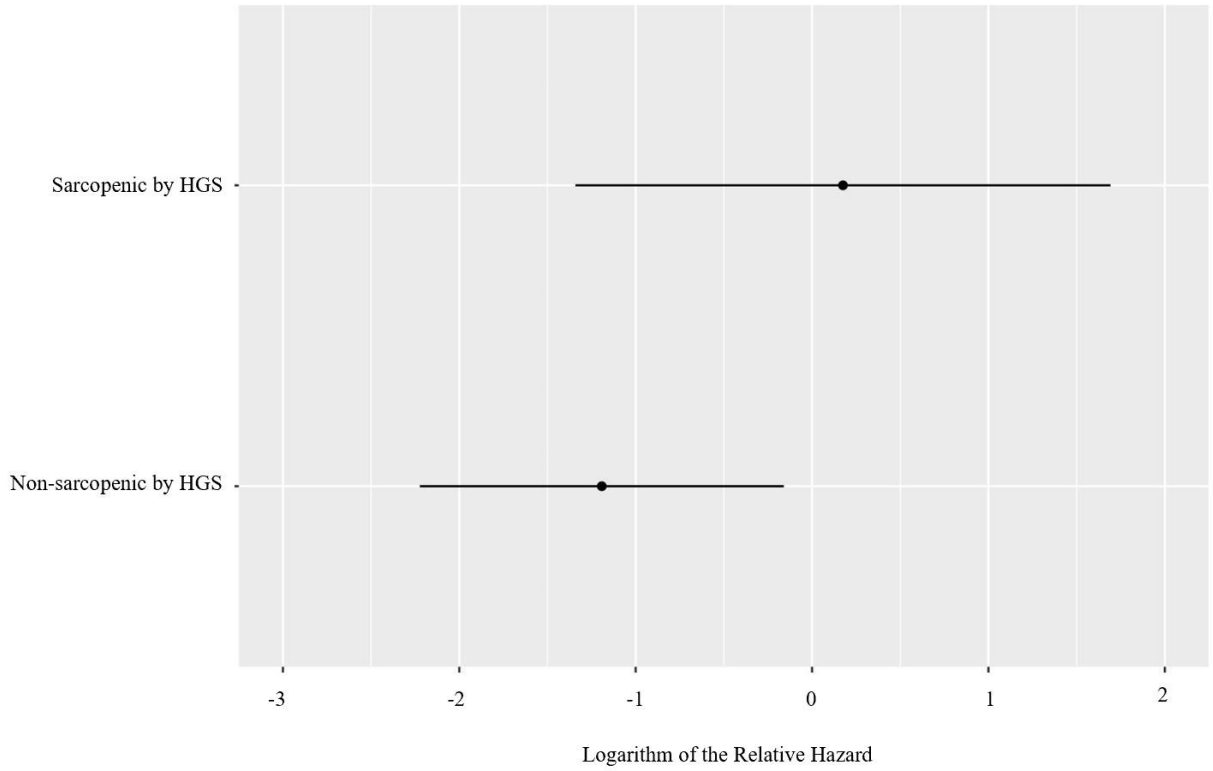

Figure 2. Logarithm of the relative hazard graph demonstrating the differing risk of IBD-related hospitalizations between non-sarcopenic (HGS: ≥16 kg for females, ≥27 kg for males) and sarcopenic (HGS: <16 kg for females, <27 kg for males).

4.3.5 Effect of Malnutrition on IBD-Related Hospital Admissions and Surgeries

When focusing on the SGA, neither the calculated HR nor aHR values were found to be statistically significant, indicating that upon both univariable and multivariable analysis, SGA score was not significantly associated with an altered risk of IBD-related hospitalizations or surgeries. Interestingly, when multivariable analysis was conducted, although not significant this frailty tool returned aHR values that suggest a lesser risk of adverse outcomes as the SGA score increases (IBD-related hospitalizations: aHR 0.822, P=0.720; IBD-related surgeries: aHR 0.433, P=0.297).

Figure 3 illustrates the logarithm of the relative hazard of IBD-related hospitalizations between the Well (A) and Moderate (B) groupings of the SGA.

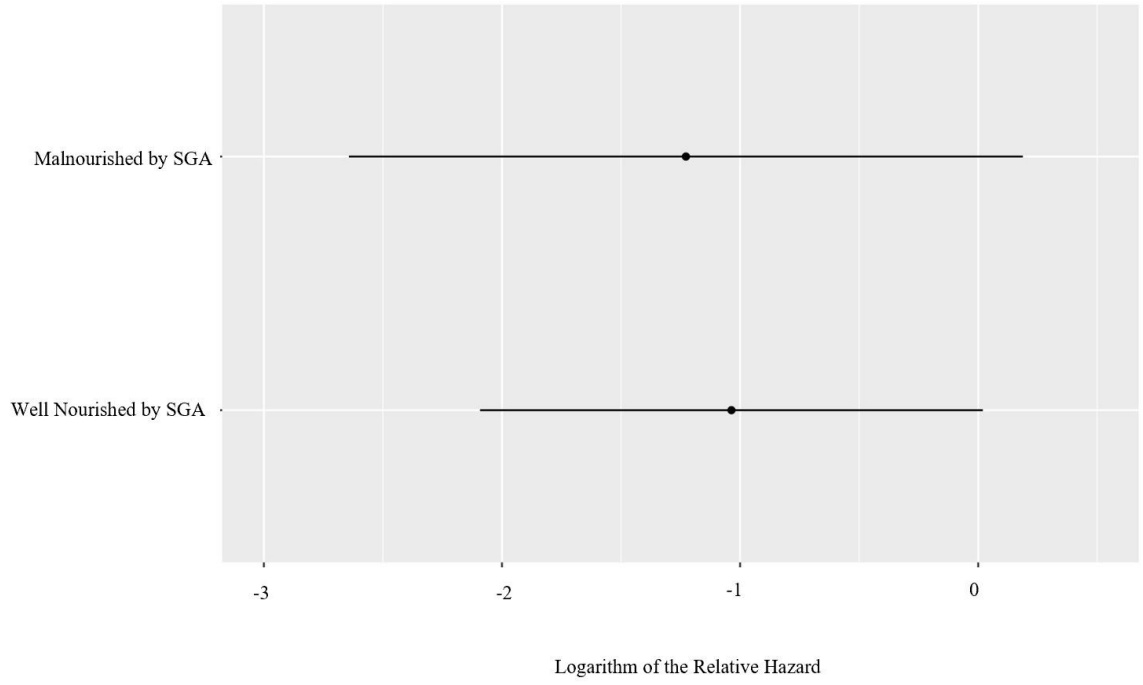

Figure 3. Logarithm of the relative hazard graph demonstrating the differing risk of IBD-related hospital admissions between well nourished (SGA A) and malnourished (SGA B) patients.

Upon univariable logistic regression analysis, the abPG-SGA in its ordinal form returned statistically significant HR values for both IBD-related hospitalizations (HR 1.084, P=0.002) and IBD-related surgeries (HR 1.077, P=0.030). However, upon multivariable analysis, the ordinal abPG-SGA was only found to be independently associated with an increased risk of IBD-related hospitalizations (aHR 1.071, P=0.030).

In contrast, as demonstrated by Table 10, when both univariable and multivariable regression analyses was completed for the abPG-SGA as a categorical variable (no malnutrition risk: 0 – 5, risk of malnutrition: ≥6), no statistically significant HRs or aHRs were calculated.

The logarithm of the relative hazard graphs of IBD-related hospitalizations for the abPG-SGA categories and the abPG-SGA ordinal score are illustrated by Figure 4A and 4B, respectively.

