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Dying Tt Save Your Colon? Changing the Way We Look at Ulcerative Colitis

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Abstract

Treatment options for mesalamine-refractory ulcerative colitis (UC) include chronic immunosuppressive medications or colectomy surgery. Current treatment paradigms presume the patients' foremost desire is to avoid surgery and therefore view surgery as a consequence of medication failure. However, immunosuppressive therapy may not be ideal for all patients due to unclear durable efficacy and potential lethal serious adverse events (SAEs). We sought to quantify UC patients' risk tolerance of chronic immunosuppression to avoid colectomy.

We first conducted a meta-analysis of all-cause and cause-specific mortality in both Crohn's disease (CD) and UC, and examined the effect of study design on this outcome. We found elevated all-cause and cause-specific mortality in both UC and CD including colorectal-, pulmonary- and non-alcoholic liver disease-related relative mortality. We further found little evidence that study design impacted all-cause relative mortality summary estimates.

We next conducted a study examining the reliability of the 6-Point Mayo score, a simple two-item non-invasive non-physician driven index, for measuring UC disease activity. We found the 6-Point Mayo to strongly correlate with more extensive disease assessment tools, with a similar sensitivity, specificity and ROC area under the curve for patient-defined clinical remission.

With these insights, we conducted a discrete choice experiment to quantify the UC patients' mean maximum acceptable risk for life-threatening SAEs associated with immunosuppressant therapy to avoid colectomy surgery with various outcomes. We found that UC patient tolerance for medical and surgical risks do not conform to conventional preference-elicitation methodology assumptions. UC patients were willing to accept very high levels of fatal SAEs to avoid an ostomy. However, if a durable medication-induced remission could not be achieved, patients were equally satisfied with J-pouch surgery. Several important clinical phenotypes impacted patient risk tolerances. This is the first empirical demonstration that UC patients view a well-functioning J-pouch as equivalent to mild clinical disease. It further demonstrates that patients value medication efficacy and suggests that clinical remission, rather than response, be the preferred outcome for therapy trials and treatment algorithms. Our findings underline the need for rigorous methodologies to accurately measure patient-preferences; and suggest potential avenues to enhance UC patient autonomy and facilitate shared decision-making.

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DYING TO SAVE YOUR COLON? CHANGING THE WAY WE LOOK AT ULCERATIVE

Dedications

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My son, Charak. He makes every day worth it.

My husband, Rahul. For everything.

ABSTRACT

WHAT IS YOUR COLON WORTH TO YOU? CHANGING THE WAY WE LOOK AT ULCERATIVE COLITIS

Meenakshi Bewtra

James D. Lewis

Treatment options for mesalamine-refractory ulcerative colitis (UC) include chronic immunosuppressive medications or colectomy surgery. Current treatment paradigms presume the patients' foremost desire is to avoid surgery and therefore view surgery as a consequence of medication failure. However, immunosuppressive therapy may not be ideal for all patients due to unclear durable efficacy and potential lethal serious adverse events (SAEs). We sought to quantify UC patients' risk tolerance of chronic immunosuppression to avoid colectomy.

We first conducted a meta-analysis of all-cause and cause-specific mortality in both Crohn's disease (CD) and UC, and examined the effect of study design on this outcome. We found elevated all-cause and cause-specific mortality in both UC and CD including colorectal-, pulmonary- and non-alcoholic liver disease-related relative mortality. We further found little evidence that study design impacted all-cause relative mortality summary estimates.

We next conducted a study examining the reliability of the 6-Point Mayo score, a simple two-item non-invasive non-physician driven index, for measuring UC disease activity. We found the 6-Point Mayo to strongly correlate with more extensive disease assessment tools, with a similar sensitivity, specificity and ROC area under the curve for patient-defined clinical remission.

With these insights, we conducted a discrete choice experiment to quantify the UC patients' mean maximum acceptable risk for life-threatening SAEs associated with immunosuppressant therapy to avoid colectomy surgery with various outcomes. We found that UC patient tolerance for medical and surgical risks do not conform to conventional preference-elicitation methodology assumptions. UC patients were willing to accept very high levels of fatal SAEs to avoid an ostomy. However, if a durable medication-induced remission could not be achieved, patients were equally satisfied with J-pouch surgery. Several important clinical phenotypes impacted patient risk tolerances. This is the first empirical demonstration that UC patients view a well-functioning J-pouch as equivalent to mild clinical disease. It further demonstrates that patients value medication efficacy and suggests that clinical remission, rather than response, be the preferred outcome for therapy trials and treatment algorithms. Our findings underline the need for rigorous methodologies to accurately measure patient-preferences; and suggest potential avenues to enhance UC patient autonomy and facilitate shared decision-making.

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INTRODUCTION

Overview of Ulcerative Colitis

UC is a chronic relapsing remitting form of inflammatory bowel disease (IBD) with no known medical cure. UC affects over a half a million people in the United States alone and is rising in both incidence and prevalence.[1] Patients with UC have inflammatory disease limited to their colon. Disease activity can result in diarrhea, abdominal pain, anemia, fatigue, and other systemic symptoms. Disease activity can range from remission (no symptoms) to moderate-severe (more than six bloody bowel movements a day with fevers, increased heart rate, and anemia) or even fulminant disease (more than ten bloody bowel movements a day, passage of blood alone from the rectum, anemia requiring blood transfusions, and severe abdominal pain). These patients are additionally at risk for developing dilation of their colon that can result in perforation, with an extremely high morbidity and mortality.[1-3] UC predominantly affects young adults in the 2nd and 3rd decade of life, resulting in significant economic burden from both chronic treatment and lost productivity.

Surgical Treatment in Ulcerative Colitis

UC patients are in a unique position because disease is limited to the colon; therefore surgery, specifically total proctocolectomy, provides a surgical "cure." The two most common operations performed for UC are total proctocolectomy with end ileostomy and restorative ileal pouch anal anastomsosis (IPAA). The former entails a permanent ileostomy while the latter avoids this, but is associated with frequent bowel movements, the risk of pouchitis and the risk of fecal incontinence.

Risks of Surgical Treatment in Ulcerative Colitis

Surgery has its own risks[4-6]; and quality of life following surgery is not perfect. Those having total proctocolectomy with end ileostomy will have a permanent external draining ileostomy. Those having IPAA surgery still have six bowel movements a day on average. This means that some patients will have more bowel movements than prior to their colectomy. Additionally, patients with IPAA surgery are at risk for having fecal incontinence.

Reported rates of serious infectious complications (including septic complications, pelvic abscesses and wound dehiscence) range from 1%-10% and may be institution and procedure-dependent, and related to pre-operative medication exposure (including corticosteroid use).[4,6,7] Mortality rates with elective colectomy range are no higher than 1% at 35 months; and as low as 0.5% at 33 months.[3-6]

Medical Treatment in Ulcerative Colitis

Mesalamine (5-ASA) has proven to be a safe and effective therapy for UC. However, 5-ASA fails to induce a clinical remission in 50% or more of UC patients.[8-14] For patients in whom 5-ASA therapy is inadequate to control their disease, corticosteroids are frequently used. Unfortunately, over 50% of patients either will suffer disease recurrence upon discontinuation of corticosteroids, or will be unable to taper off corticosteroids at all due to recurrent disease at lower doses of the drug.[15] Therefore, alternatives to corticosteroid therapy have been developed. Cyclosporine and tacrolimus have also been used as a bridge to immunomodulator therapy for refractory UC, particularly in patients who have failed to respond to intravenous corticosteroids.[16,17] Immunomodulators include the medications 6-mercaptopurine (6-MP) and its prodrug azathioprine. These are thiopurine analogs that modulate the immune response by

inhibiting both T- and B-cell lymphocytes, interfering with natural killer cells, and inhibiting suppressor T-cell function and cell-mediated immunity[18]. An alternative to the thiopurines include the anti-TNF medications including the medication infliximab, a chimeric monoclonal antibody that is 75% human and 25% murine[19]. Infliximab targets tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine that plays a central role in the initiation and promotion of the inflammatory cascade, and is a key mediator in several disease states including endotoxin-induced sepsis, rheumatoid arthritis, and the cachexia associated with malignancy. Infliximab is approved by the FDA for treatment of UC. Several other anti-TNF medications have more recently been approved or will likely be approved for UC, including adalimumab and golimumab (fully human monoclonal antibodies to TNF-α), and certolizumab pegol (a PEGylated Fab antibody fragment to TNF-α).

Risks of Medical Treatment in Ulcerative Colitis

While corticosteroids have been the mainstay of therapy for UC patients with disease flares, corticosteroids are associated with numerous well-characterized side effects with long-term use including near inevitable occurrence of bone disease and cataracts. Corticosteroids have been associated with a 2-3 times increased odds of infection, including post-operative infections, serious infections and opportunistic infections.[20-22] Finally, corticosteroids have been associated with an increased mortality risk.[20,23]

Both the thiopurine analogs and anti-TNF medications suppress the immune system and modulate the inflammatory system in an attempt to reduce inflammatory activity in the colon and prevent relapses. Because of the chronic nature of UC, these medications are for long-term use. For those not pursuing definitive surgical treatment,

usage of these medications typically is planned for an indefinite duration. Rates of infection for those on thiopurine analogs and anti-TNF therapy are as high as 5% per year.[21,24-26] The thiopurine analogs and anti-TNF therapies also may increase the risk of certain cancers including an increased risk of cervical dysplasia and non-melanoma skin cancer.[27-29] The risk of lymphoma associated with thiopurine analogs and anti-TNF use that may be as much as four times that of the general population; with combination therapy, this risk increases to 6-10 times that of the general population.[30-33] A particularly aggressive and nearly universally fatal form of lymphoma, called hepatosplenic T-cell lymphoma (HSTCL), is associated with immunosuppression, particularly in young adults.[34-36] By virtue of retaining their colon, IBD patients also have a lifetime risk of colon cancer that is as high as three times that of the general population. [37]

Despite this, UC patients treated with medical therapy were believed to have a normal life expectancy. However, two recent studies question that assumption. In a study by Roberts et al. examining patients who were admitted to the hospital in England for their UC, those patients pursuing chronic medical therapy had a two-times increased odds of mortality compared to those pursuing an elective colectomy surgery over the ensuing three years.[38] A similar record-linkage study in Scotland found that those patients pursuing an elective colectomy had a significantly improved survival compared to those admitted emergently to the hospital for their UC, even after adjustment for age, gender and comorbidity status.[39]

Additionally, as with any medical therapies, there is the risk of medication failure with thiopurine analogs and anti-TNF's. In randomized-controlled trials of the thiopurine analogs for induction of remission for UC, there was no difference between the drugs

and placebo or mesalamine.[18,40] In contrast, they have been shown to be effective as steroid sparing agents and in the maintenance of remission in ulcerative colitis, although in placebo-controlled studies, 36% failed to maintain remission at one year.[18]

Several clinical trials have evaluated the efficacy of infliximab in UC. The two largest, Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively), evaluated the efficacy of infliximab for induction and maintenance of disease remission in UC. In ACT 1, 69.4% of patients receiving 5mg/kg infliximab achieved and maintained remission at week 30, with similar findings reproduced in the ACT 2 trial.[41]

Based upon these studies, at least one-third of patients who start immunomodulators or anti-TNFs will fail either induction or maintenance of remission. The consequences of incompletely treated disease as a result of medication failure are poorly understood. However, indirect evidence suggests that these patients are at increased risk of morbidity and mortality. In some, active UC can progress to severe or fulminant disease, and rarely perforation of the colon. Therefore, these patients are at an increased risk of death from uncontrolled disease alone. Patients who require an emergent colectomy have an immediate post-operative mortality rate between 0.6% and 7.4%.[3,42-44] Recently, in a sample representative of the U.S., it was shown that emergent colectomy had a substantially higher mortality rate than elective colectomy for UC. In this study, the overall in-hospital mortality rate for UC patients undergoing an elective total abdominal colectomy was 0.7%; however, for those who had a colectomy following an emergent or urgent admission, the mortality rate was as high as 7.4%.[3] Similarly, in a comparison of elective and emergent colectomy surgery in Britain, mortality rates three years after emergent colectomy were 13.2% compared to 3.7% for elective colectomy (adjusted odds ratio 3.04, $p<0.001$).[38]

Overview of Decision Making in Ulcerative Colitis

If surgery for UC resulted in a completely normal quality of life, the choice between medical and surgical therapy would be obvious. Because this is not the case, physicians and their patients have traditionally accepted the risks of medical therapies and considered surgery an option of "last resort." At a national level, while immunosuppressant and prolonged corticosteroid use in UC has increased, surgical rates have not changed significantly over the past several decades or may be decreasing.[45-47] The algorithm of making colectomy surgery the product of medication failure rests on the presumption that the patient's foremost desire is to avoid surgery. However, for some patients, chronic immunosuppressive therapy may not be ideal due to unclear durable efficacy and potential lethal serious adverse events (SAEs).

Because all potential therapies (medical and surgical) have potential risks and benefits, and thus implications for patient quantity and quality of life, patient collaboration in decision-making is essential. The last few decades have seen an increased importance placed on patient preferences in healthcare.[48,49] Patient preferences arguably play a critical role in health care outcomes, and an increasing premium is being placed on patient autonomy and shared decision-making: patients' preferences for therapies influence adherence, compliance and satisfaction with therapies, which in turn influences overall care. In turn, understanding patient preferences for risks and benefits of therapies can inform physicians in their daily interaction with patients; regulators in setting thresholds for therapy efficacy and risk; and national organizations in setting treatment guidelines. Thus, rigorous methodologies capable of accurately quantifying patient preferences in large patient populations are needed to include UC patients' voices in an increasingly complex decision process regarding their care.

Time Trade-Off and Standard-Gamble Studies in Ulcerative Colitis

Health-state utility is a well-known cardinal index of the quality of a given health state. Utilities can be measured at population or individual levels, and vary as people's health changes. Changes in health states can be expressed as incremental utility elicited by either time-tradeoff or standard-gamble question formats. Utilities can be converted to quality-adjusted life years (QALYs) that are used in cost-utility analysis. QALYs weight durations in each health state by the average utility of that state and facilitate health-outcome comparisons across groups of people, health outcomes and durations.