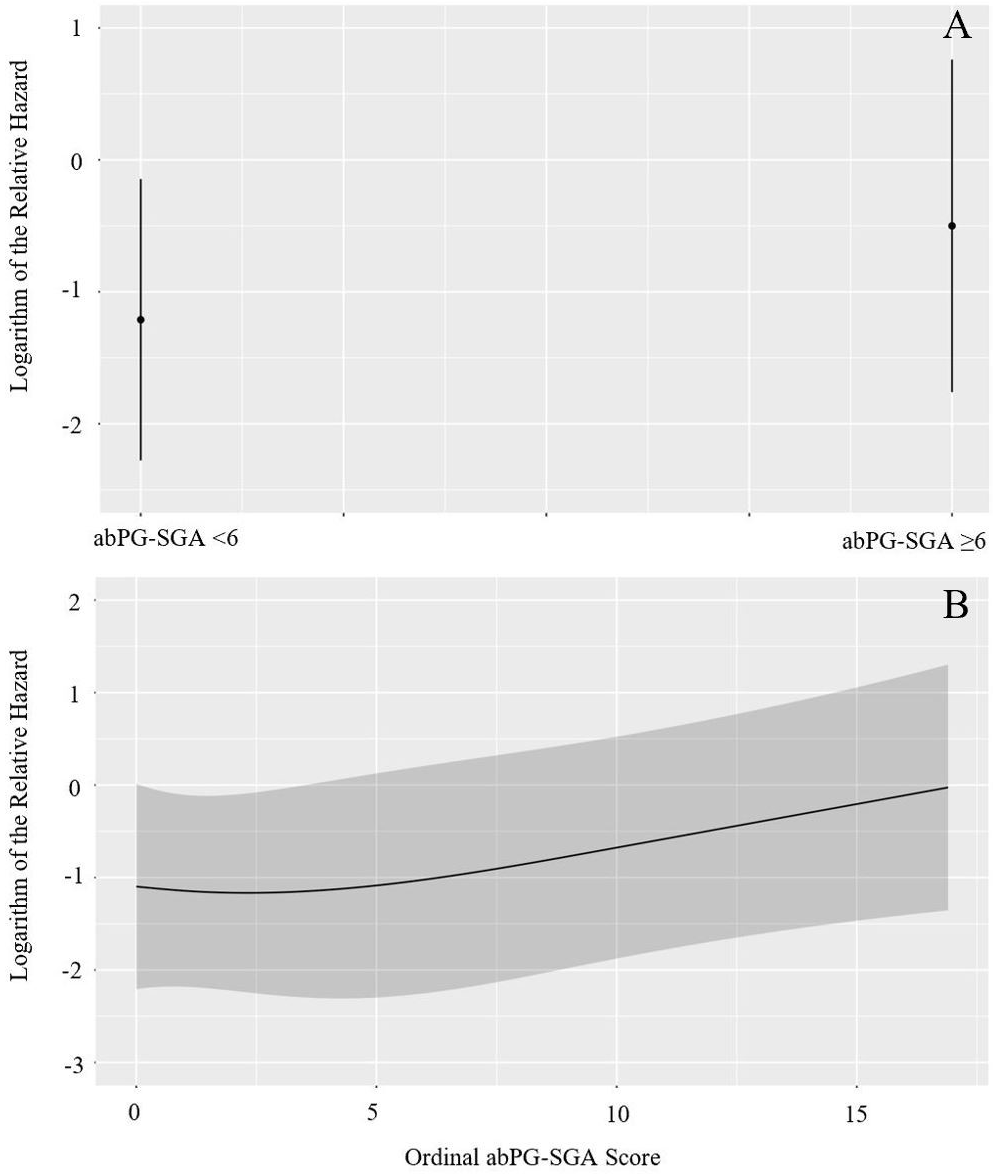

Figure 4. (A) Logarithm of the relative hazard graph demonstrating the risk of IBD-related hospitalizations between no risk of malnutrition (abPG-SGA <6) and risk of malnutrition (abPG-SGA ≥6), (B) logarithm of the relative hazard graph demonstrating the risk of IBD-related hospitalizations as ordinal abPG-SGA score increases.

Finally, upon the conduction of univariable logistic regression analyses for the categories of medium (scores 3 – 4) and high (scores ≥5) risk on the SaskIBD-NRT, all HRs were found to be significant, indicating an increased risk of both IBD-related hospitalizations and surgeries between those deemed as low risk of malnutrition compared to those deemed as either medium or high risk. However, upon multivariable analysis, only the high risk of malnutrition category was associated with an increased risk of IBD-related hospitalizations (aHR 4.578, P=0.014). As shown in Table 10, all other aHRs were not found to be statistically significant.

When considered as an ordinal variable, similar results were found, as the only statistically significant aHR was found between the ordinal SaskIBD-NRT score and IBD-related hospitalizations (aHR 1.370, P=0.018).

The logarithm of the relative hazard graphs of IBD-related hospitalizations for the SaskIBD-NRT categories and the SaskIBD-NRT ordinal score are illustrated by Figure 5A and 5B, respectively.

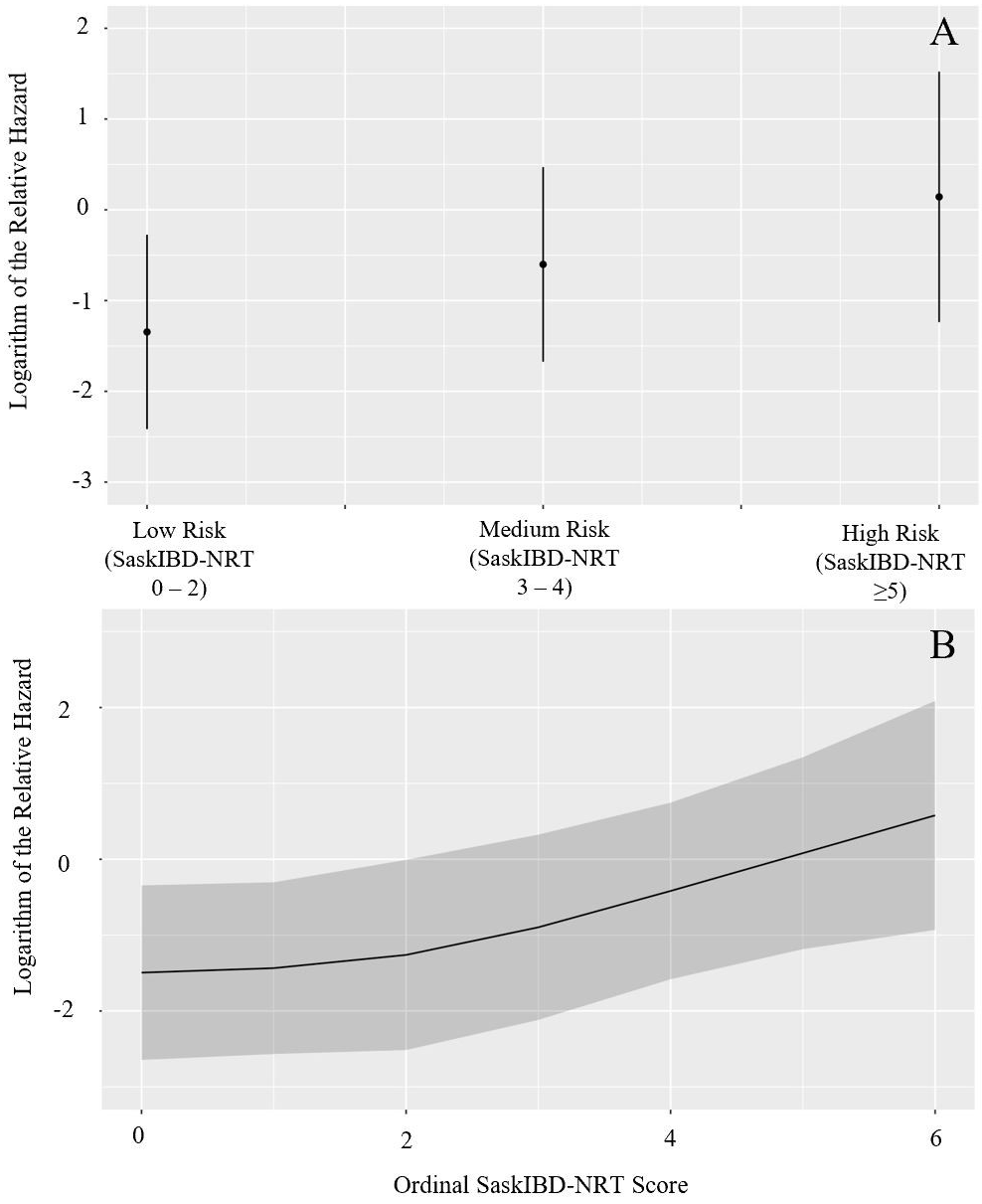

Figure 5. (A) Logarithm of the relative hazard graph demonstrating the risk of IBD-related hospitalizations between low risk of malnutrition (SaskIBD-NRT 0 – 2), medium risk of malnutrition (SaskIBD-NRT 3 – 4), and high risk of malnutrition (SaskIBD-NRT ≥5), (B) logarithm of the relative hazard graph demonstrating the risk of IBD-related hospitalizations as ordinal SaskIBD-NRT score increases.