In time-trade-off (TTO) studies, respondents evaluate specific treatment-outcome scenarios and are asked how much of a reduction in expected life years they would accept for living in perfect health instead of living the rest of their expected lifetime in the compromised health state. Health-state utility is measured as the ratio of equivalent years in perfect health to years in compromised health.

Standard-gamble (SG) studies elicit the highest level of risk of the worst imaginable health state (usually assumed to be death) respondents would accept in return for best possible health. Setting the utility of death at zero and the utility of best possible health at 1, and assuming that expected utility is the sum of outcomes weighted by probabilities, one minus the indicated risk of death indicates the health-state utility.

A number of TTO and SG studies have evaluated preferences of UC patients for continued medical management of UC versus colectomy surgery.[50-54] Overall, these studies suggest that UC patients view colectomy surgery and the post-surgery state with significantly diminished quality of life, thus supporting current treatment algorithms of making colectomy surgery an option of last resort. However, at least one of these studies found that optimal utility (used in Markov modeling for various treatment

decisions) was highly variable among UC patients with total colectomy being the optimal treatment choice for 37% of their patient sample. When utilizing the average utility for analysis, medical therapy was superior to colectomy surgery. However, this substantial variability in utilities was reflected in their sensitivity analysis, in which only one-third of patients had highly reliable optimal treatment decisions in modeling.[50]

Limitations of Time Trade-Off and Standard-Gamble Studies in Ulcerative Colitis

Using traditional methods such as TTG and SG to obtain utility values for QALY estimation has been widely accepted for health-technology assessment because these methods allow for a simple method of integrating mortality, morbidity and preferences for therapies into a single estimation representing the equivalent years of perfect health. This allows for relatively simple comparisons with other QALY-based measurements (including some quality of life questionnaires) and utilization of these QALYs for cost-utility analyses.

However, it is this simplicity that can become problematic due to inaccurate assumptions regarding patient preferences. TTO and SG studies suffer from a number of fundamental limitations that have been recognized for several decades.[55-59] The clinically-artificial method of eliciting patient utilities in TTO/SG studies employs cardinal-utility, a ratio-scale metric rejected by nineteenth-century utility theorists in favor of ordinal-utility measures. Ordinal utility is the basis of virtually all subsequent applied-economics research.[60]

Numerous validity tests of QALY studies also have rejected the assumptions of independence, procedural and description invariance, linearity over time and comparability across groups of patients.[61,62] Furthermore, in the interest of simplicity,

conventional TTO and SG applications assume that health history or current health state do not affect relative preferences. Moreover, conventional health-state utility measurement techniques are unable to capture the impact of acute conditions, treatment risks, or process-related factors such as the method of administration or treatment duration. Such factors can play a significant role in understanding UC patients' preferences for treatments.

Discrete Choice Experiments

Discrete choice experiments (DCEs; also known as choice-format conjoint analysis) employ a multi-attribute preference-elicitation technique that quantifies the strength of preferences for features of products, services or health-care interventions. Interventions, such as medical or surgical treatments in IBD, derive value from their specific attributes, features or outcomes, including treatment efficacies, tolerability, convenience, and potential SAE risks. In turn, each of these attributes has varying levels, such as efficacy rates or adverse risk rates. DCEs recognize that patients have preferences of varying strengths for different attributes and are willing to accept tradeoffs among various levels. DCEs systematically elicit tradeoffs among constructed outcome combinations to generate choice data that quantifies implicit decision weights indicating relative utility for both individual treatment attributes (such as the specific risks and benefits) as well as the treatment option as a whole. Because DCEs measure the rate at which patients accept tradeoffs among different treatment attributes, it is also possible to calculate a maximum acceptable risk or maximum probability of an adverse event that participants are willing to tolerate in exchange for a given treatment benefit. DCE increasingly has been applied in the field of healthcare for eliciting patient preferences for a range of medical and surgical therapies across many disease states.[63-69]

Advantages of Discrete Choice Experiments

One of the most powerful advantages of DCE is that it does not require the restrictive assumptions of conventional QALY metrics. By offering realistic benefit-risk tradeoff scenarios within a non-expected utility framework, DCEs more accurately quantify preference data, from which utility is derived. Houtven et al. showed how to derive maximum acceptable risk from generalized utility theory with an example using a DCE study in IBD.[62]

As patient preferences play a key role in patient satisfaction, which in turn influences adherence and ultimately clinical outcomes, DCE-measured preference data are more patient-centered than QALYs. Furthermore, by measuring preferences for attributes of a medical therapy as well as the therapy overall, DCE also provides information on the total value of an intervention or on the marginal effect of modifying a single factor on the value. By collecting data within carefully devised experimental designs, DCEs can introduce variability and reduce or even completely eliminate collinearity, making possible more precise estimates of attribute contributions to therapy utilities. This also allows for preference measurement on future interventions including those that may not be currently available. This, in turn, can allow quantification of patients' risk thresholds that can help physicians, drug manufacturers and regulators when contemplating appropriate indications for existing or new therapies, or treatment algorithms.

The majority of DCE studies in IBD have been done in Crohn's disease, another type of IBD that can occur throughout the GI tract. These robust studies have examined CD patients preferences for therapy goals; willingness to accept life-threatening SAEs in exchange for medication efficacy; and variations in preferences by providers and patients. In UC, DCE has been used to evaluate UC patient preferences for various

aspects of 5-ASA therapy.[70] No prior DCE analysis, however, has examined the risk tolerance UC patients have for escalation of medical therapy versus colectomy surgery, a central issue for over 50% of UC patients whose disease cannot be controlled with 5-ASA therapy alone.

Summary

With an increasing number of immunosuppressant medical therapies being offered, rigorously quantifying UC patients' risk tolerances includes their voice in an increasingly-complex treatment paradigm. Identifying patient subgroups that are more or less willing to accept surgery can inform physicians caring for these patients. Determining risk and efficacy levels for which colectomy surgery is preferable to medical therapy can inform drug efficacy trials and treatment algorithms in UC.

A conceptual model of our thesis studies is shown in Figure 1.1. We hypothesized that UC patients perceive the benefits of medical versus surgical therapy and have a quantifiable risk tolerance for medical therapy SAEs in preference to colectomy surgery; however, this tolerance is modified by both clinical factors (e.g. age, gender, disease duration, disease activity, etc.) as well as treatment factors (efficacy, surgical outcome). To test this hypothesis, we use DCE to determine the mean maximum acceptable risk (MAR) for SAEs associated with immunosuppressant therapy in UC that patients are willing to accept to avoid colectomy with ostomy, IPAA or IPAA complicated by fecal incontinence. We also evaluated how clinical characteristics and therapy efficacy affect tolerance for medical therapy risks in preference to surgery (Chapter 4).

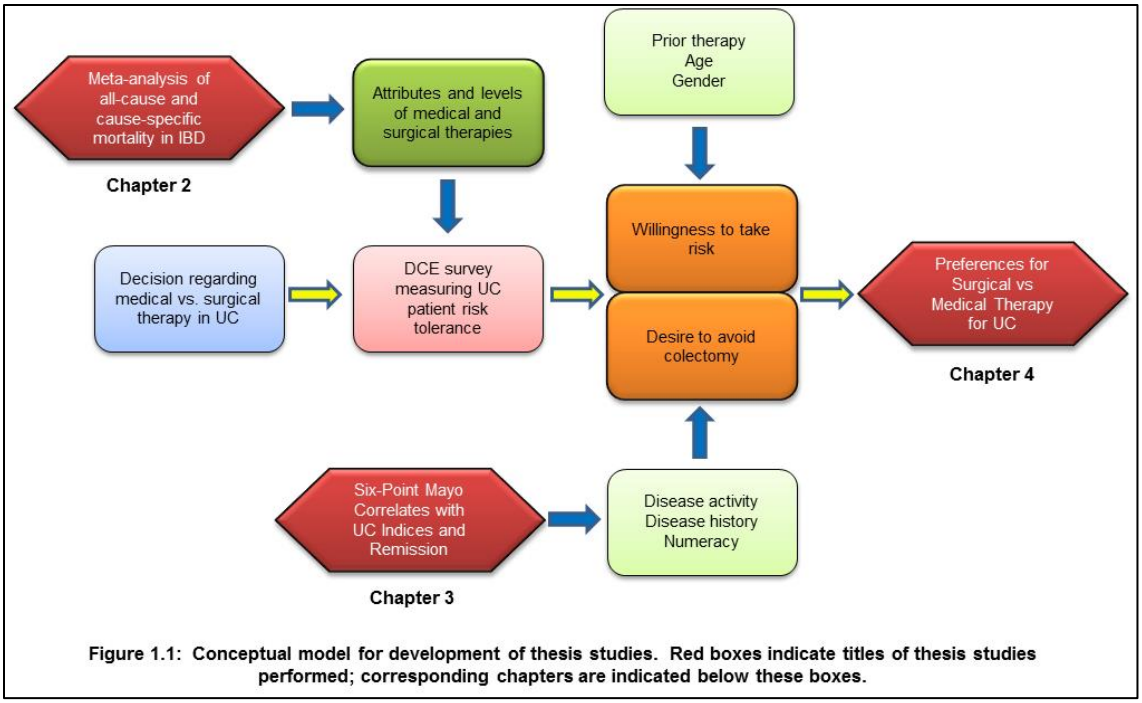

Figure 1.1: Conceptual model for development of thesis studies. Red boxes indicate titles of thesis studies performed; corresponding chapters are indicated below these boxes.

In developing the DCE survey instrument, we additionally conducted two separate but related studies. To limit cognitive burden and numeracy concerns, specifically confusion over conditional probabilities (the probability of an SAE conditional on the probability of having the outcome), we sought to describe all treatment benefits as certain and all treatment risks as known probabilities. One such attribute was that of mortality from colorectal cancer, a risk associated with pursuance of medical therapy (and retention, therefore, of one's colon). While prior work had demonstrated an up to three-times increased risk of colon cancer development in UC patients compared to the general population,[37] no evidence existed regarding the risk of colon cancer mortality in UC. Single-center studies are often underpowered when examining outcomes such as mortality. Meta-analysis is a statistical methodology for combining similar studies to obtain more precise effect estimates. However, prior meta-analyses examining this issue have come to inconsistent conclusions.[71-74] Furthermore, some meta-analyses

have included only population-based studies, others only inception cohorts; none of the recent meta-analyses have included referral center-based studies; and many neglected to examine specific causes of death including colorectal cancer. Therefore, we undertook a meta-analysis of all-cause mortality and cause-specific mortality related to colorectal cancer, non-alcoholic liver disease, pulmonary disease and cardiovascular disease in both UC and CD (Chapter 2). Additionally, we sought to determine how results of population-based studies, inception cohorts, and single- or multi-center studies vary.

We also hypothesized that one clinical factor affecting risk tolerance in UC would be disease activity at the time of DCE survey completion. Currently, no gold-standard for disease activity severity assessment in UC exists. However, at least 14 disease activity indices do exist, many of which include invasive testing, laboratory tests, and/or physician assessment that can make studies costly, difficult to implement and can deter patient enrollment, especially with repeated measurements.[75] Purely patient-driven disease assessment indices include the Simple Clinical Colitis Activity Index (SCCAI), which has been shown to have robust validity and reliability.[76,77] While the SCCAI is completely patient-driven, it includes some variables such as extra-intestinal manifestations that may be ambiguous to patients and thus cause incorrect patient-reporting of current disease activity. Additionally, the quantity of questions in the SCCAI can make it cumbersome in studies with repeated measurements.

In contrast, a purely patient-driven 6-Mayo score has been infrequently utilized in clinical research studies in UC. Two prior studies have found that the 6-Point Mayo score correlates well with the full Mayo Clinic Score, an index most commonly used in clinical trials but requiring both a flexible sigmoidoscopic and physician evaluation.[78,79]

However, no studies had sought to correlate the 6-Point Mayo with disease severity indices outside of the Mayo scoring system. We hypothesized that the much-simpler two-question 6-Point Mayo would have comparable sensitivity, specificity and receiver operating characteristic (ROC) area under the curve for patient-defined clinical remission as the SCCAI. We therefore sought to evaluate how the 6-Point Mayo score correlated with the SCCAI and a single Likert-scale of patient defined disease activity (Chapter 3). We further sought to perform a validation study in a separate patient population.

The results of these studies have several important implications. For UC patients, and the physicians and surgeons caring for them, these results provide information regarding disease outcomes, improve understanding of UC patient risk tolerances, and provide avenues for enhancing informed consent and shared decision-making for UC patients. For clinical researchers, findings from these studies provide avenues for simpler non-invasive disease severity assessment. The results of these studies also set new thresholds for therapies and therapeutic guidelines in UC. Finally, our findings inform future funding proposals aimed at evaluating causes of morbidity and mortality in IBD, measuring activity in UC, and assessing the impact of interventions such as education on IBD patient risk tolerances.

CHAPTER 2: Crohn's Disease and Ulcerative Colitis Are Associated with Elevated Standardized Mortality Ratios: A Meta-Analysis

Short Title: IBD Mortality Meta-Analysis

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Abbreviations: Crohn's disease (CD); inflammatory bowel disease (IBD); standardized mortality ratio (SMR); ulcerative colitis (UC)

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Abstract:

Background:

Evidence regarding all-cause and cause-specific mortality in inflammatory bowel disease (IBD) is conflicting, and debate exists over appropriate study design to examine these important outcomes. We conducted a comprehensive meta-analysis of all-cause and cause-specific mortality in both Crohn's disease (CD) and ulcerative colitis (UC), and additionally examined various effects of study design on this outcome.

Methods:

A systematic search of PubMed and EMBASE was conducted to identify studies examining mortality rates relative to the general population. Pooled summary standardized mortality ratios (SMR) were calculated using random effects models.

Results:

35 original articles fulfilled the inclusion and exclusion criteria, reporting all-cause mortality SMRs varying from 0.44 to 7.14 for UC; and 0.71-3.20 for CD. The all-cause mortality summary SMR for inception- and population-cohort UC studies was 1.19 (95% CI 1.06-1.35). The all-cause mortality summary SMR for inception- and population-cohort CD studies was 1.38 (95% CI 1.23-1.55). Mortality from colorectal cancer, pulmonary disease and nonalcoholic liver disease was increased whereas mortality from cardiovascular disease was decreased.

Conclusions:

Patients with UC and CD have higher rates of death from all causes, colorectal-cancer, pulmonary disease, and nonalcoholic-liver disease.