4.3.6 Effect of Frailty, Sarcopenia, and Malnutrition on Proportion of Time Spent in Hospital for IBD-Related Reasons

When the proportion of time spent in hospital for IBD-related reasons was analyzed using multiple regression analysis, the only significant finding was frailty as defined using the abPG-SGA, where those with an abPG-SGA score of ≥6 have a significantly increased IBD-related hospitalization proportion compared to those with scores <6 (β=0.001786, P=0.013). In contrast, frailty as defined using any of the other given assessments or screening tools was not found to be significantly associated with a greater IBD-related hospitalization proportion. The values calculated for all frailty assessments and screening tools can be seen in Table 11.

Table 11. Multiple Regression Analysis for the Proportion of Time Spent in Hospital for all Frailty, Sarcopenia, and Malnutrition Assessments and Screening Tools

Measurement Value	Mean Hospitalization Proportion (±SD)	Unstandardized Beta Coefficient	P-value*
CFS			
Categorized Score (≥4)	0.0026 (±0.0056)	0.000949	0.302
HGS: Sarcopenia (females <16 kg, males <27 kg)	0.0024 (±0.0057)	0.001567	0.125
SGA: Moderate Malnutrition (B)	0.0020 (±0.0055)	0.000440	0.563
abPG-SGA			
Malnutrition Risk (≥6)	0.0030 (±0.0063)	0.001786	**0.013**
SaskIBD-NRT			
Categorized Score (≥3)	0.0025 (±0.0040)	0.000819	0.123

abPG-SGA, abridged patient-generated Subjective Global Assessment; CFS, Clinical Frailty Scale; HGS, handgrip strength; SaskIBD-NRT, Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool; SD, standard deviation; SGA; Subjective Global Assessment.

*Significant differences between subgroups at P<0.05. Bold values indicate statistically significant differences between groups.

4.3.7 Correlation Between the CFS, HGS, SGA, abPG-SGA, SaskIBD-NRT, the CCI, and Chronological Age

When a bivariate two-tailed correlation test was completed for the given frailty measurement tools, the assessments with the highest correlation coefficient were the ordinal forms of the abPG-SGA and SaskIBD-NRT at a Spearman correlation coefficient of 0.593 (P<0.001). The Spearman correlation coefficients of between each remaining variable were found to be low to moderate, with the exception of HGS with both abPG-SGA and SaskIBD-NRT which did not return significant coefficients. While the SGA (r=0.190, P=0.015), HGS (r=0.177, P=0.024), and the SaskIBD-NRT (r=0.213, P=0.006) were found to have significant correlations with chronological age, all three of these correlations can be considered negligible due to their size.[161] These correlations are displayed in a Spearman hierarchical cluster in Figure 6.

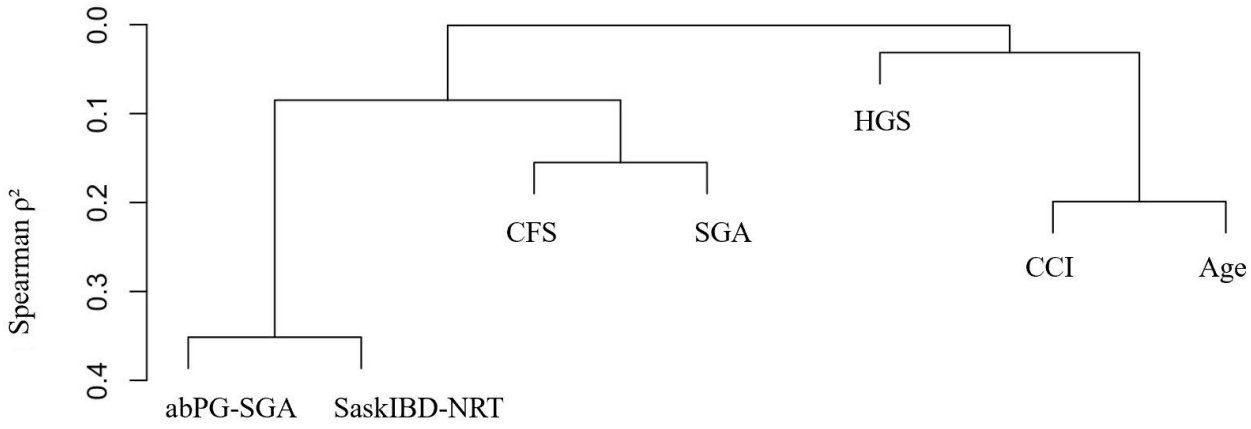

Figure 6. A dendrogram displaying the Spearman hierarchical clustering of the abPG-SGA, the SaskIBD-NRT, the CFS, the SGA, HGS, the CCI, and age.

Chapter 5: Discussion

While studies have been conducted that focus on the association between frailty, sarcopenia, or malnutrition and adverse clinical outcomes in the IBD population, none have incorporated the CFS to determine the presence of frailty. Although a single study has been completed concentrating on the association between sarcopenia, as determined using HGS, and adverse outcomes in IBD patients, a number of limitations limit the findings of this study.[162] Further, the study by Liu et al. was conducted with a homogenous inpatient IBD population, and called for the conduction of a study focused on an outpatient IBD population. While other previous topics exist related to the concept of frailty in IBD, the majority of literature on this topic focuses on the CDM of frailty through population-based health administrative data and does not allow for specific quantitative data to be analyzed. This influenced the decision to utilize frailty assessments and screening tools that allowed for the capture of granular clinical patient data in the present study.

This prospective multicenter study is the first to examine the association between multiple facets of frailty and the risk of IBD-related hospital outcomes and surgeries in an outpatient IBD population. Our results suggest that frailty, as determined using HGS, the abPG-SGA, or the SaskIBD-NRT, is associated with an increased risk of IBD-related hospital admissions in an adult IBD outpatient population. Further, our findings demonstrate that frailty, as defined using the abPG-SGA, is associated with an increased proportion of time spent in hospital for IBD-related reasons.

The primary aim of this prospective study focusing on the association between frailty, as measured using the CFS, HGS, SGA abPG-SGA, and SaskIBD-NRT, and IBD-related hospitalizations and surgeries was to provide evidence of the relationship between markers of

frailty and adverse clinical outcomes in the adult IBD population. We hypothesized that as frailty increased, or as physiological reserve decreased, these patients would be subject to an increased risk of IBD-related hospitalizations and surgeries.

5.1 Key Findings

In this study, we assessed the potential association between frailty, as measured through the CFS, HGS, abPG-SGA, SGA, and SaskIBD-NRT, and adverse clinical outcomes (IBD-related hospitalization outcomes [admission, proportion of time in hospital] and IBD-related surgeries) in an adult IBD outpatient population. It was determined that patients defined as frail through HGS (aHR 3.922, P=0.034), the abPG-SGA (ordinal form: aHR 1.071, P=0.030), or the SaskIBD-NRT (ordinal form: aHR 1.370, P=0.018; categorical form, high risk [score ≥5]: aHR 4.578, P=0.014) each had a significantly increased risk of IBD-related hospital admissions. Finally, frailty as defined using the abPG-SGA (β 0.001786, P=0.013) was associated with an increased proportion of time spent in hospital for IBD-related reasons.

5.2 Relationship Between Frailty, Sarcopenia, and Malnutrition

Though frailty, sarcopenia, and malnutrition can be considered distinct concepts, an interconnected relationship and significant overlap exists between these conditions.[90,163,164] As previously discussed, frailty can be defined as either a syndrome or a state.[72–75] The frailty measurement tools used in this study all define frailty as a syndrome. First, the CFS is regarded as a subjective, or clinical, judgement tool that focuses on diagnosing global frailty.[70,91] In contrast, HGS is deemed an assessment of the physical phenotype of frailty.[71,91,165–167] Specifically, HGS has been reported to be a valid measurement tool of physical frailty in outpatients with chronic diseases such as liver cirrhosis, and further is considered to be a key

component of frailty.[17,71,165] When considering the SGA, abPG-SGA, and SaskIBD-NRT, these assessments and screening tools all incorporate the aspects of unintentional weight loss, occurrence of GI symptoms, and alterations in dietary intake.[104,105,108] Further, physical functioning is also factored into both the SGA and the abPG-SGA.[104,105] The inclusion of the abPG-SGA was also supported by a recent cross-sectional study, which backed the use of this screening tool to detect the risk of malnutrition in IBD outpatients.[160] When considering the relationship between malnutrition and frailty, previous studies that have assessed the association between frailty and adverse outcomes in adult IBD patients have included malnutrition as a frailty-defining diagnosis.[109,110] Further, several frailty assessment tools, such as the Johns Hopkins ACG Frailty Indicator and the Hospital Frailty Risk Score, incorporate malnutrition as a valid factor in determining the presence of frailty.[16,89] For these reasons, the SGA, abPG-SGA, and SaskIBD-NRT were also considered to be assessments and screening tools for the physical model of frailty.

As outlined by Kochar et al., and as stated previously, frailty is a multifaceted syndrome or state characterized by an increased degree of vulnerability, a reduction in physiologic reserve, and a decreased capacity to handle stressors.[168] When a randomized control trial focusing on interventions to reduce frailty was conducted, the results demonstrated that the adoption of appropriate exercise and nutrition plans significantly reduced the prevalence of physical frailty.[169] While that study did not focus on an IBD population, its findings appear to indirectly support the use of sarcopenia and malnutrition assessments and screening tools in order to determine the presence of physical frailty, as interventions that target these concepts caused a direct reduction in frailty as measured through the Fried physical model.[17,169]

As demonstrated by Figure 6, as well as the calculated Spearman correlation coefficients, the factors focused on by each assessment method and screening tool, namely the CFS, HGS, the SGA, the abPG-SGA, and the SaskIBD-NRT, vary. This indicates the need for multiple frailty assessments to be performed in order to accurately capture a comprehensive scope of physiologic reserve.

5.3 Association Between Markers of Frailty and IBD-Related Adverse Clinical Outcomes

Similar to the applicability of the Anna Karenina principle in relation to human microbiome-associated diseases, this principle is also appropriate to characterize the multifaceted nature of frailty.[170] As demonstrated by Figure 6, and by the calculated Spearman correlation coefficients near the end of Chapter 4, each frailty assessment or screening tool, with the exception of the abPG-SGA and the SaskIBD-NRT, did not have a highly correlated relationship with any other tool. This demonstrates that each of the given measurement methods focuses on a different aspect of frailty, and when used together allow for a comprehensive evaluation of the physiologic reserve and functional capacity of an individual. This administration of multiple tools to assess frailty is supported by Sousa-Santos et al., who reported a similar result in relation to the co-existence of frailty facets.[171] Further, Figure 6 also serves to demonstrate that frailty is a distinct concept from chronological age, and that the assessment or screening of frailty provides added value to the complete examination of outpatients with IBD as opposed to simply just focusing on age.

As a whole, this is the first study to report significant independent associations between HGS, the abPG-SGA, and the SaskIBD-NRT and adverse clinical outcomes in an IBD outpatient population. This significant association between frailty and IBD-related hospitalizations mirrors the results of retrospective studies that define frailty using population-based administrative

health data.[111,133,140] These findings provide evidence that frailty, which encompasses a heightened state of vulnerability and the decreased ability to cope with stressors, is significantly associated with an increased risk of IBD-related hospital admissions in adult IBD outpatients.

The exploratory outcome of proportion of time spent in hospital due to IBD-related reasons was also focused on in the present study. Specifically, frailty as defined by the abPG-SGA was significantly associated with an increased proportion of time spent in hospital, while frailty as defined by the CFS, HGS, the SGA, or the SaskIBD-NRT was not found to have a significant association with the proportion of time spent in hospital.

Focusing on the scales used for the markers of frailty, each was analyzed as both an ordinal and a categorical variable where appropriate. In particular, the CFS, abPG-SGA, and SaskIBD-NRT were all analyzed in both forms, whereas HGS was not analyzed in its continuous form, and SGA was already a dichotomous categorical variable. Concentrating on the CFS, abPG-SGA, and SaskIBD-NRT, the use of these tools in their original ordinal forms allow for more precise analyses in relation to the risk of adverse outcomes to be made. Specifically, when the ordinal scores of these assessments and screening tools are categorized, whether in a dichotomous or trichotomous manner, granular data related to the frailty, or physiologic reserve, of each individual is not maintained. In order to maintain the best predictive power for these tools, the ordinal frailty values should remain in place of general categories. Further, the variations in possible score values of ordinal assessments and tools may allow for a greater degree of reliability and precision in comparison to categorical ones.[172] It is possible that this concept is demonstrated by the results of the present study, as although not significant, the association trend for both IBD-related hospital admissions and surgeries of the SGA appeared to be in an opposite

direction than that of the abPG-SGA, indicating greater reliability and precision of the abPG-SGA as a predictive tool.

A systematic review was recently conducted that focused on the predictive value of malnutrition assessments and screening tools for adverse outcomes in the IBD population.[173] This review determined that the available data related to the predictive value of the SGA for adverse outcomes is equivocal, where the only outcome this malnutrition assessment independently predicted was LOS. The findings of our study appear to mirror those reported by Li et al., as frailty defined using the SGA was not found to be significantly associated with any outcomes.[173]

5.4 Future Directions

The present study has identified multiple areas in which further research should be conducted. First, the given frailty assessments and screening tools (CFS, HGS, abPG-SGA, SGA, and SaskIBD-NRT) should be used in a prospective cohort study focusing on IBD inpatients to determine if similar results are found in relation to this outpatient study. Next, validation of the administration of the CFS by research assistants and other staff should be completed in order to ensure accurate values are assigned to research participants, as currently the administration of this assessment is only validated in clinicians with relevant experience in the field.[70]

While HGS has been validated as a marker of physical frailty in other patient populations, a study validating its use in the IBD population should be conducted to confirm that it is indeed appropriate to assess physical frailty in IBD outpatients.[17,71,165] Focusing on previous research that has been completed in the field of frailty in IBD, frailty indices developed from population-based health administrative data may not accurately reflect frailty in the IBD population, as these indices rely on the CDM model of frailty. While a valid definition route, our present study, and

specifically Figure 6, demonstrates that the accumulation of deficits is indeed closely associated with chronological age in IBD outpatients. Therefore, a larger prospective study should be conducted with the aim of creating an IBD-specific predictive tool that incorporates multiple aspects of frailty.