Key words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, mortality, meta-analysis

Introduction:

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic intestinal inflammatory diseases. Due to the chronic and sometimes severe nature of this disease, there is obvious need to elucidate both all-cause and cause-specific mortality, as this has important implications for patients and more globally for issues such as public health planning.

Meta-analysis is a statistical methodology for combining similar studies to obtain a more precise effect estimate. Prior meta-analyses examining this issue have come to inconsistent conclusions, perhaps because of different inclusion criteria (Table 2.1).[71-74]

TABLE 2.1: Prior meta-analyses of IBD mortality

	IBD type	**Included studies (publication year)**	**Outcomes**	**SMR (95% CI)**
Canavan et al., 2007[71]	CD	All study types (1980-2004)	All-cause mortality	1.52 (1.3-1.7)
Dorn et al., 2007[72]	CD UC	All study types (1981-2006)	Cardiovascular mortality	(0.8-1.1) 0.9 (0.8-1.0)
Jess et al., 2007[73]	UC	Inception-cohort studies (1982-2005)	All-cause mortality CRC mortality Cardiovascular mortality Respiratory disease mortality Non-alcoholic liver disease mortality	1.1 (0.9-1.2) 1.9 (1.0-3.8) 0.9 (0.7-1.1) 1.6 (1.3-2.0) 4.0 (2.5-6.5)
Duricova et al., 2010[74]	CD	Population-based studies	All-cause mortality All-cause cancer mortality Pulmonary cancer mortality Malignant melanoma mortality CRC mortality Pulmonary mortality	1.39 (1.3-1.5) 1.50 (1.2-1.9) 2.72 (1.4-5.5) 10.0 (1.2-36.1) 1.3 (0.5-3.3) 1.4 (0.7-2.2)

Specifically, some meta-analyses have included only population-based studies, others only inception cohorts; and none of the recent meta-analyses have included referral center-based studies. Furthermore, many focused only on all-cause mortality

neglecting specific causes of death, critical information if one is to plan interventions to reduce IBD-related mortality.

Therefore, we undertook a meta-analysis of all-cause mortality and cause-specific mortality related to colorectal cancer, non-alcoholic liver disease, pulmonary disease and cardiovascular disease in both UC and CD. Additionally, we sought to determine how results of population-based studies, inception cohorts, and single- or multi-center studies vary.

Materials and Methods:

Search strategy:

To identify published studies on this topic, a systematic search of PubMed was performed on November 12, 2011. The search used the keywords and MESH headings inflammatory bowel disease or ulcerative colitis or Crohn's disease combined with colorectal cancer or colon cancer or rectal cancer or pulmonary disease or cardiovascular disease or hepatic disease or mortality or death or survival. A comprehensive search of reference lists in prior meta-analyses and original studies retrieved by this method was performed to identify additional reports. This approach identified 15,577 papers published between 1941 and 2011. Application of the limitations "English language journal papers" and "human studies" yielded 11,234 papers for analysis (Figure 2.1). An search of EMBASE using the same keywords and MESH headings was performed and no additional appropriate papers were identified.

Inclusion and exclusion criteria:

Only full length peer-reviewed English language or English-translated papers reporting observational study results were included to allow full evaluation of study methods and results (such as study inclusion criteria, follow-up time, specific details of how cause specific mortality was determined, methods of ascertainment of data and calculation of outcome measures). All-cause and/or cause-specific mortality had to be reported as either standardized mortality ratio (SMR), relative risk (RR), incidence rate ratio (IRR), hazard ratio (HR) or odds ratio (OR) with or without 95% confidence intervals. When two or more publications reported on the same patient population only the most recent study results were included. Application of these criteria resulted in 35 original papers for analysis (Figure 2.1).

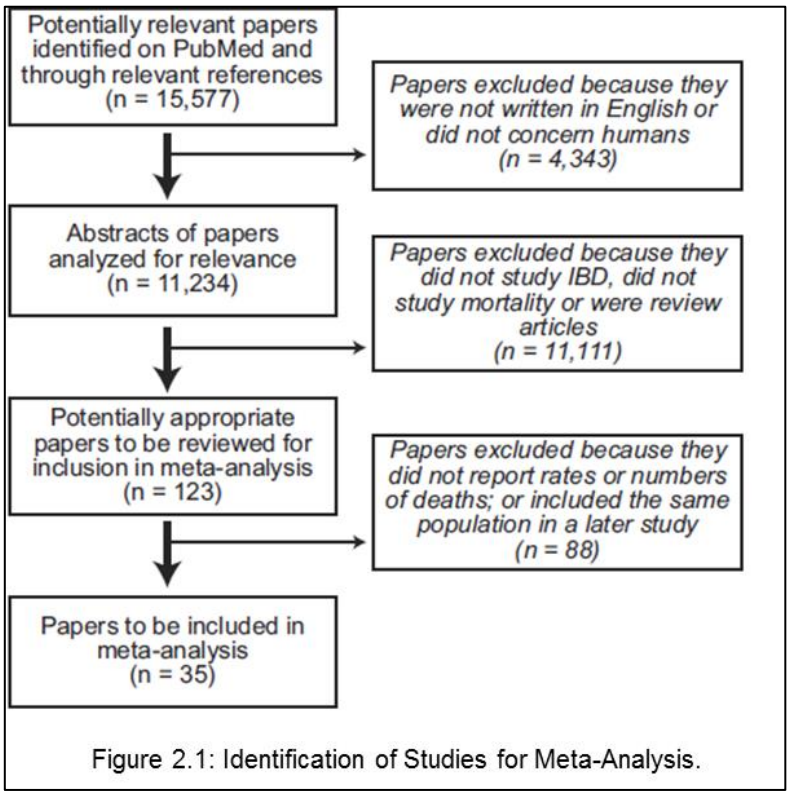

Figure 2.1: Identification of Studies for Meta-Analysis.

Data Collection:

Included papers were reviewed in detail by two reviewers (MB and either LK or JDL; discrepancies were decided by concensus and if necessary by the third reviewer JDL) to determine number of patients, gender distribution, number of UC and CD patients, calendar year of publication, decade of the middle year of patient observation, mortality rates and/or observed and expected numbers of deaths, 95% confidence intervals, region of IBD

population, type of study population and study design. In two studies, a lower 95% CI of 0.0 was reported.[80,81] To allow this to be included in the summary calculations, we approximated the lower bound to 0.025 (i.e. the midpoint between 0 and 0.049).

Studies were categorized into the following groups based on the source of the study population: single or multi-center study if all patients observed came from the same center or group of physicians; population-based if the IBD population was identified within a defined geographic area; inception cohort if it was explicitly stated that patients received their initial IBD diagnosis during their time within the cohort or if the study explicitly stated it was a population-based inception cohort.

Statistical Analysis:

The outcome of interest was the relative mortality rate as compared to the general population and respective 95% CIs. In the event that 95% CIs were not calculated but observed and expected values were given, 95% CIs were calculated using the Rothman-Greenland method. Because all but one study reported results in terms of the SMR, we used this as our summary measure of relative risk. Pooled SMRs with 95% CI for all-cause and cause-specific mortality were calculated using STATA's metan command, which uses the DerSimonian and Laird method, a random- effects model that incorporates both between-study and within-study variation.

Statistical heterogeneity was assessed two ways. First, the I^2 index and χ^2 test were used to investigate differences among studies with respect to SMRs. Additionally, sub-group analyses were performed to assess potential sources of heterogeneity separately due to the following available patient- and study-level factors: region of study, study type, and decade of the middle year of patient observation. Meta-

regression analysis was also performed for heterogeneity of the all-cause SMR due to cohort size and middle year of patient observation. Cumulative meta-analysis was performed to examine all-cause mortality. Funnel plots of the log SMR versus its standard error were performed to assess publication bias for analyses with five or more studies. Begg's rank correlation method and Egger's regression were used to test the correlation between effect and sample size.

Ethical Considerations: The study protocol was reviewed by the Institutional Review Board at the University of Pennsylvania and met the criteria for exempt status.

Results:

Study Characteristics:

A total of 35 studies were included, of which 10 were inception cohorts, 13 were population-based cohort studies, 8 were single-center studies, and 4 were multi-center studies (Table 2.2). These studies included all studies used in prior meta-analyses excluding one abstract used in a meta-analysis by Jess et al.[73] and one study used in the meta-analysis by Canavan et al for which data were not available.[71,82]

TABLE 2.2: Studies included in meta-analysis

Study	Location	Median Follow-up (months)	Study Source	Population Size	Mortality studied
Romberg-Camps (2010)[81]	Netherlands	67.2-93.6	Inception cohort	UC: 630 CD: 476	All-cause CV Pulmonary
Solberg (2009)[83]	Norway	Not reported	Inception cohort	UC: 519 CD: 237	All-cause
Hutfless (2007)[84]	N. America	81.6	Population-based	UC: 5238 CD: 3241	All-cause CRC CV Pulmonary Hepatic
Canavan (2007)[85]	UK	288	Population-based	CD: 394	All-cause
Park (2007)[86]	Korea	62.5	Single center	UC: 304	All-cause
Jess (2007)[87]	Denmark	Not reported	Inception cohort	UC: 1575 CD: 641	All-cause
Hoie (2007)[88]	EC-IBD	35	Inception cohort	UC: 775	All-cause CV Pulmonary
Delaunoit (2006)[89]	N. America	Not reported	Single center	UC: 249 CD: 49	CRC
Jess (2006)[90]	N. America	168	Inception cohort	UC: 378 CD: 314	All-cause CV Pulmonary
Wolters (2006)[91]	EC-IBD	372	Inception cohort	CD: 371	All-cause CV Pulmonary
Masala (2004)[92]	Italy	177.6	Population cohort	UC: 689 CD: 231	All-cause CRC CV
Card (2003)[93]	UK	Not reported	Population-based	UC: 8301 CD: 5960	All-cause
Winther (2003)[94]	Denmark	228	Inception cohort	UC: 1160	All-cause CRC CV Pulmonary Liver
Uno (2003)[95]	Japan	Not reported	Multi-center	CD: 544	All-cause CRC
Jess (2002)[96]	Denmark	204	Inception cohort	CD: 374	All-cause† CV Pulmonary
Viscido (2001)[80]	Italy	73.2	Multi-center	UC: 2066	All-cause CRC CV Pulmonary Liver
Farrokhyar (2001)[97]	UK	99.6	Inception cohort	UC: 365 CD: 196	All-cause
Katoh (2000)[98]	Japan	Not reported	Single center	UC: 117	All-cause
Ishibashi (1999)[99]	Japan	192 (UC) 188.4 (CD)	Population cohort	UC: 174 CD 66	All-cause CRC
Saro (1999)[100]	Spain	Not reported	Population cohort	UC: 261 CD: 259	All-cause

Palli (1998)[101]	Italy	121.2	Population cohort	UC: 689 CD: 231	All-cause†† CRC CV Pulmonary
Davoli (1997)[102]	Italy	60	Single center	UC: 508	All-cause CV
Persson (1996)[103]	Sweden	Not reported	Inception cohort	UC: 1547 CD: 1251	All-cause CRC CV Pulmonary Liver
Cottone (1996)[104]	Southern Europe	93.6	Single center	CD: 531	All-cause CRC
Stewenius (1995)[105]	Sweden	Not reported	Population cohort	UC: 462	All-cause Pulmonary
Probert (1993)[106]	UK	Not reported	Population cohort	UC: 1014	All-cause
Ekbom (1992)[107]	Sweden	Not reported	Population cohort	UC: 3121 CD: 1655	All-cause CRC CV Pulmonary Hepatology
Probert (1992)[108]	UK	Not reported	Population cohort	CD: 610	All-cause
Weterman (1990)[109]	Netherlands	Not reported	Single center	CD: 671	All-cause
Gyde (1982)[110]	UK	189.6	Multi-center	UC: 676	All-cause CV Pulmonary
Eason (1982)[111]	New Zealand	72	Multi-center	UC: 456 CD: 137	All-cause CRC CV
Prior (1981)[112]	UK	Not reported	Single center	CD: 513	All-cause CV Pulmonary
Ritchie (1978)[113]	UK	Not reported	Single center	UC: 269	All-cause
Gilat (1976)[114]	Israel	93.6	Population cohort	UC: 504	All-cause
Iversen (1968)[115]	Denmark	Not reported	Population cohort	UC: 231	All-cause

**CRC: colorectal cancer; CV: cardiovascular*
† Given more recent all-cause mortality rates for this population, only pulmonary and cardiovascular mortality was used in the current study
†† Given more recent all-cause, CRC and CV mortality rates for this population, only pulmonary mortality was used in the current study

Overall, there were 32,269 patients with CD and 18,952 patients with UC. The year of publication ranged from 1968-2010. The median duration of follow-up (when provided) was 83.4 months for UC and 204 months for CD.

All-cause Mortality

The reported SMRs for all-cause mortality in patients with UC ranged from 0.44 (95% CI 0.12-1.12) to 7.14 (95% CI 1.47 to 20.70).[86,100] The all-cause mortality summary SMR for UC was 1.16 (95% CI 1.04-1.29) (Table 2.3). When combining inception cohort and population-based studies, the all-cause mortality summary SMR for UC was 1.19 (95% CI 1.06-1.35).

TABLE 2.3: Standardized Mortality Ratios

	SummarySMR	L95%	U95%	I^2	Het p-value	# studies
Overall: UC	1.16	1.04	1.29	84%	0.00	25
Overall: CD	1.46	1.30	1.63	71%	0.00	19
Colorectal cancer: UC	2.82	1.68	4.74	80%	0.00	7
Colorectal cancer: CD	3.12	0.97	10.10	73%	0.00	6
Cardiovascular disease: UC	0.90	0.80	1.02	39%	0.09	11
Cardiovascular disease: CD	1.00	0.88	1.13	0.0%	0.73	9
Pulmonary disease: UC	1.41	1.12	1.77	39%	0.10	10
Pulmonary disease: CD	1.60	1.24	2.05	0.0%	0.43	8
Nonalcoholic liver disease: UC	2.26	1.14	4.49	55%	0.06	5
Nonalcoholic liver disease: CD	2.82	1.52	5.21	0.0%	0.63	3

The reported SMRs for all-cause mortality in CD patients ranged from 0.71 (95% CI 0.51-1.01) to 3.20 (95% CI 0.38-11.50).[100,108] The all-cause mortality summary SMR for CD was 1.46 (95% CI 1.30-1.63) (Table 2.3). When combining inception cohort and population-based studies, the all-cause mortality summary SMR for CD was 1.38 (95% CI 1.23-1.55).