In addition, further research is warranted in relation to biomarkers of frailty in the IBD population. Specifically, an exploration of these factors, such as IL-6, IL-8, IL-1, and CRP, should be conducted in order to better understand how they relate to immunosenescence in these patients.[174]

5.5 Strengths and Limitations

The first notable strength of this study was the inclusion of a wide variety of assessment methods in order to determine the presence of frailty in our patient population. As demonstrated by the Spearman correlations stated near the end of Chapter 4 as well as in Figure 6, these frailty tools evaluate differing aspects of patients, allowing for the determination of the aspects that best assess the risk of adverse outcomes in this population. A second strength included in the given project is the patient selection, where a homogenous population was achieved through the inclusion of only IBD outpatients. This aspect of the study may have reduced selection bias, as the confounder of inpatient status was not present. Third, the mean follow-up length for all participants was over three and a half years, improving upon the short follow-up limitation of a very similar study.[162] Finally, when again looking at the limitations of a similar study that focused on the association between sarcopenia and adverse outcomes in the IBD population, our study was multicenter as compared to single center, allowing for the representation of a wider range of IBD patients.[162] The present study is also one of the few prospective studies that explores the concept of frailty in IBD, and further includes a well-phenotyped IBD cohort where

both the disease phenotype and severity were well documented and could be accounted for as confounders. Further, this study focused on frailty as defined by clinical parameters, which is a strength in comparison to other studies which have utilized population-based administrative health data to define frailty as these clinical parameters allow for granular patient data to be captured.[109,110,133]

In contrast to the stated strengths, some limitations also impacted the present study. First and foremost, the low number of outcomes (IBD-related hospitalizations: n=27, IBD-related surgeries: n=13) is a major limitation in relation to the findings. As the primary aim of the study was to determine if an association exists between the given frailty indices and adverse clinical outcomes, these low number of occurrences for IBD-related hospitalizations and surgeries respectively may have impacted the significance of the reported associations. Next, the administration of the CFS by research assistants may have impacted the accuracy of the given scores. While all research assistants were trained on how to score the CFS to ensure consistency between assessors, the tool was developed to be administered by those who have appropriate clinical experience.[70] Further, while it has been reported that a variety of healthcare professionals, such as physicians, physician assistants, nurse practitioners, nurses, pharmacists, and nutritionists, can correctly assess frailty using the CFS, there is no available data on the accuracy of scores determined by research assistants.[175] The limitation of therapy non-compliance is also relevant to this study, as patients may not have followed the treatment plan set out by their healthcare provider, which may have resulted in IBD-related hospitalizations or surgeries.

5.6 Conclusion

In this prospective observational cohort study, we aimed to determine if frailty was independently associated with the risk of adverse clinical outcomes in an outpatient IBD population. Our results reflect that frailty, as defined using HGS, the abPG-SGA, and the SaskIBD-NRT was independently associated the risk of IBD-related hospitalizations in this population. Further, frailty as defined through the abPG-SGA was independently associated with an increased proportion of time spent in hospital for IBD-related reasons. These findings indicate that frailty assessments and screening tools should be incorporated into the comprehensive evaluation, alongside chronological age, of IBD outpatients in order to best tailor their care. Future prospective studies should be conducted not only with the aims of validating existing frailty-defining tools in the IBD population, but also with creating an IBD-specific frailty tool that integrates multiple facets of frailty in order to tailor care for all IBD patients.

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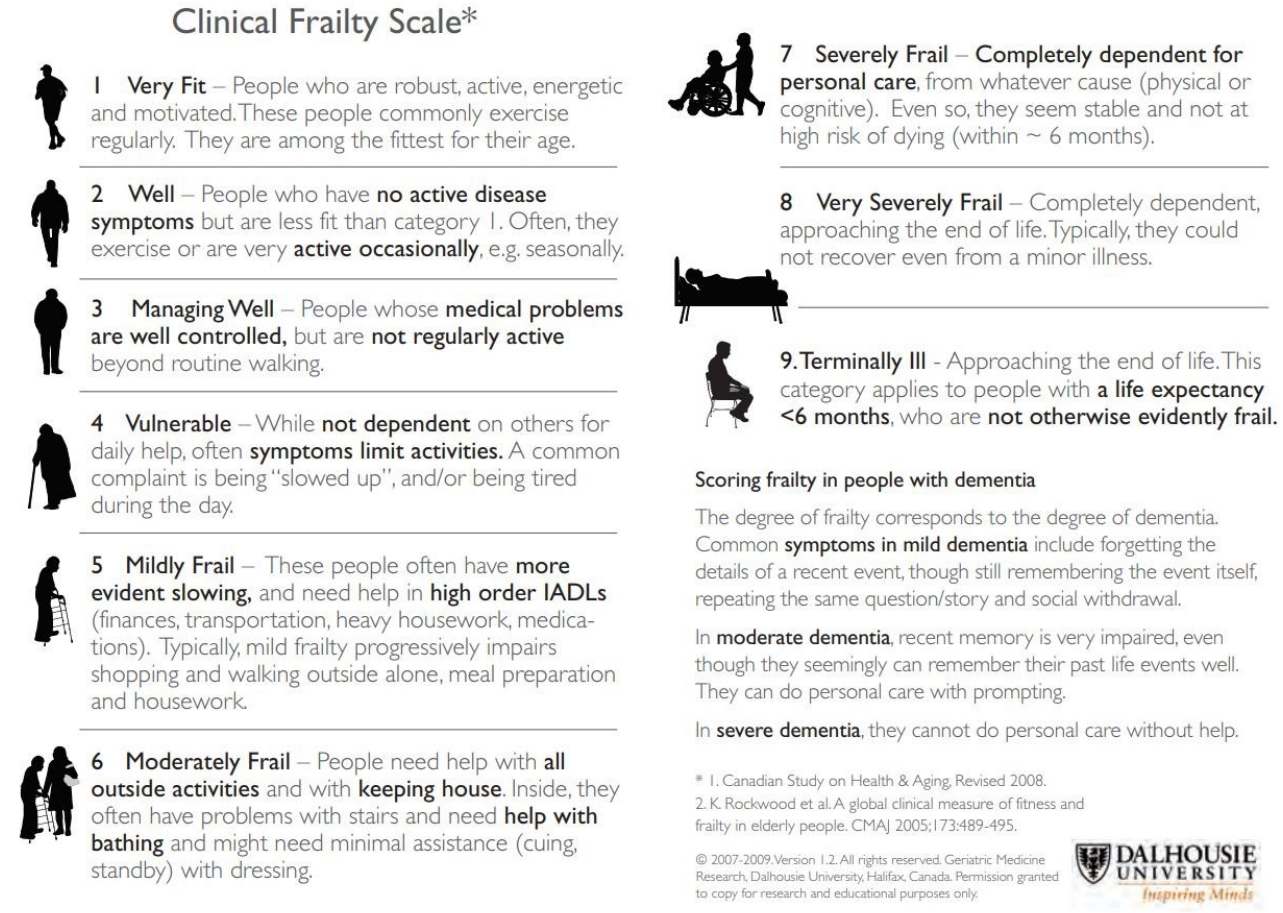
Appendices

Appendix 1 (A1): Clinical Frailty Scale Scoring System

(Adopted from: Canadian Study on Health & Aging, Revised 2008. Rockwood et al., 2005.)[70]



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Appendix 2 (A2): Malnutrition Scoring Systems

A 2-1: Subjective Global Assessment Scoring Sheet

(Adopted from: Consensus Document Dietitian/Nutritionists from the Nutrition Education Materials Online, "NEMO" team, 2009).

Subjective Global Assessment

Name:
Date:

Medical History			A	B	C
WEIGHT	Usual weight……	Current weight……			
Wt change past 6 months	Amount weight loss…….	% weight loss……..			
0-<5% loss			*		
5-10% loss				*	
>10% loss					*
Weight change past 2 weeks		Amount……..			
No change; normal weight			*		
Increase to within 5%			*		
Increase (1 level above)			*	*	
No change, but below usual wt				*	
Increase to within 5-10%				*	
Decrease					*
DIETARY INTAKE					
No change; adequate			*		
No change; inadequate				*	
Change		**Duration of change**……..			
Suboptimal diet				*	
Full liquid				*	
Hypocaloric liquid					*
Starvation					*
Intake borderline; increasing			*		
Intake borderline; decreasing				*	
Intake poor; no change				*	*
Intake poor; increasing				*	
Intake poor; decreasing					*
GASTROINTESTINAL SYMPTOMS					
	Frequency (never, daily, no. of times/week)	Duration (<2wk, >2wk)			
Nausea	……	……			
Vomiting	……	……			
Diarrhoea	……	……...			
Anorexia	……	……...			
None; intermittent			*		
Some (daily >2 week)				*	
All (daily >2 week)					*
FUNCTIONAL CAPACITY					
No dysfunction		Duration of change ……..	*		
Difficulty with ambulation/normal activities				*	
Bed/chair-ridden					*
Change past 2 week					
Improved			*		
No change				*	
Regressed					*

This is a consensus document from Dietitian/ Nutritionists from the Nutrition Education Materials Online, "NEMO", team.
Disclaimer: http://www.health.qld.gov.au/masters/copyright.asp Posted: May 2009
Due for Review: April 2019

Physical examination	A	B	C
SUBCUTANEOUS FAT			
Under the eyes	Slightly bulging area		Hollowed look, depression, dark circles
Triceps	Large space between fingers		Very little space between fingers, or fingers touch
Biceps	Large space between fingers		Very little space between fingers, or fingers touch
MUSCLE WASTING			
Temple	Well-defined muscle/flat	Slight depression	Hollowing, depression
Clavicle	Not visible in Males; may be visible but not prominent in females	Some protrusion; may not be all the way along	Protruding/prominent bone
Shoulder	Rounded	No square look; acromion process may protrude slightly	Square look; bones prominent
Scapula/ribs	Bones not prominent; no significant depressions	Mild depressions or bone may show slightly; not all areas	Bones prominent; significant depressions
Quadriceps	Well rounded; no depressions	Mild depression	Depression; thin
Calf	Well developed		Thin; no muscle definition
Knee	Bones not prominent		Bones prominent
Interosseous muscle between thumb and forefinger	Muscle protrudes; could be flat in females		Flat or depressed area
OEDEMA (related to malnutrition)	No sign	Mild to moderate	Severe
ASCITES (related to malnutrition)	No sign	Mild to moderate	Severe
OVERALL SGA RATING	**A**	**B**	**C**

Adapted from: Detsky et al., 1994[8]; Baxter Healthcare Corporation, 1993; McCann, 1996 (Ferguson, Bauer, Banks, Capra, 1996)©

A 2-2: Abridged Patient-Generated Subjective Global Assessment Scoring Sheet

(Adopted from: Vigano et al., 2014.)[176]

Centre universitaire de santé McGill — McGill University Health Centre

☐ HME *MCH* ☒ MGH *HGM* ☐ HRV *RVH*
☐ HNM *MNH* ☐ ITM *MCI* ☐ CL *LC*

* F M U – 0 5 0 9 *

Autoévaluation nutritionnelle globale subjective - Version abréviée (ANGS)

Abridged-Scored patient-generated subjective global assessment (PG-SGA)

Numéro de dossier / Unit Number / Nom du patient / Patient's Name

1. Poids (voir la feuile de travail 1) / *Weight (see worksheet 1)* — **Section 1**

Résumé de mon poids actuel et récent / *Summary of my current and recent weight* (Encercler / *Circle* (kg) / *lbs* (meters) / *ft*)

Actuellement, je pèse environ *I currently weigh about* _____ kg / lbs	**Il y a six mois je pesais environ** *Six months ago I weighed about* _____ kg / lbs
Je mesure environ *I am about* _____ metres / ft	**Au cours des deux dernières semaines, mon poids :** *During the past two weeks, my weight has :*
Il y a un mois, je pesais environ *One month ago, I weighed about* _____ kg / lbs	☐ **Est resté stable (0)** *Has not changed (0)* ☐ **A augmenté (0)** *Has increased (0)* ☐ **A diminué (1)** *Has decreased (1)*

2. Apport alimentaire / *Food Intake* — **Section 2**

Par rapport à ce que je mange d'habitude, je dirais que la quantité de nourriture que j'ai consommé le mois dernier est :
As compared to my normal intake, I would rate my food intake during the past month as :

☐ **Inchangée (0)** *Unchanged (0)* ☐ **Plus grande (0)** *More than usual (0)* ☐ **Plus petite (1)** *Less than usual (1)*

Maintenant, je mange : *I am now taking :*		
	☐ **De la nourriture normale, mais moins que d'habitude (1)** *Normal food but less than normal amount (1)*	☐ **Uniquement des suppléments nutritionnels (3)** *Only nutritional supplements (3)*
	☐ **Peu de nourriture solide (2)** *Little solid food (2)*	☐ **Très peu de choses (4)** *Very little of anything (4)*
	☐ **Seulement des liquides (3)** *Only liquids (3)*	☐ **Seulement par alimentation par sonde ou voie i.v. (0)** *Only tube feedings or onlly nutrition by vein (0)*

3. Symptômes / *Symptoms* — **Section 3**

Au cours des deux dernières semaines, les problèmes suivants m'ont empêché(e) de manger suffisament (cochez touts les cases qui s'appliquent):
I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply) :

☐ **Aucune difficulté à manger (0)** *No problems eating (0)*	☐ **Les aliments ont un drôle/n'ont plus de goût (1)** *Things taste funny or have no taste (1)*	☐ **Bouche sèche (1)** *Dry mouth (1)*
☐ **Pas d'appétit, pas envie de manger (3)** *No appetite, just did not feel like eating (3)*	☐ **Difficulté à avaler (2)** *Problems swallowing (2)*	☐ **Les aliments ont une odeur désagréable (1)** *Smells bother me (1)*
☐ **Nausées (1)** *Nausea (1)*	☐ **Vomissements (3)** *Vomiting (3)*	☐ **Impression de satiété (1)** *Feel full quickly (1)*
☐ **Constipation (1)** *Constipation (1)*	☐ **Diarrhée (3)** *Diarrhea (3)*	
☐ **Présence d'ulcères buccaux (2)** *Mouth sores (2)*	☐ **Fatigue (1)** *Fatigue (1)*	
☐ **Douleur; précisez à quel endroit (3) :** *Pain; Where ? (3) :*		
☐ **Other* (1) (par exemple: dépression, manque d'argent, problèmes de dents) :** *Other* (1) (for example: depression, money, or dental problems) :*		

4. Capacités fonctionelles / *Activities and Functioning* — **Section 4**

Voici dans quelle mesure j'ai pu accomplir mes activités habituelles durant le mois dernier :
Over the past month, I would generally rate my activity as :

☐ **Capable d'accomplir mes activités habituelles, sans restriction (0)** *Normal with no limitations (0)*

☐ **Capable d'accomplir mes activités habituelles, mais avec restrictions (1)** *Not my normal self, but able to be up and about with fairly normal activities (1)*

☐ **Incapable d'accomplir la plupart de mes activités habituelles, et ai passé moins de la moitié des journées au lit ou au fauteuil (2)** *Not feeling up to most things but in bed or chair less than half the day (2)*

☐ **Capable d'accomplir très peu de mes activités habituelles et ai passé a plus partie de mes journées au lit ou au fauteuil (3)** *Able to do little activity and spend most of the day in bed our chair (3)*

☐ **Ai dû passer presque tout mon temps au lit, ne me levant que très rarement (3)** *Pretty much bedridden, rarely out of bed (3)*

5. Score cumulatif pour les sections 1 à 4 : / *Additive Score of Sections 1-4 :* ☐ **A**

Signature / *Signature*

Date et heure / *Date and time* A A Y Y / M M / J D 00:00

A 2-3: Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool Scoring Sheet

(Adopted from: Haskey et al., 2014.)[108]

Nutrition screening item	Score
1. Have you experienced nausea, vomiting, diarrhea or poor appetite for greater than two weeks?	"no symptoms"=0, "1-2 symptoms"=1, "≥3 symptoms"=2
2. Have you lost weight in the last month without trying?	"no"=0, "unsure"=1, "yes"=see below
IF YES, how much weight have you lost?	"<5 lbs"=0, "5-10 lbs"=1, "10-15 lbs"=2, ">15 lbs"=3
3. Have you been eating poorly because of a decreased appetite?	"no"=0, "yes"=2
4. Have you been restricting any foods or food groups?	"no"=0, "yes"=2

Total score: 0-2=low risk, 3-4=medium risk, ≥5=high risk.