There was significant heterogeneity in the all-cause summary SMR across levels of patient- and study-level factors for both UC and CD (Table 2.4). Twelve studies reported on gender-specific overall mortality for UC and CD, with a possible trend towards higher relative mortality in females (Table 2.4). However, there remained significant among-study heterogeneity when examining men and women separately.

TABLE 2.4: All-Cause Standardized Mortality Ratios*†

		Pooled ES	L95%	U95%	I^2	Het p-value	# studies
	UC						
Men		1.10	0.94	1.28	56%	0.01	12
Women		1.29	1.01	1.64	76%	0.00	12
	CD						
Men		1.32	1.11	1.57	55%	0.01	12
Women		1.63	1.38	1.93	57%	0.01	12
	UC all-cause						
North America		0.92	0.74	1.14	55%	0.14	2
United Kingdom		1.21	0.96	1.54	86%	0.00	5
North Europe		1.23	1.10	1.40	79%	0.00	8
South Europe		1.01	0.69	1.49	80%	0.00	4
Other countries		1.14	0.65	2.01	76%	0.00	5
EC-IBD		1.09	0.86	1.38	…..	…..	1
	CD all-cause						
North America		1.36	1.19	1.54	0%	0.35	2
United Kingdom		1.30	0.99	1.72	90%	0.00	5
North Europe		1.54	1.29	1.84	73%	0.01	5
South Europe		1.62	1.23	2.14	0%	0.62	3
Other countries		1.29	0.72	2.33	0%	0.89	3
EC-IBD		1.85	1.30	2.55	…..	…..	1
	UC all-cause						
Inception		1.08	0.97	1.21	67%	0.00	8
Population		1.32	1.07	1.63	90%	0.00	10
Single-center		1.03	0.77	1.38	22%	0.28	4
Multi-center		1.16	0.73	1.83	90%	0.00	3
All-studies		1.16	1.04	1.29	84%	0.00	25
	CD all-cause						
Inception		1.34	1.15	1.56	49%	0.08	6
Population		1.39	1.18	1.64	77%	0.00	8
Single-center		2.06	1.78	2.38	0%	0.68	3
Multi-center		1.25	0.67	2.32	0%	0.67	2
All-studies		1.46	1.30	1.63	71%	0.00	19
	UC all-cause						
Decade 2000s		0.44	0.12	1.12	….	….	1
Decade 1990s		1.04	0.83	1.31	90%	0.00	6
Decade 1980s		1.05	0.99	1.12	0%	0.77	7

Decade 1970s		1.21	1.01	1.45	74%	0.00	8
Decade 1960s		2.26	1.79	2.86	0%	0.42	2
Decade 1950s		1.70	1.48	2.06	…..	…..	1
	CD all-cause						
Decade 2000s		…..	…..	…..	…..	…..	0
Decade 1990s		1.54	1.32	1.79	54%	0.07	5
Decade 1980s		1.14	0.84	1.55	62%	0.02	6
Decade 1970s		1.42	1.27	1.59	35%	0.18	6
Decade 1960s		2.09	1.79	2.43	0%	0.49	2
Decade 1950s		…..	……	…..	…..	….	0

**Numbers of studies reporting from respective regions of the world: North America (3); United Kingdom (8); Northern Europe (9); Southern Europe (6); Other Regions (6); European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD) (2)*

† *Decade refers to decade of the middle year of patient observation in study*

Meta-regression was carried out to explore evidence that between-study heterogeneity could be due to cohort size or decade of the middle year of patient observation, two variables universally available in all studies. For all-cause mortality in UC and CD, the SMR was not associated with cohort size (p=0.71 and p=0.43 respectively) or decade of middle year of patient observation (p=0.06 and p=0.28 respectively).

Subgroup analyses were performed stratified by geographic region (Table 2.4). Despite the reduced number of studies, there remained significant heterogeneity in most of the regional subgroup analyses for all-cause mortality.

Study Type

Figure 2.2 shows the similarity of the population-based studies and inception cohort studies examining all-cause mortality in UC. Inception cohort, single-center and

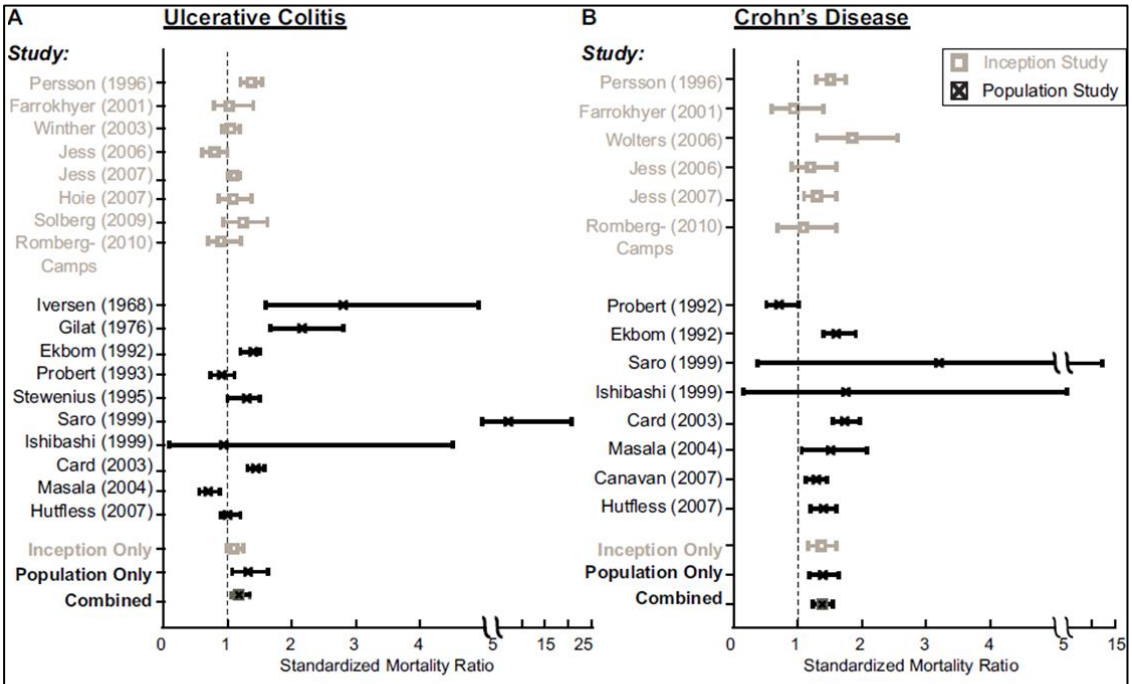

Figure 2.2: Standardized Mortality Ratios for UC and CD. The SMR from individual trials is denoted with inception cohort studies in grey and population cohort studies in black. Horizontal bars represent upper and lower 95% confidence intervals. The final three values represent the overall all-cause standardized mortality ratio for inception cohort studies, population cohort studies or inception and population cohort studies combined.

multi-center studies all showed non-significant SMRs of similar elevated magnitude [summary SMRs 1.08 (95% CI 0.97-1.21), 1.03 (95% CI 0.77-1.38) and 1.16 (95% CI 0.73-1.83) respectively)]. A significantly elevated SMR was observed for population-based studies (summary SMR 1.32, 95% CI 1.07-1.63) (Table 2.4). However, this estimate fell within the range of mortality estimates for other study types and there remained significant heterogeneity within the subgroup of population-based studies (Table 2.4 and Figure 2.2). Therefore, heterogeneity of the all-cause mortality summary estimate could not be accounted for by study type for UC.

For all-cause mortality in CD, higher SMRs were reported in single-center studies than for inception or population based studies [(summary SMRs 2.06 (95% CI 1.78-2.38), 1.34 (95% CI 1.15-1.56) and 1.39 (95% CI 1.18-1.64) respectively)]. Multi-center

studies had a non-significant all-cause summary SMR of 1.25 (95% CI 0.67-2.32). These data suggest that heterogeneity among CD studies was partly explained by inclusion of single-center studies. However, significant heterogeneity remained in the inception and population-based studies ($p=0.08$ and $p \leq 0.01$ respectively).

Cumulative meta-analysis was carried out to examine how the summary mortality estimate for all-cause mortality in UC and CD changed with successive published inception and inception plus population-based cohort studies (see Figure 2.3). For UC, the dates of inception-cohort studies ranged from 1996 to 2010; and ranged from 1968 to 2009 for population-based cohort studies. The summary mortality estimate for both study cohort types was attenuated over time (see Figure 2.3). In the inception cohort only studies, the summary mortality estimate became non-significant over time (SMR 1.08, 95% CI 0.97-1.21). The addition of population cohort studies yielded a very similar summary estimate that remained slightly elevated over time (SMR 1.17, 95% CI 1.04-1.32). Additional cumulative meta-analysis was performed removing the studies from 1968 and 1976; the resulting dates of studies ranged from 1992-2010. The summary all-cause mortality estimates remained very similar to that of inception-only studies (SMR 1.10, 95% CI 0.99-1.23).

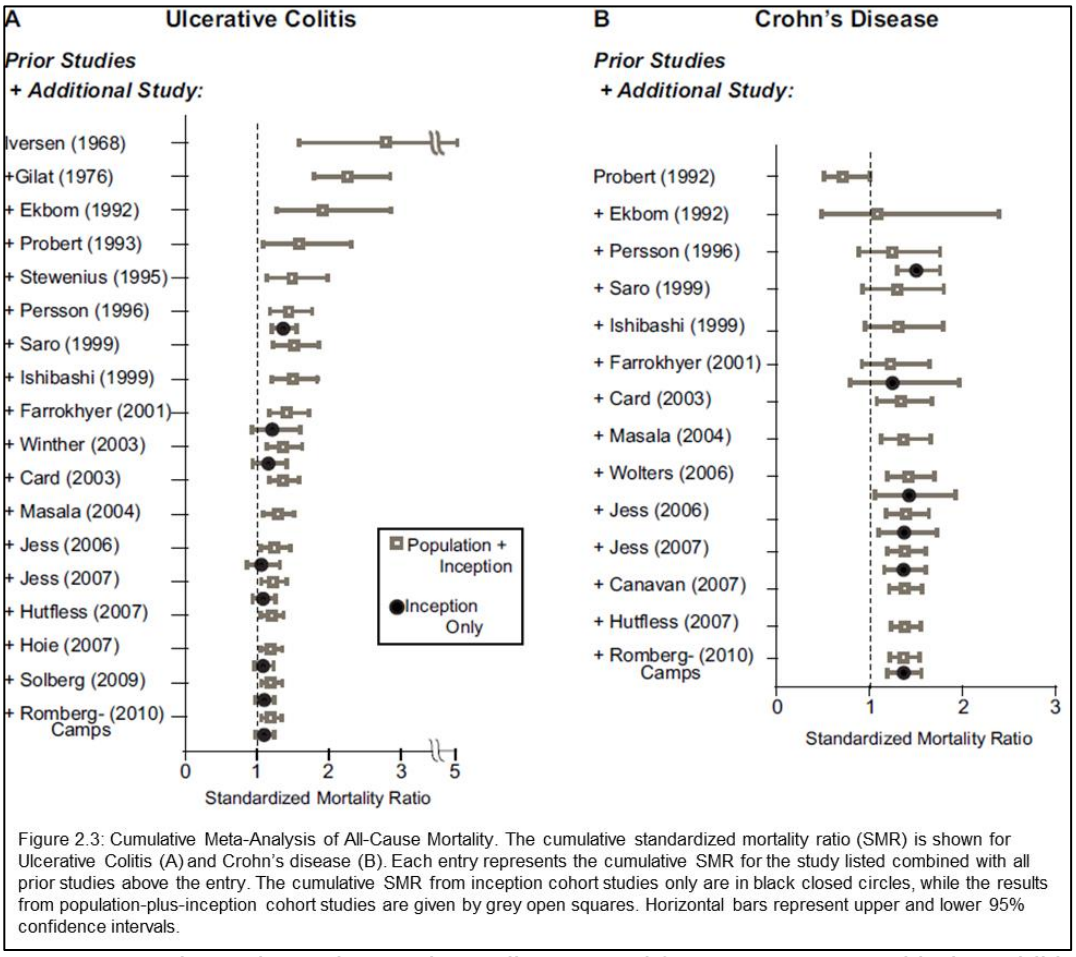

Figure 2.3: Cumulative Meta-Analysis of All-Cause Mortality. The cumulative standardized mortality ratio (SMR) is shown for Ulcerative Colitis (A) and Crohn's disease (B). Each entry represents the cumulative SMR for the study listed combined with all prior studies above the entry. The cumulative SMR from inception cohort studies only are in black closed circles, while the results from population-plus-inception cohort studies are given by grey open squares. Horizontal bars represent upper and lower 95% confidence intervals.

For CD, inception cohort-only studies ranged from 1996-2010; with the addition of population cohort studies, the date of the studies ranged from 1992-2010 (see Figure 2.3). The summary mortality estimate for all-cause mortality remained fairly constant over time for both inception cohort studies alone and inception plus population cohort studies (SMR 1.34, 95% CI 1.15-1.56; and SMR 1.37, 95% CI 1.22-1.53 respectively).

Analysis of Cause Specific Mortality

Significantly elevated SMRs for colorectal cancer, pulmonary disease, and nonalcoholic liver disease were observed in UC; and significantly elevated SMRs for

pulmonary disease and nonalcoholic liver disease were observed in CD (Table 3). However, for patients with UC and CD, the SMR for cardiovascular disease related mortality rates was not significant; and for patients with CD, the SMR for colorectal cancer mortality was not significant, although there appeared to be a trend towards significance. Significant heterogeneity was observed for CRC-related mortality in UC and CD. There was borderline heterogeneity for hepatic- and cardiovascular-related mortality in UC (Table 2.3). Because of the small number of studies, all study types were included in cause specific mortality analysis (Table 2.3); and only qualitative comparisons were made across geographic region or study type for cause specific mortality (Table 2.5). Differences in definitions of cause specific mortality are summarized in Table 2.6.

Table 2.5. Cause-specific Standardized Mortality Estimates*†

		Summary SMR	**L95%**	**U95%**	**I^2**	**Heterogeneity p-value**	**# studies**
	UC						
Colorectal cancer: men		1.80	1.04	3.12	0.0%	0.36	2
Colorectal cancer: women		0.73	0.26	2.04	0.0%	0.59	2
Cardiovascular disease: men		0.93	0.69	1.24	41%	0.13	6
Cardiovascular disease: women		0.93	0.69	1.25	21%	0.28	6
Pulmonary disease: men		1.13	0.59	2.17	46%	0.12	5
Pulmonary disease: women		1.55	1.07	2.26	0.0%	0.87	4
Nonalcoholic liver disease: men		NS					
Nonalcoholic liver disease: women		1.67	0.04	9.28	….	….	1
	CD						
Colorectal cancer: men		3.50	1.64	7.45	….	….	1
Colorectal cancer: women		NS					
Cardiovascular disease: men		0.87	0.61	1.25	0.0%	0.82	5
Cardiovascular disease: women		1.22	0.70	2.11	53%	0.08	5
Pulmonary disease: men		1.54	0.91	2.63	0.0%	0.62	5

Pulmonary disease: women		2.054	1.408	2.997	0.0%	0.56	5
Nonalcoholic liver disease: men		NS					
Nonalcoholic liver disease: women		3.60	1.00	9.20	….	….	1
	UC Colorectal cancer						
North America		1.60	0.90	2.80	….	….	1
United Kingdom		NS					
North Europe		2.60	1.27	5.29	79.4 %	0.01	3
South Europe		2.31	0.87	6.09	54.7 %	0.14	2
Other countries		9.93	4.67	17.3	….	….	1
EC-IBD††		NS					
	UC Cardiovascular disease						
North America		0.76	0.52	1.13	65.9 %	0.09	2
United Kingdom		0.70	0.45	1.10	….	…..	1
North Europe		1.01	0.90	1.15	16.9 %	0.31	4
South Europe		0.72	0.56	0.93	0.0%	0.79	3
Other countries		NS					
EC-IBD††		1.07	0.71	1.54	….	….	1
	UC Pulmonary disease						
North America		1.15	0.84	1.59	0.0%	0.56	2
United Kingdom		0.80	0.36	1.60	….	….	1
North Europe		1.64	1.34	2.00	0.0%	0.57	5
South Europe		0.18	0.00	1.10	….	….	1
Other countries		NS					
EC-IBD††		2.01	1.00	3.60	….	….	1
	UC Nonalcoholic liver disease						
North America		1.20	0.40	2.60	….	….	1
United Kingdom		NS					
North Europe		3.50	2.05	5.98	22.4 %	0.28	3
South Europe		0.50	0.03	3.00	….	…	1
Other countries		NS					
EC-IBD††		NS					
	CD Colorectal cancer						
North America		1.90	0.90	3.70	….	…	1
United Kingdom		NS					
North Europe		1.08	0.24	4.81	34.4 %	0.22	2
South Europe		3.86	0.86	17.20	0.0%	0.45	2
Other countries		64.4	7.72	232.5 0	….	…	1
EC-IBD††		NS					

	CD Cardiovascular disease						
North America		0.96	0.77	1.19	0.0%	0.41	2
United Kingdom		0.80	0.50	1.38	….	….	1
North Europe		1.03	0.88	1.21	0.0%	0.78	4
South Europe		0.65	0.24	1.41	….	….	1
Other countries		NS					
EC-IBD††		1.49	0.74	2.66	….	….	1
	CD Pulmonary disease						
North America		1.89	1.35	2.64	0.0%	0.94	2
United Kingdom		0.90	0.42	2.06	….	….	1
North Europe		1.28	0.81	2.03	0.0%	0.50	4
South Europe		NS					
Other countries		NS					
EC-IBD††		2.66	0.72	6.80	….	….	1
	CD Nonalcoholic liver disease						
North America		2.60	1.00	5.30	….	….	1
United Kingdom		NS					
North Europe		3.10	1.24	7.73	0.0%	0.36	2
South Europe		NS					
Other countries		NS					
EC-IBD††		NS					
	UC Colorectal cancer						
Inception		2.85	1.59	4.69	….	….	1
Population		2.60	1.21	5.61	86.4 %	0.00	5
Single-center		NS					
Multi-center		3.46	1.58	6.57	….	….	1
	UC Cardiovascular disease						
Inception		1.00	0.82	1.23	49.4 %	0.10	5
Population		0.90	0.79	1.04	29.6 %	0.24	4
Single-center		0.65	0.26	1.34	….	….	1
Multi-center		0.76	0.56	1.02	0.0%	0.66	2
	UC Pulmonary disease						
Inception		1.60	1.22	2.10	11.4 %	0.34	5
Population		1.49	1.24	1.80	0.0%	0.41	4
Single-center		NS					
Multi-center		0.49	0.13	1.94	51.7 %	0.15	2
	UC Nonalcoholic liver disease						
Inception		4.80	2.07	9.45	….	….	1
Population		1.91	0.79	4.60	57.4	0.10	3

					%		
Single-center		NS					
Multi-center		0.50	0.03	3.00	….	….	1
	CD Colorectal cancer						
Inception		0.30	0.01	1.67	….	….	1
Population		1.82	1.03	3.22	0.0%	0.97	3
Single-center		5.40	0.60	19.00	….	….	1
Multi-center		64.40	7.72	232.50	….	….	1
	CD Cardiovascular disease						
Inception		0.97	0.79	1.19	0.0%	0.60	5
Population		1.04	0.88	1.22	0.0%	0.49	3
Single-center		0.80	0.50	1.38	….	….	1
Multi-center		NS					
	CD Pulmonary disease						
Inception		1.67	1.11	2.49	0.0%	0.75	5
Population		1.33	0.52	3.39	65.0 %	0.09	2
Single-center		0.90	0.42	2.06	….	….	1
Multi-center		NS					
	CD Nonalcoholic liver disease						
Inception		0.91	0.02	5.10	….	….	1
Population		2.99	1.59	5.62	0.0%	0.62	2
Single-center		NS					
Multi-center		NS					
	UC Colorectal cancer						
Decade 2000s		NS					
Decade 1990s		1.53	0.92	2.53	0.0%	0.71	2
Decade 1980s		3.30	0.94	11.67	87.5 %	0.00	3
Decade 1970s		3.76	2.50	5.66	46.7 %	0.17	2
Decade 1960s		NS					
Decade 1950s		NS					
	UC Cardiovascular disease						
Decade 2000s		NS					
Decade 1990s		0.92	0.74	1.13	34.5 %	0.21	4
Decade 1980s		0.94	0.73	1.20	18.2 %	0.29	3
Decade 1970s		0.89	0.69	1.16	74.1 %	0.02	3
Decade 1960s		NS					
Decade 1950s		0.70	0.45	1.10	….	….	1
	UC Pulmonary						

	disease						
Decade 2000s		NS					
Decade 1990s		1.33	0.84	2.11	36.1 %	0.21	3
Decade 1980s		0.67	0.08	5.69	80.5 %	0.02	2
Decade 1970s		1.60	1.25	2.03	0.0%	0.41	4
Decade 1960s		NS					
Decade 1950s		0.80	0.36	1.60	….	….	1
	UC Nonalcoholic liver disease						
Decade 2000s		NS					
Decade 1990s		1.20	0.40	2.60	….	….	1
Decade 1980s		0.70	0.15	3.20	0.0%	0.72	2
Decade 1970s		3.82	2.46	5.93	0.0%	0.47	2
Decade 1960s		NS					
Decade 1950s		NS					
	CD Colorectal cancer						
Decade 2000s		NS					
Decade 1990s		1.87	0.94	3.72	0.0%	0.85	2
Decade 1980s		18.73	1.65	212.59	75.1 %	0.05	2
Decade 1970s		1.08	0.24	4.81	34.4 %	0.22	2
Decade 1960s		NS					
Decade 1950s		NS					
	CD Cardiovascular disease						
Decade 2000s		NS					
Decade 1990s		1.03	0.84	1.28	0.0%	0.47	4
Decade 1980s		0.90	0.50	1.50	…..	…..	1
Decade 1970s		1.01	0.85	1.19	0.0%	0.42	3
Decade 1960s		0.80	0.50	1.38		…..	1
Decade 1950s		NS					
	CD Pulmonary disease						
Decade 2000s		NS					
Decade 1990s		1.91	1.35	2.69	0.0%	0.50	3
Decade 1980s		1.38	0.59	2.71	…..	….	1
Decade 1970s		1.45	0.88	2.41	8.1%	0.34	3
Decade 1960s		0.90	0.42	2.06		…..	1
Decade 1950s		NS					
	CD Nonalcoholic liver disease						
Decade 2000s		NS					
Decade 1990s		2.60	1.00	5.30	….	….	1
Decade 1980s		NS					
Decade 1970s		3.10	1.24	7.73	0.0%	0.36	2
Decade 1960s		NS					
Decade 1950s		NS					

**NS—no studies; EC-IBD--European Collaborative Study Group of Inflammatory Bowel Disease*

†*Decade refers to decade of the middle year of patient observation in study*

Table 2.6: Table of included diagnoses (ICD codes) for cause-specific mortality

Study	Colorectal cancer	Cardiovascular disease	Pulmonary disease	Nonalcoholic liver disease
Romberg-Camps (2010)[81]	NA	ICD10: 099-118	ICD10: 122–134	NA
Solberg (2009)[83]	NA	NA	NA	NA
Hutfless (2007)[84]	ICD9: 153–154 ICD10: C18–C20	ICD9: 390-459 ICD10: I00 –I99	ICD9: 466 –519 ICD10: J02–J98	ICD9: 571 ICD10: K70–K76
Canavan (2007)[85]	NA	NA	NA	NA
Park (2007)[86]	NA	NA	NA	NA
Jess (2007)[87]	NA	NA	NA	NA
Hoie (2007)[88]	NA	ICD10: 099-118	ICD10: 122-134	NA
Delaunoit (2006)[89]	NR	NA	NA	NA
Jess (2006)[90]	NA	ICD9: 390–459	ICD9: 460–519	NA
Wolters (2006)[91]	NA	NR	NR	NA
Masala (2004)[92]	ICD9: 153–154	ICD9: 390–459	NA	NA
Card (2003)[93]	NA	NA	NA	NA
Winther (2003)[94]	ICD10: C18-C20.9	ICD10: I00-I52.9	ICD10: J00-99	ICD10: K71-77.9
Uno (2003)[95]	NR	NA	NA	NA
Jess (2002)[96]	NA	ICD10: I00-25, I27, I30-52	ICD10: J00-99	NA
Viscido (2001)[80]	ICD9: 153-154	ICD9: 390-459	ICD9: 460~519	ICD9: I 55
Farrokhyar (2001)[97]	NA	NA	NA	NA
Katoh (2000)[98]	NA	NA	NA	NA
Ishibashi (1999)[99]	ICD9: 153-154	NA	NA	NA
Saro (1999)[100]	NA	NA	NA	NA
Palli (1998)[101]	ICD9: 153-154	ICD9: 390–459	ICD9: 460–519	NA
Davoli (1997)[102]	NA	ICD9: 390-459	NA	NA
Persson (1996)[103]	ICD9: 153–154	ICD9: 390–458	ICD9: 460–519	ICD9: (570–573 excluding 571.0
Cottone (1996)[104]	NR	NA	NA	NA
Stewenius (1995)[105]	NA	NA	NR	NA
Probert (1993)[106]	NA	NA	NA	NA
Ekbom (1992)[107]	ICD7: 153–154 ICD8: 153–154	ICD7: 400-468 ICD8: 390-458	ICD7: 470-527 ICD8: 480-519	ICD7: 580-583 (excluding 5811) ICD8: 570-573 (excluding 5170)
Probert (1992)[108]	NA	NA	NR	NA
Weterman (1990)[109]	NA	NA	NR	NA
Gyde (1982)[110]	NA	ICD7: 400-468	ICD7: 470-527	NA
Eason (1982)[111]	NR	NR	NA	NA
Prior (1981)[112]	NA	ICD7: 400-468	ICD7: 470-527	NA
Ritchie (1978)[113]	NA	NA	NA	NA
Gilat (1976)[114]	NA	NA	NA	NA
Iversen (1968)[115]	NA	NA	NA	NA

NA: Not Applicable; NR: Not Reported

Publication Bias

There was no evidence of publication bias for all-cause mortality or cause-specific mortality for UC or CD (p>0.09 for all tests).

Discussion:

The present meta-analysis shows a small increase in all-cause mortality for both UC and CD. Cause-specific analysis reveals significantly increased mortality from CRC, pulmonary disease and nonalcoholic liver disease for UC; and from pulmonary and nonalcoholic liver disease for CD. Cardiovascular-related mortality was not elevated for either UC or CD, which is congruent with prior meta-analysis[72].

We examined geographic region, time period and study design as potential sources of heterogeneity, but none entirely explained the observed heterogeneity among all-cause mortality.

This is the first meta-analysis to conclude that patients with UC have an increased mortality rate relative to the general population. We observed this in the overall analysis of all-cause mortality, in population-based studies, in population plus inception cohort studies, but not in inception cohort studies alone. A prior meta-analysis of inception cohort studies by Jess et al also did not observe a significantly increased mortality rate relative to the general population.[73] Of note, our meta-analysis included four new inception cohort studies not included by Jess et al.[81,83,87,97] However, we also categorized five studies in the Jess meta-analysis as population-based but not inception cohorts because it was not specifically stated that patients received their initial IBD diagnosis during their time within the cohort or the study did not explicating state it was an inception-cohort study.[92,94,105-107,111] Additionally, we excluded abstracts from our

analysis while there was one abstract included in the Jess meta-analysis. These conservative efforts in study inclusion and classification may have contributed to the slightly different results. However, importantly, the summary SMRs for inception and population-based studies were similar in magnitude (UC inception 1.08, population 1.32; CD inception 1.34, population-based 1.39) and as expected combining inception cohorts and population-based studies yielded similar results (UC 1.17 (95% CI 1.04-1.32); CD 1.37 (95% CI 1.22-1.53)).