Appendix 3 (A3): Associations Between Confounding Variables and Frailty

A 3-1: Associations Between Confounding Variables and Frailty as Defined by the CFS

Variable	CFS <4 (n=146)	CFS ≥4 (n=17)	P-value*
Age			
Mean age, years (SD)	42.2 (16.3)	42.8 (12.6)	0.87
Sex			
Male	74 (50.7%)	6 (35.3%)	0.23
Female	72 (49.3%)	11 (64.7%)	
Montreal Classification			
MCUC (n=58)			
1	1 (1.8%)	0 (0.0%)	0.54
2	15 (27.3%)	0 (0.0%)	
3	39 (70.9%)	3 (100.0%)	
MCCD (n=105)			
Age at Diagnosis			
≤16 years	18 (19.8%)	3 (21.4%)	0.50
17 – 40 years	56 (61.5%)	10 (71.4%)	
>40 years	17 (18.7%)	1 (7.1%)	
Disease Location			
Terminal Ileum	24 (26.4%)	2 (14.3%)	0.42
Colonic	19 (20.9%)	2 (14.3%)	
Ileocolonic	48 (52.7%)	10 (71.4%)	
Upper GI Involvement			
Yes	14 (15.4%)	0 (0.0%)	0.12
No	77 (84.6%)	14 (100.0%)	
Disease Behavior			
Inflammatory	42 (46.2%)	6 (42.9%)	0.48
Stricturing	26 (28.6%)	6 (42.9%)	
Penetrating	23 (25.3%)	2 (14.3%)	
Perianal Fistula(e)			
Present	22 (24.2%)	1 (7.1%)	0.15
Absent	69 (75.8%)	13 (92.9%)	
Disease Activity			
pMayo Score (n=58)			
Mean score (SD)	1.2 (1.7)	3.7 (2.1)	0.17
HBI Score (n=105)			
Mean score (SD)	3.3 (3.8)	6.3 (3.8)	**0.01**
Previous IBD-Related Surgeries			
None	112 (76.7%)	11 (64.7%)	0.27
Small Bowel Resection / Stricturoplasty	17 (11.6%)	3 (17.6%)	
Ileocecal Resection	12 (8.2%)	3 (17.6%)	
Segmental Colonic Resection	5 (3.4%)	0 (0.0%)	
Biologic Medication			
None	37 (25.3%)	1 (5.9%)	0.19
Previous	5 (3.4%)	1 (5.9%)	
Current	104 (71.2%)	15 (88.2%)	
Steroids			
None	41 (28.1%)	4 (23.5%)	0.44
Previous	87 (59.6%)	9 (52.9%)	
Current	18 (12.3%)	4 (23.5%)	
Presence of CCI Comorbidities			
0 Comorbidities	113 (77.4%)	11 (64.7%)	0.25
≥1 Comorbidity	33 (22.6%)	6 (35.3%)	

A 3-2: Associations Between Confounding Variables and Frailty as Defined by HGS

Variable	Non-Sarcopenic HGS (n=149)	Sarcopenic HGS (n=14)	P-value*
Age			
Mean age, years (SD)	41.2 (15.0)	53.8 (20.1)	**0.04**
Sex			
Male	75 (50.3%)	5 (35.7%)	0.30
Female	74 (49.7%)	9 (64.3%)	
Montreal Classification			
MCUC (n=58)			
1	1 (2.0%)	0 (0.0%)	0.58
2	14 (28.0%)	1 (12.5%)	
3	35 (70.0%)	7 (87.5%)	
MCCD (n=105)			
Age at Diagnosis			
≤16 years	21 (21.2%)	1 (16.7%)	0.09
17 – 40 years	63 (63.6%)	2 (33.3%)	
>40 years	15 (15.2%)	3 (50.0%)	
Disease Location			
Terminal Ileum	25 (25.3%)	1 (16.7%)	**0.01**
Colonic	17 (17.2%)	4 (66.7%)	
Ileocolonic	57 (57.6%)	1 (16.7%)	
Upper GI Involvement			
Yes	14 (14.1%)	0 (0.0%)	0.32
No	85 (85.9%)	6 (100.0%)	
Disease Behavior			
Inflammatory	45 (45.5%)	3 (50.0%)	0.72
Stricturing	31 (31.3%)	1 (16.7%)	
Penetrating	23 (23.2%)	2 (33.3%)	
Perianal Fistula(e)			
Present	22 (22.2%)	1 (16.7%)	0.75
Absent	77 (77.8%)	5 (83.3%)	
Disease Activity			
pMayo Score (n=58)			
Mean score (SD)	1.2 (1.7)	2.1 (2.4)	0.31
HBI Score (n=105)			
Mean score (SD)	3.7 (4.0)	3.0 (3.6)	0.66
Previous IBD-Related Surgeries			
None	109 (73.2%)	14 (100.0%)	0.17
Small Bowel Resection / Stricturoplasty	20 (13.4%)	0 (0.0%)	
Ileocecal Resection	15 (10.1%)	0 (0.0%)	
Segmental Colonic Resection	5 (3.4%)	0 (0.0%)	
Biologic Medication			
None	35 (23.5%)	3 (21.4%)	0.77
Previous	5 (3.4%)	1 (7.1%)	
Current	109 (73.2%)	10 (71.4%)	
Steroids			
None	43 (28.9%)	2 (14.3%)	0.17
Previous	88 (59.1%)	8 (57.1%)	
Current	18 (12.1%)	4 (28.6%)	
Presence of CCI Comorbidities			
0 Comorbidities	118 (79.2%)	6 (42.9%)	**0.002**
≥1 Comorbidity	31 (20.8%)	8 (57.1%)	

A 3-3: Associations Between Confounding Variables and Frailty as Defined by the SGA

Variable	SGA A (Well Nourished) (n=136)	SGA B (Mild Malnourishment) (n=27)	P-value*
Age			
Mean age, years (SD)	40.8 (15.1)	49.9 (17.7)	**0.02**
Sex			
Male	72 (52.9%)	8 (29.6%)	**0.03**
Female	64 (47.1%)	19 (70.4%)	
Montreal Classification			
MCUC (n=58)			
1	1 (2.2%)	0 (0.0%)	0.87
2	12 (26.1%)	3 (25.0%)	
3	33 (71.7%)	9 (75.0%)	
MCCD (n=105)			
Age at Diagnosis			
≤16 years	21 (23.3%)	1 (6.7%)	0.34
17 – 40 years	54 (60.0%)	11 (73.3%)	
>40 years	15 (16.7%)	3 (20.0%)	
Disease Location			
Terminal Ileum	23 (25.6%)	3 (20.0%)	0.11
Colonic	15 (16.7%)	6 (40.0%)	
Ileocolonic	52 (57.8%)	6 (40.0%)	
Upper GI Involvement			
Yes	13 (14.4%)	1 (6.7%)	0.41
No	77 (85.6%)	14 (93.3%)	
Disease Behavior			
Inflammatory	41 (45.5%)	7 (46.7%)	0.93
Stricturing	28 (31.1%)	4 (26.7%)	
Penetrating	21 (23.3%)	4 (26.7%)	
Perianal Fistula(e)			
Present	22 (24.4%)	1 (6.7%)	0.12
Absent	68 (75.6%)	14 (93.3%)	
Disease Activity			
pMayo Score (n=58)			
Mean score (SD)	1.2 (1.7)	1.8 (2.3)	0.44
HBI Score (n=105)			
Mean score (SD)	3.2 (3.5)	6.6 (5.3)	**0.03**
Previous IBD-Related Surgeries			
None	104 (76.5%)	19 (70.4%)	0.24
Small Bowel Resection / Stricturoplasty	15 (11.0%)	5 (18.5%)	
Ileocecal Resection	14 (10.3%)	1 (3.7%)	
Segmental Colonic Resection	3 (2.2%)	2 (7.4%)	
Biologic Medication			
None	32 (23.5%)	6 (22.2%)	0.08
Previous	3 (2.2%)	3 (11.1%)	
Current	101 (74.3%)	18 (66.7%)	
Steroids			
None	38 (27.9%)	7 (25.9%)	0.11
Previous	83 (61.0%)	13 (48.1%)	
Current	15 (11.0%)	7 (25.9%)	
Presence of CCI Comorbidities			
0 Comorbidities	106 (77.9%)	18 (66.7%)	0.21
≥1 Comorbidity	30 (22.1%)	9 (33.3%)	