Inception cohorts by definition include all follow-up time in the early stages of disease but may not be able to follow patients for a sufficiently long time period in the later years of disease to fully assess long-term risk of mortality, in particular cancer-related mortality and mortality related to long-term complications of IBD. In contrast, non-inception population-based cohorts include some patients in the early stages of disease and others with late stage disease. Thus inception cohorts are better suited to capture early mortality as their observation time occurs at the onset of disease; while population-based studies are better suited to capture late mortality given their observation time occurs at any stage of disease. It has been suggested that all-cause mortality from UC peaks within the first year of diagnosis.[1,116-118] If this were the case, inception cohort studies would be expected to observe higher all-cause mortality rates than population-based studies. Unfortunately, in our study, we were unable to assess whether the relative risk of mortality varied by years after IBD diagnosis.

We used cumulative meta-analysis and meta-regression to examine trends in relative mortality rates over time. We hypothesized that, over time, the overall mortality rates for IBD patients would move towards 1.0. For UC, this was evident examining the earliest studies with continued improvement over the range of the cumulative meta-

analysis, and from our analysis excluding the two earliest studies where the summary SMR is not significantly elevated. This may be due to improved surgical options for UC over time. However, for CD, overall mortality has not shown a significant change over time. Given that there were no studies meeting our inclusion criteria documenting mortality rates in the 2000's, it remains possible that there has been a decrease in mortality due to improved medical therapy in recent years. Given the shift in treatment patterns including more frequent use of thiopurines, methotrexate and anti-TNFα therapies, this is an important question for future research.[46,119]

This current study suggests multiple potential sources of elevated mortality including CRC, and pulmonary- and hepatic-disease, some of which may be preventable deaths (Table 3). Prior meta-analyses and reviews of these studies have found elevated pulmonary-related mortality in IBD, with observed causes including COPD (CD) and pneumonia (UC).[73,74,120] Our current meta-analysis evaluated a greater number of studies and found similarly elevated pulmonary-related relative mortality for both UC and CD. It is plausible that similar causes drove our all cause mortality findings as well, raising potential avenues for intervention including increase use of smoking cessation counseling and pneumonia and influenza vaccines.

Similarly to Jess et al, we observed an elevated relative risk of death for non-alcoholic liver disease mortality in UC.[73] It has long been recognized that patients with UC are at an increased risk of primary sclerosing cholangitis (PSC) and its complications.[121] We also found that CD patients had a slightly higher relative risk of dying from liver disease. This finding raises the question of whether PSC is more aggressive in CD, under recognized in CD,[122] or if another form of liver disease is driving this increased mortality, such as fatty liver disease. These findings suggest potential

utility of monitoring in IBD patients for liver disease, although this has never been proven in clinical trials.

Death from CRC-related mortality has long been described in IBD, although the two most recent meta-analyses showed a non-significant or marginally significantly increased CRC-related mortality in CD and UC, respectively.[73,74] Our current meta-analysis found an elevated risk of relative mortality for CRC in UC and a trend towards an elevated risk of CD. Our inclusion of single and multi-center studies could have contributed to this. In our stratified analysis for UC, all study types yielded elevated relative risks of mortality for CRC, although multi-center studies did contribute the highest risk (see Table 5). In contrast, for CD, there was an elevated relative risk of mortality for the population-based studies and the two referral-based studies, but not for the inception-based study (see Table 5). It is possible, as discussed above, that inception cohorts were not able to follow patients for a sufficiently long time period to capture long-term mortality such as colorectal cancer.

It is plausible that the relative risk of CRC mortality is decreasing over time, as access to care and screening for CRC has increased.[123] Although we were underpowered to make strong correlations, there appeared to be a trend towards decreased relative mortality over decade time in UC, although not in CD (see Table 5). This could reflect greater awareness of the need for CRC surveillance in UC, although recent evidence argues against this.[124] Alternatively, there could be more frequent use of chemopreventative agents such as mesalamine in UC than in CD, albeit these chemopreventative effects have not been definitively proven.[125] Finally, reduction in CRC-related relative mortality among IBD patients would need to exceed that observed in the general population for this to be evident as a relative risk reduction. Increased

CRC screening in the general population could obscure improvements in CRC-related mortality among patients with IBD when using relative risk estimates as the summary measure.

There are several limitations in this study. In some cases, cause of death was ascertained from death certificates and therefore subject to potential misclassification bias. As described above, there is the potential for misclassification of inception versus population cohort studies. SMRs are only age- and sex-adjusted; therefore other characteristics of the study populations may have contributed to heterogeneity. For example, we were unable to assess whether current or former smoking contributed to excess mortality. Disease severity was not assessed in the included studies and therefore we were unable to assess heterogeneity in overall mortality by disease severity. Finally, we could not determine whether the attributable risk of death due to IBD differs by age. These all remain important questions.

In summary, this is the largest and most comprehensive meta-analysis evaluating all-cause and cause-specific mortality in IBD to date. This is the first meta-analysis to observe an elevated overall relative mortality for patients with UC. We found little evidence of significant differences in all-cause relative mortality summary estimates for population- versus inception-based studies for either UC or CD. We also confirmed the previously reported increased all-cause relative mortality for patients with CD. Additionally, we have found statistically increased colorectal-, pulmonary- and non-alcoholic liver disease-related relative mortality for UC; and a statistically increased pulmonary- and non-alcoholic liver disease-related relative mortality for CD. Cardiovascular-related relative mortality was not elevated for either UC or CD. Further

work evaluating specific etiologies of these cause-specific mortalities is likely to be illuminating.

CHAPTER 3: Patient-Driven Six-Point Mayo Score Correlates with Disease Indices and Patient-Defined Remission in Ulcerative Colitis

Short Title: Six-Point Mayo Correlates with UC Indices and Remission

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Abbreviations: Inflammatory bowel disease (IBD); ulcerative colitis (UC); Simple Clinical Colitis Activity Index (SCCAI); Receiver operating characteristics (ROC)

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James D. Lewis: study concept and design; data interpretation; critical revision of manuscript

Abstract:

Background & Aims:

There is a need for a simple, non-invasive patient-driven disease assessment instrument to facilitate clinical research in ulcerative colitis (UC). Therefore, we sought to determine the reliability of a simple two-item index that does not require physician contact, knowledge of extraintestinal manifestations, endoscopy, stool or blood tests to measure disease activity.

Methods:

A cross-sectional study was conducted to assess the correlation of the 6-Point Mayo score with the Simple Clinical Colitis Activity Index (SCCAI) and a single Likert-scale of patient-defined disease activity. Spearman's correlation, sensitivity, specificity and area under the receiver-operator curves (ROC) were calculated. Subgroup analysis was conducted in patients with more severe UC, defined as current or prior exposure to immunosuppressant therapy. A separate validation study was conducted in which additional analysis was performed evaluating performance characteristics in left-sided and pancolitis UC.

Results:

The 6-Point Mayo score was strongly correlated with the SCCAI (rho = 0.71, $p<0.0001$) and with patient-driven reported disease activity (rho = 0.65, $p<0.0001$). The SCCAI was similarly correlated with patient-driven reported disease activity (rho = 0.66, $p<0.0001$). Using a cut point of 1.5, the 6-Point Mayo score had a sensitivity of 83% and a specificity of 72% for patient-defined remission; and a sensitivity of 89% and a specificity of 67% for SCCAI-defined remission (score <2.5). The 6-Point Mayo score and SCCAI had similar accuracy of predicting patient-defined remission, with an area

under the ROC curve of 0.84 and 0.87, respectively. Addition of the SCCAI urgency and general well-being questions to the 6-Point Mayo resulted in an area under the ROC curve of 0.90. Similar findings were seen in the populations of patients with current or prior exposure to immunosuppressant therapy; however, addition of the SSCAI urgency and general well-being in this population did not significantly improve the discriminative ability of the index. In the external validation study, strong correlations were again seen between the 6-Point Mayo score and SCCAI (rho = 0.73, p <0.0001) and patient-driven reported disease activity (rho = 0.63; p < 0.0001); and between the SCCAI and patient-driven reported disease activity (rho = 0.73; p <0.0001). These significant correlations remained when examining patients with left-sided colitis and pan-colitis UC. In the full validation cohort, the 6-Point Mayo score had a sensitivity of 90% and a specificity of 65% for patient-defined remission; and a sensitivity of 95% and specificity of 79% for SCCAI-defined remission. Both the 6-Point Mayo score and SCCAI had similar accuracy of predicting patient-defined remission, with an area under the ROC curve of 0.80 and 0.87, respectively. Addition of both the SCCAI general well-being and urgency components significantly improved the 6-Point Mayo ability to predict patient-defined remission. None of the clinical activity indices examined (the 6-Point Mayo, the SCCAI or a single Likert-scale of patient-defined disease activity) had good correlations with the UC Endoscopic Index of Severity (UCEIS).

Conclusions:

The 6-Point Mayo score correlates strongly with the SCCAI and with patient-reported disease activity and represents a simple option for assessing disease activity in UC in clinical trials and observation studies without requiring direct physician contact. The addition of information regarding urgency and general well-being improved the test operating characteristics.

Background:

Ulcerative colitis (UC) is a chronic relapsing inflammatory disease of the colon. Assessment of disease severity is useful in the conduct of clinical research related to UC. Often disease activity needs to be assessed not only at study initiation but at repeated time points throughout the study. Currently, no gold-standard for disease severity assessment in UC exists. However, at least 14 disease activity indices have been developed, many of which include invasive testing, laboratory tests, and/or physician assessment that can make studies costly, difficult to implement and can deter patient enrollment, especially with repeated measurements.[75] Therefore, there is a need for a simple, non-invasive patient-driven disease assessment instrument.

One disease severity index that does not require physician assessment, invasive testing or laboratory tests is the Simple Clinical Colitis Activity Index or SCCAI (Table 3.1).[126] This index includes six variables that were found to best predict the original Powell-Tuck classification of UC remission: bowel frequency during the day and night, urgency of defecation, blood in the stool, general well-being and extra-colonic manifestations of UC. The SCCAI has been shown to have robust discriminative and construct validity as well as test-retest reliability and responsiveness to change; and a score of < 2.5 points has been shown to correlate with Patient-Defined Remission.[76,77] It has also been shown to correlate well with invasive indices of UC disease activity.[127] While the SCCAI is completely patient-driven, it includes some variables such as extra-intestinal manifestations that may be ambiguous to patients and thus cause incorrect patient-reporting of current disease activity. Additionally, the quantity of questions in the SCCAI can make it cumbersome in studies with repeated measurements.

The Mayo Score is the index most commonly used in clinical trials and consists of only four items: stool frequency, rectal-bleeding, flexible sigmoidoscopic examination

and a physician global assessment (Table 3.1).[128] A non-invasive 9-Point Mayo or Partial Mayo incorporates stool frequency, rectal bleeding and the physician's global assessment. The Partial Mayo has been found to correlate closely with the full Mayo score, and to independently have strong discriminative and construct validity and responsiveness to change in disease activity.[77,78] However, this scoring system still requires face-to-face evaluation with a physician. Therefore, a purely patient-driven 6-Point Mayo has also been infrequently utilized. Two prior studies have found that the 6-Point Mayo correlates very well with the Partial and Full Mayo scores, and a cut-off of 1.5 has been shown to correlate with patient-defined remission.[78,79] However, no study has sought to correlate the 6-Point Mayo score with disease severity indices outside of the Mayo scoring system. Therefore, the aim of our study was to assess the correlation of the 6-Point Mayo score with the SCCAI and a single Likert-scale of patient defined disease activity (Table 3.1). We also sought to evaluate correlations between the 6-Point Mayo, the SCCAI and patient-defined disease activity in patients with more severe disease, as defined as current or prior exposure to immunosuppressant therapy. To further confirm these findings, we conducted a validation study in a separate population of UC patients with defined disease distribution.

Table 3.1: Components of the SCCAI, 6-Point Mayo and single patient-driven disease activity question

SCCAI remission < 2.5	6-Point Mayo remission < 1.5	Single Patient-Driven Disease Activity Question remission = perfect or very good
Bowel frequency (day) 0 = 1-3 1 = 4-6 2 = 7-9 3 = >9 Bowel frequency (night) 1 = 1-3 2 = 4-6 Urgency of defecation 1 = Hurry 2 = Immediately 3 = Incontinence Blood in stool 1 = Trace 2 = Occasionally frank 3 = Usually frank General well-being 0 = Very well 1 = Slightly below par 2 = Poor 3 = Very poor 4 = Terrible Arthritis, Pyoderma gangrenosum, Erythema nodosum, Uveitis 1 per manifestation	Stool frequency 0 = Normal 1 = 1-2 more than normal 2 = 3-4 more than normal 3 = 5+ more than normal Rectal Bleeding 0 = No blood seen 1 = Streaks of blood < 50% 2 = Obvious blood > 50% 3 = Blood passes alone	"Please check what you would describe as your ulcerative colitis disease activity over the past 3 days" Perfect (no symptoms) Very good (very little symptoms) Good (mild symptoms) Moderately active Severe

Materials and Methods

Data for the initial study were acquired from a recently completed mailed questionnaire-based conjoint analysis study conducted at the University of Pennsylvania and Dartmouth-Hitchcock Medical Center. The purpose of this conjoint analysis study was to assess patient preferences for surgical versus medical therapy for a UC disease flare. The study included patients ≥ 18 years old with an International Statistical Classification of Diseases (ICD)-9 code for UC (556.0-556.6 and 556.8-556.9), no concomitant ICD-9 code for Crohn's disease (555.0-555.2, 555.9) and an outpatient gastroenterology clinic visit within the prior 24 months. The survey included two separate questions asking participants if they had UC. To be included in this substudy,

participants had to answer both questions in the affirmative and have no missing data for any of the disease severity questions that are described below.

The survey instrument included all aspects of the SCCAI and the 6-Point Mayo score. Illustrations and descriptions aimed at a 6-grade reading level were used to illustrate the extra-intestinal manifestation questions in the SCCAI to limit patient confusion or lack of understanding of the medical terminology in the index. Furthermore, we included a single patient-driven disease activity question that read, "Please check what you would describe as your ulcerative colitis activity over the past 3 days." There were six possible responses to this question (Table 3.1).

The validation study utilized the same SCCAI and 6-Point Mayo indices questions (including the illustrations and descriptions) as well as the single patient-driven disease activity question utilized in the initial study. This study was administered to consecutively enrolled clinic patients in separate prospective cohort study at the University of Pennsylvania (IBD Immunology Initiative or I3 study). All patients were ≥ 18 years old with an ICD-9 code for UC (556.0-556.6 and 556.8-556.9) confirmed by a gastroenterologist and verified by review of the patient's electronic medical record. Patients also had to be capable of providing informed consent. Review of the patient's electronic medical record also served to confirm disease extent (left-sided colitis versus extensive colitis).

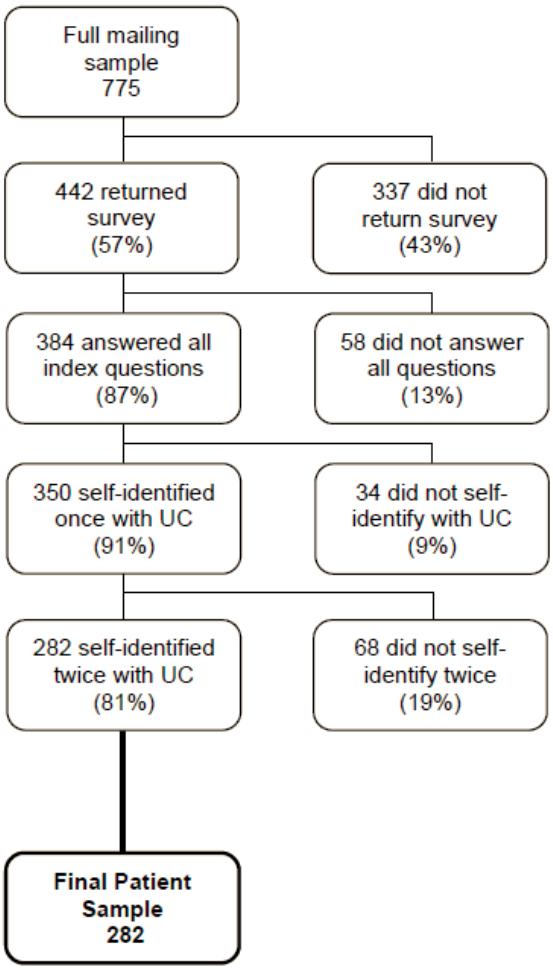
Descriptive statistics were used to describe patients included in the study. Continuous variables are reported as medians; and categorical variables as proportions. Correlations were measured using Spearman correlation coefficients (rho). To assess sensitivity and specificity for the SCCAI and the 6-point Mayo we used the patient-driven disease activity question as the gold standard. Clinical remission was defined as a self-assessment of perfect or very good (minimal disease activity). Receiver operating

characteristic (ROC) curves were generated and area under the ROC curves (AUC) for different disease indices were computed. Logistic regression modeling and chi-square tests were used to compare AUC from different ROC curves. SAS v.9.1 was used for data management and analysis. The study design was approved by the Institution Review Boards at both the University of Pennsylvania and Dartmouth Hitchcock Medical Center

Results

Initial Survey

Figure 3.1: Identification of Initial Study Patient Population



The survey for the initial study was mailed to 775 UC patients and responses were received from 442 patients (57% response rate). We had limited information on non-responders, but men were less likely to respond (data not shown). After applying the exclusion criteria, 282 participants were included in the final analysis (Figure 3.1).

Baseline demographics of the initial survey population are shown in Table 3.2. The majority of respondents were female and

Caucasian with a mean age of 47 years. Most had UC for more than one year with a mean duration of disease of 13 years. 29% stated they were having a current flare of their UC. The majority of respondents were on or had been on some form of 5-ASA therapy for their UC. The majority also had prior exposure to corticosteroids, although only 11% were currently taking corticosteroids. Approximately one-third of respondents were currently on some form of immunosuppressant therapy (including thiopurine, cyclosporine, methotrexate or anti-TNF therapies) and an additional 20% had prior exposure to immunosuppressant therapy for their UC (Table 3.2).

Table 3.2: Summary of Patient Characteristics*

Characteristic	Patients (N = 282)
Gender, n (%)	
Female	167 (59)
Male	115 (41)
Age	
Median (IQR)	45 years (34-59)
Mean (SD)	47 years (16)
Site n (%)	
Dartmouth-Hitchcock Medical Center	27 (10)
Hospital of the University of Pennsylvania	255 (90)
Race n (%)	
Caucasian	251 (91)
African-American	12 (4)
Asian	4 (1)
Other	8 (3)
Smoking status, n (%)	
Current smoker	13 (5)
Past smoker	100 (38)
Never smoked	157 (58)
Length of time with UC, n (%)	
< 1 year	1 (<1)
1-5 years	47 (17)
5-10 years	76 (28)
≥ 10 years	152 (55)
When last active UC symptoms were experienced, n(%)	
Currently or within last 3 months	98 (37)
3-6 months ago	27 (10)
6 months to one year ago	30 (11)
Greater than one year ago	113 (42)
5-ASA (oral and/or rectal)	
Current use	168 (60)
Past use	104 (37)
Corticosteroids (oral and/or rectal)	
Current use	32 (11)
Past use	173 (61)
Azathioprine/6-MP	
Current use	52 (18)
Past use	74 (26)
Cyclosporine and/or tacrolimus	
Current use	7 (2)
Past use	4 (1)
Methtrexate	
Current use	1 (<1)
Past use	8 (3)
Anti-TNF therapies (infliximab, adalimumab, certolizumab)	
Current use	40 (14)
Past use	46 (16)
Current immunosuppressant use (azathioprine, 6-MP, cyclosporine, tacrolimus methotrexate, anti-TNF)	91 (32)
Past immunosuppressant use (azathioprine, 6-MP, cyclosporine, tacrolimus methotrexate, anti-TNF)	61 (22)

*Missing data excluded for each category

SCCAI, 6-Point Mayo and Patient Assessment of Disease Activity

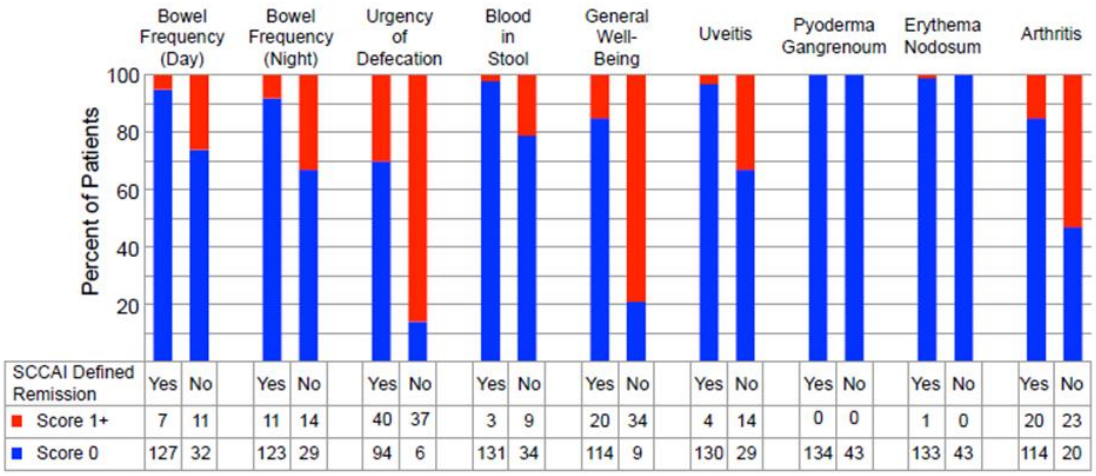
The results of the disease severity assessments for the full survey population are shown in Table 3.3. 63% of the surveyed population were in a remission defined by the 6-point Mayo or patient-driven activity question. Notably, however, only 53% were in a remission defined by the SCCAI. Among the 152 patients who had prior or current exposure to immunosuppressant therapy, there were slightly higher SCCAI mean and median scores; and overall, 4% fewer patients were in remission across each of the indices. Again, a fewer percentage of patients with prior or current exposure to immunosuppressant therapy were considered to be in a remission by the SCCAI (49%) compared to either the 6-point Mayo (59%) or patient-driven disease activity question (59%).

Table 3.3: Results of Disease Severity Indices in Initial Study Population

DISEASE SEVERITY INDICES Full Survey Population (n = 282)					
	Mean score	**Median score**	**Minimum score**	**Maximum score**	**Percent in Remission**
SCCAI	2.8	2	0	16	53% (score < 2.5)
6 Point Mayo	1.3	1	0	6	63% (score < 1.5)
Patient-Driven Question	2.2	2	1	6	63% (score 1 or 2)
DISEASE SEVERITY INDICES Exposure (current and past) to Immunosuppressant Therapy *(azathioprine, 6-MP, cyclosporine, tacrolimus, methotrexate, anti-TNFs)* (n = 152)					
SCCAI	3	3	0	16	49% (score < 2.5)
6 Point Mayo	1.4	1	0	6	59% (score < 1.5)
Patient-Driven Index	2.3	2	1	6	59% (score 1 or 2)

Additional analysis was therefore conducted to explore why remission rates were lower with the SCCAI than with the 6-Point Mayo (Figure 3.2A) or patient-driven disease activity (Figure 3.2B). In patients in a remission defined by the 6-Point Mayo score, three SCCAI questions appeared to be responsible for the discrepancy between the 6-Point Mayo and the SCCAI, with over 50% of those with active disease (as defined by

the SCCAI) answering in the affirmative to the questions: urgency, general-well being and presence/absence of arthritis (Figure 3.2A). Similar results were seen when using the patient-driven disease activity question to define remission (Figure 3.2B).



SCCAI Defined Remission	Bowel Frequency (Day)		Bowel Frequency (Night)		Urgency of Defecation		Blood in Stool		General Well-Being		Uveitis		Pyoderma Gangrenoum		Erythema Nodosum		Arthritis	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Score 1+	7	11	11	14	40	37	3	9	20	34	4	14	0	0	1	0	20	23
Score 0	127	32	123	29	94	6	131	34	114	9	130	29	134	43	133	43	114	20

Figure 3.2A: Evaluation of patients in a 6-Point Mayo remission. The lower table divides patients by their SCCAI remission status and shows breakdown of responses to individual components of the SCCAI.

SCCAI Defined Remission	Bowel Frequency (Day)		Bowel Frequency (Night)		Urgency of Defecation		Blood in Stool		General Well-Being		Uveitis		Pyoderma Gangrenoum		Erythema Nodosum		Arthritis	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Score 1+	10	12	13	16	40	34	5	15	16	26	4	11	0	0	1	0	21	22
Score 0	126	30	123	26	96	8	131	27	120	16	132	31	136	42	135	42	115	20

Figure 3.2B: Evaluation of patients in a remission as defined by a single Likert-scale of patient-defined disease activity. The lower table divides patients by their SCCAI remission status and shows breakdown of responses to individual components of the SCCAI.

Correlation of patient-driven disease assessment, SCCAI and 6-Point Mayo

In the overall population, the 6-Point Mayo score was strongly correlated with the SCCAI, with a spearman correlation coefficient (rho) of 0.71 ($p < 0.0001$). It was also

strongly correlated with the patient-driven disease activity question (rho = 0.65, p < 0.0001). A similarly significant correlation was seen with the SCCAI and the single patient-driven disease activity question with a spearman correlation coefficient of 0.66 (p < 0.0001). When examining those patients with current or prior immunosuppressant exposure, the correlations were similarly strong: 6-Point Mayo and SCCAI rho = 0.73 (p < 0.0001); 6-Point Mayo and patient-driven question rho = 0.67 (p < 0.0001); and SCCAI and patient-driven question rho = 0.66 (p < 0.0001).

Sensitivity, Specificity and ROC curves to Identify Patient-Defined Remission

Using a cut point of 1.5, the 6-Point Mayo remission score had a sensitivity of 83% and a specificity of 72% for patient-defined remission; and a sensitivity of 89% and specificity of 67% for SCCAI remission defined as a score of < 2.5. The SCCAI had a sensitivity of 76% and a specificity of 87% for patient-defined remission. In patients with current or past immunosuppressant therapy exposure, the 6-Point Mayo remission score had a sensitivity of 82% and specificity of 73% for patient defined remission; and a sensitivity of 91% and specificity of 71% for SCCAI remission. The SCCAI had a sensitivity of 73% and a specificity of 86% for patient-defined remission.

We defined remission using a single patient-driven disease activity question as perfect or very good under the assumption that patients would be unlikely to seek additional therapy if they considered themselves to have very good control of their disease. However, we repeated the assessment of the sensitivity and specificity of the 6-Point Mayo and SCCAI defining remission as only those who answered their disease activity as “perfect.” This resulted in a lower specificity for both scoring systems: 6-Point Mayo sensitivity 89% and specificity 50%; SCCAI sensitivity 83% and specificity 61%.