A 3-4: Associations Between Confounding Variables and Frailty as Defined by the abPG-SGA

Variable	abPG-SGA <6 (n=126)	abPG-SGA ≥6 (n=37)	P-value*
Age			
Mean age, years (SD)	41.3 (16.2)	45.7 (14.3)	0.12
Sex			
Male	70 (55.6%)	10 (27.0%)	**0.002**
Female	56 (44.4%)	27 (73.0%)	
Montreal Classification			
MCUC (n=58)			
1	1 (2.1%)	0 (0.0%)	0.62
2	11 (23.4%)	4 (36.4%)	
3	35 (74.5%)	7 (63.6%)	
MCCD (n=105)			
Age at Diagnosis			
≤16 years	18 (22.8%)	4 (15.4%)	0.72
17 – 40 years	48 (60.8%)	17 (65.4%)	
>40 years	13 (16.5%)	5 (19.2%)	
Disease Location			
Terminal Ileum	19 (24.1%)	7 (26.9%)	0.82
Colonic	15 (19.0%)	6 (23.1%)	
Ileocolonic	45 (57.0%)	13 (50.0%)	
Upper GI Involvement			
Yes	14 (17.7%)	0 (0.0%)	**0.02**
No	65 (82.3%)	26 (100.0%)	
Disease Behavior			
Inflammatory	36 (45.6%)	12 (46.2%)	0.78
Stricturing	23 (29.1%)	9 (34.6%)	
Penetrating	20 (25.3%)	5 (19.2%)	
Perianal Fistula(e)			
Present	21 (26.6%)	2 (7.7%)	**0.04**
Absent	58 (73.4%)	24 (92.3%)	
Disease Activity			
pMayo Score (n=58)			
Mean score (SD)	0.9 (1.5)	3.0 (1.9)	**0.006**
HBI Score (n=105)			
Mean score (SD)	2.7 (3.2)	6.6 (4.6)	**<0.001**
Previous IBD-Related Surgeries			
None	98 (77.8%)	25 (67.6%)	0.52
Small Bowel Resection / Stricturoplasty	13 (10.3%)	7 (18.9%)	
Ileocecal Resection	11 (8.7%)	4 (10.8%)	
Segmental Colonic Resection	4 (3.2%)	1 (2.7%)	
Biologic Medication			
None	29 (23.0%)	9 (24.3%)	**0.03**
Previous	2 (1.6%)	4 (10.8%)	
Current	95 (75.4%)	24 (64.9%)	
Steroids			
None	35 (27.8%)	10 (27.0%)	0.08
Previous	78 (61.9%)	18 (48.6%)	
Current	13 (10.3%)	9 (24.3%)	
Presence of CCI Comorbidities			
0 Comorbidities	100 (79.4%)	24 (64.9%)	0.07
≥1 Comorbidity	26 (20.6%)	13 (35.1%)	

A 3-5: Associations Between Confounding Variables and Frailty as Defined by the SaskIBD-NRT

Variable	SaskIBD-NRT 0 – 2 (Low Risk) (n=121)	SaskIBD-NRT 3 – 4 (Medium Risk) (n=28)	P-value*	SaskIBD-NRT ≥5 (High Risk) (n=14)	P-value*
Age					
Mean age, years (SD)	40.6 (16.4)	46.5 (13.9)	0.06	48.7 (12.4)	**0.04**
Sex					
Male	67 (55.4%)	10 (35.7%)	-	3 (21.4%)	**0.02**
Female	54 (44.6%)	18 (64.3%)		11 (78.6%)	
Montreal Classification					
MCUC (n=58)					
1	1 (2.1%)	0 (0.0%)	-	0 (0.0%)	0.38
2	10 (21.3%)	4 (57.1%)		1 (25.0%)	
3	36 (76.6%)	3 (42.9%)		3 (75.0%)	
MCCD (n=105)					
Age at Diagnosis					
≤16 years	19 (25.7%)	2 (9.5%)	-	1 (10.0%)	0.21
17 – 40 years	42 (56.8%)	17 (81.0%)		6 (60.0%)	
>40 years	13 (17.6%)	2 (9.5%)		3 (30.0%)	
Disease Location					
Terminal Ileum	17 (23.0%)	4 (19.0%)	-	5 (50.0%)	0.16
Colonic	15 (20.3%)	3 (14.3%)		3 (30.0%)	
Ileocolonic	42 (56.8%)	14 (66.7%)		2 (20.0%)	
Upper GI Involvement					
Yes	14 (18.9%)	0 (0.0%)	-	0 (0.0%)	**0.03**
No	60 (81.1%)	21 (100.0%)		10 (100.0%)	
Disease Behavior					
Inflammatory	35 (47.3%)	10 (47.6%)	-	3 (30.0%)	0.73
Stricturing	21 (28.4%)	6 (28.6%)		5 (50.0%)	
Penetrating	18 (24.3%)	5 (23.8%)		2 (20.0%)	
Perianal Fistula(e)					
Present	19 (25.7%)	4 (19.0%)	-	0 (0.0%)	0.17
Absent	55 (74.3%)	17 (81.0%)		10 (100.0%)	
Disease Activity					
pMayo Score (n=58)					
Mean score (SD)	0.9 (1.5)	4.0 (1.6)	**0.002**	2.0 (0.8)	0.06
HBI Score (n=105)					
Mean score (SD)	2.0 (1.9)	7.4 (5.1)	**<0.001**	8.4 (3.2)	**<0.001**
Previous IBD-Related Surgeries					
None	98 (81.0%)	15 (53.6%)	-	10 (71.4%)	**0.01**
Small Bowel Resection / Stricturoplasty	9 (7.4%)	9 (32.1%)		2 (14.3%)	
Ileocecal Resection	11 (9.1%)	2 (7.1%)		2 (14.3%)	
Segmental Colonic Resection	3 (2.5%)	2 (7.1%)		0 (0.0%)	
Biologic Medication					
None	26 (21.5%)	10 (35.7%)	-	2 (14.3%)	**0.002**
Previous	3 (2.5%)	0 (0.0%)		3 (21.4%)	
Current	92 (76.0%)	18 (64.3%)		9 (64.3%)	
Steroids					
None	34 (28.1%)	7 (25.0%)	-	4 (28.6%)	0.25
Previous	75 (62.0%)	14 (50.0%)		7 (50.0%)	
Current	12 (9.9%)	7 (25.0%)		3 (21.4%)	
Presence of CCI Comorbidities					
0 Comorbidities	95 (78.5%)	17 (60.7%)	-	12 (85.7%)	0.09
≥1 Comorbidity	26 (21.5%)	11 (39.3%)		2 (14.3%)	