Figure 3.3A ROC Curves for Single Question Remission

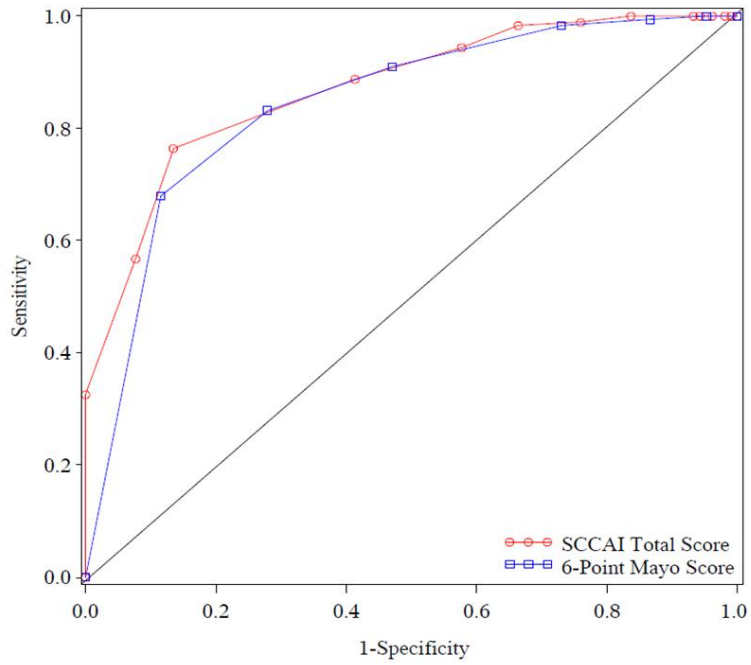
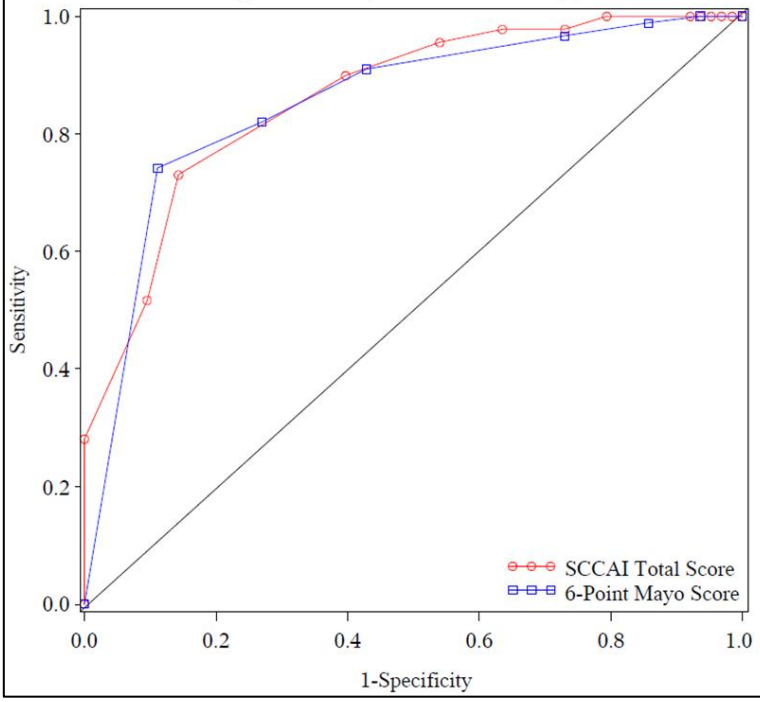


Figure 3.3B ROC Curves for Single Question Remission Among Patients Exposed to Immunosuppressants



The ROC curves in the total population for the SCCAI and the 6-Point Mayo predicting patient-defined remission are shown in Figure 3.3A and Figure 3.3B. The SCCAI area under the curve was 0.87 and the 6-Point Mayo area under the curve was 0.84 in the full population (Figure 3.3A). In patients exposed to immunosuppressant therapy, the ROC curves showed a similar nearly-equivalent area under the curve for SCCAI and the 6-Point Mayo with an area under the curve of 0.86 and 0.85, respectively (Figure 3.3B).

Additional analysis was conducted to evaluate if adding any of the SCCAI components (utilizing their original SCCAI scaling) to the 6-Point Mayo improved the accuracy of predicting patient-

defined disease remission (Table 3.4). Two of the SCCAI components, urgency and general well-being, significantly increased the AUC when added to the 6-Point Mayo score (p=0.04 and p=0.0008, respectively). When both components were added to the 6-Point Mayo score, the resulting ROC area under the curve was 0.90, which was significantly greater than the area under the curve for the 6-Point Mayo score alone (p=0.0002). Sequential addition of both urgency and general well-being was also performed: the addition of the SCCAI general well-being to the 6-Point Mayo already containing the SCCAI urgency question resulted in a significant improvement in ROC area under the curve (0.87 vs. 0.90, p=0.005); however, the addition of the SCCAI urgency to the 6-Point Mayo already containing the SCCAI general well-being did not reach statistical significance (0.89 vs. 0.90, p=0.16). Similar analysis was conducted looking at those patients exposed to immunosuppressant therapy; however, in this cohort, no SCCAI component reached a significantly improved AUC when added to the

6-Point Mayo score (Table 3.4).

Table 3.4: Comparison of ROC area under the curve generated by the addition of SCCAI components to the 6-Point Mayo predicting patient-defined remission.

	AUC	Chi-square p-value
Full Survey Population (n = 282)		
6-Point Mayo score (base model)	0.84	---
SCCAI component added:		
bowel frequency during the day	0.85	0.12
bowel frequency during the night	0.85	0.14
urgency of defecation	**0.87**	**0.04**
blood in the stool	0.84	0.77
general well-being	**0.89**	**0.0008**
uveitis	0.85	0.27
pyoderma gangrenosum*	---	---
erythema nodosum*	---	---
arthritis	0.85	0.30
sum of all extra-intestinal manifestations	0.85	0.19
Exposure to Immunosuppressant Therapy (n = 152)		
6-Point Mayo score (base model)	**0.85**	
SCCAI component added:		
bowel frequency during the day	0.87	0.15
bowel frequency during the night	0.86	0.63
urgency of defecation	0.88	0.15
blood in the stool	0.85	0.85
general well-being	0.88	0.10
uveitis	0.85	0.82
pyoderma gangrenosum*	--	--
erythema nodosum*	--	--
arthritis	0.85	0.97
sum of all extra-intestinal manifestations	0.85	0.84

*unable to calculate due to insufficient numbers of patients reporting these conditions

Validation Study

In the prospective I3 cohort from, 112 consecutive UC patients were consented. Of these, 61 patients had physician-identified pancolitis (47 patients) or left-sided colitis (14 patients) confirmed by the patient's electronic medical record and completed the disease severity indices without missing data. These 61 patients were included in the validation study. Baseline demographics of this population were not significantly different from the initial study population; however, a larger percentage of the validation population was currently on immunosuppressant therapy (Table 3.5).

Table 3.5: Summary of Patient Characteristics in Validation Study Cohort*

Characteristic	Patients (N = 61)
Gender, n (%)	
Female	33 (54)
Male	28 (46)
Age	
Median (IQR)	38 years (27-52)
Mean (SD)	40 years (14)
Site n (%)	
Hospital of the University of Pennsylvania	61 (100)
Race n (%)	
Caucasian	54 (89)
African-American	4 (6)
Asian	3 (5)
Other	0 (0)
Length of time with UC, n (%)	
< 1 year	0 (0)
1-5 years	9 (15)
5-10 years	18 (29)
≥ 10 years	34 (56)
5-ASA (oral and/or rectal)	
Current use	40 (66)
Past use	16 (26)
Corticosteroids (oral and/or rectal)	
Current use	7 (11)
Past use	36 (59)
Azathioprine/6-MP	
Current use	19 (31)
Past use	13 (21)
Cyclosporine and/or tacrolimus	
Current use	1 (2)
Past use	0 (0)
Methtrexate	
Current use	0 (0)
Past use	0 (0)
Anti-TNF therapies (infliximab, adalimumab, certolizumab)	
Current use	18 (30)
Past use	7 (11)
Current immunosuppressant use (azathioprine, 6-MP, cyclosporine, tacrolimus methotrexate, anti-TNF)	32 (52)
Past immunosuppressant use (azathioprine, 6-MP, cyclosporine, tacrolimus methotrexate, anti-TNF)	9 (15)

*Missing data excluded for each category

SCCAI, 6-Point Mayo and Patient Assessment of Disease Activity

The results of the disease severity assessments for the validation survey population are shown in Table 3.6. The percentage of patients in the total validation population in a remission was comparable by any of the three disease activity measurements; however, when comparing patients with pan-colitis versus left-sided colitis, a greater percentage of patients with left-sided colitis were in a remission.

Table 3.6: Results of Disease Severity Indices in Validation Study Population

DISEASE SEVERITY INDICES Full Validation Population (n = 61)					
	Mean score	**Median score**	**Minimum score**	**Maximum score**	**Percent in Remission**
SCCAI	2.4	1.0	0	12	69% (score < 2.5)
6 Point Mayo	1.2	1.0	0	6	72% (score < 1.5)
Patient-Driven Index	2.2	2.0	0	4	67% (score 1 or 2)
DISEASE SEVERITY INDICES Pan-colitis UC Population (n = 47)					
SCCAI	2.6	2.0	0	12	64% (score < 2.5)
6 Point Mayo	1.3	1.0	0	6	68% (score < 1.5)
Patient-Driven Index	2.2	2.0	0	4	64% (score 1 or 2)
DISEASE SEVERITY INDICES Left-sided UC Population (n = 14)					
SCCAI	1.6	0.5	0	11	86% (score < 2.5)
6 Point Mayo	0.9	0.5	0	5	86% (score < 1.5)
Patient-Driven Index	1.9	2.0	1	4	79% (score 1 or 2)

Correlation of patient-driven assessment, SCCAI and 6-Point Mayo

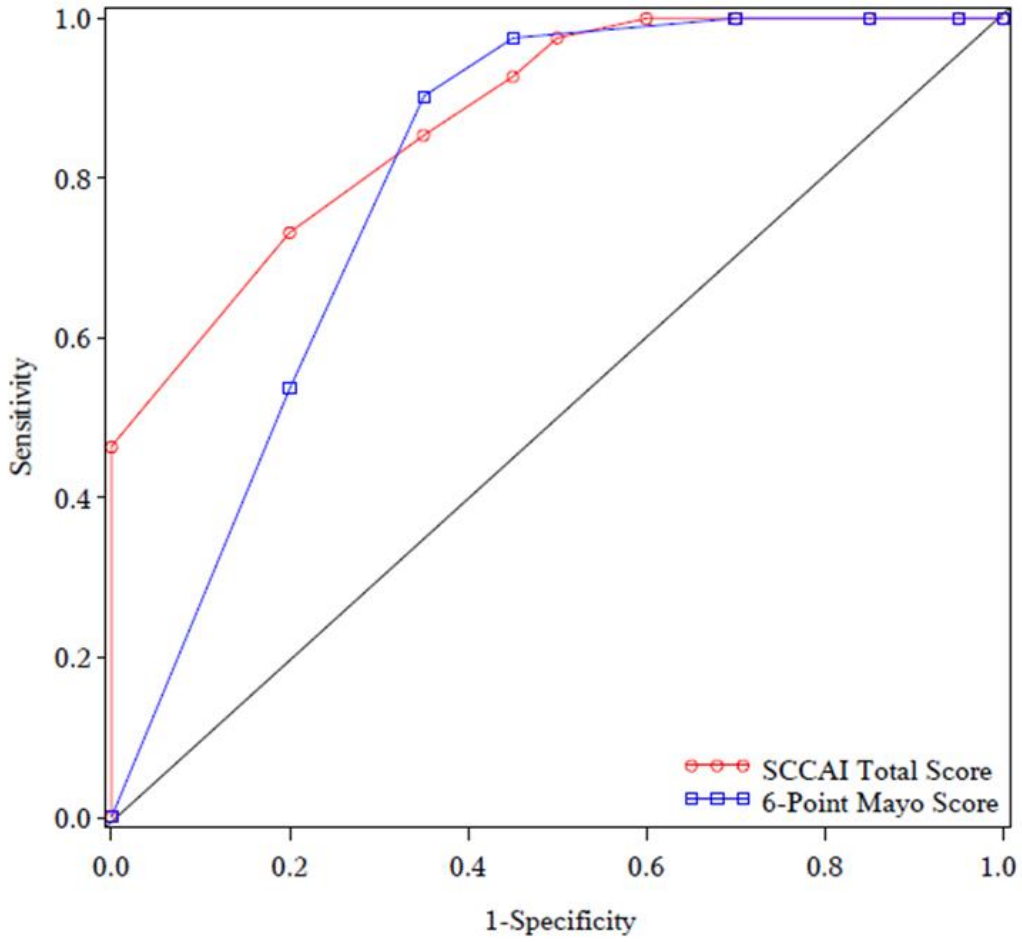
In the validation population, the 6-Point Mayo was again strongly correlated with the SCCAI (rho = 0.73, p <0.0001) and the patient-driven disease activity question (rho = 0.63, p < 0.0001). A significant correlation was also seen with the SCCAI and the single patient-driven disease activity question (rho = 0.73, p<0.0001). When examining pan-colitis and left-sided colitis subsets of the validation study, the correlations were similarly strong. In patients with pan-colitis, the correlations were rho = 0.75, p < 0.0001 (6-Point Mayo and SCCAI); rho = 0.61, p < 0.0001 (6-Point Mayo and single patient-driven disease activity question); and rho = 0.70, p < 0.0001 (SCCAI and single patient-driven disease activity question). In patients with left-sided colitis, the correlations were rho = 0.64, p < 0.0131 (6-Point Mayo and SCCAI); rho = 0.71, p < 0.0062 (6-Point Mayo and

single patient-driven disease activity question); and rho = 0.65, $p < 0.0168$ (SCCAI and single patient-driven disease activity question).

Sensitivity, Specificity and ROC curves to Identify Patient-Defined Remission

In the validation study, the 6-Point Mayo remission score (<1.5) had a sensitivity of 90% and a specificity of 65% for patient-defined remission; and a sensitivity of 95% and specificity of 79% for SCCAI remission defined as a score of < 2.5. The SCCAI had a sensitivity of 85% and a specificity of 65% for patient-defined remission. The ROC curves in the validation population for the SCCAI and the 6-Point Mayo predicting patient-defined remission are shown in Figure 3.4. The SCCAI area under the curve was 0.87 and the 6-Point Mayo area under the curve was 0.80.

Figure 3.4 ROC Curves for Single Question Remission Validation Study



Additional analysis was performed to assess if addition of individual components of the SCCAI to the 6-Point Mayo increased the accuracy of predicting patient-defined remission. Notably, only one patient responded affirmatively to any of the extra-intestinal manifestation components of the SCCAI; therefore, ROC comparisons adding these components could not be assessed. In the validation cohort, no component of the SCCAI contributed significantly to improving the accuracy of the 6-Point Mayo in predicting patient-defined remission. Based on the findings in the initial study cohort, additional analysis was run adding both the SCCAI urgency and general well-being

components to the 6-Point Mayo score (Table 3.7). The resulting ROC area under the curve was 0.89, which just reached statistical significance compared to the area under the curve with the 6-Point Mayo alone (p=0.05). Sequential addition of both urgency and well-being was also performed and not found to be significant (p=0.09 for addition of SCCAI general well-being to 6-Point Mayo already containing SCCAI urgency; and p=0.37 for addition of SCCAI urgency to 6-Point Mayo already containing SCCAI general well-being).

Table 3.7: Comparison of ROC area under the curve generated by the addition of SCCAI components to the 6-Point Mayo predicting patient-defined remission in the validation cohort.

	AUC	Chi-square p-value
Validation Survey Population (n = 61)		
6-Point Mayo score (base model)	0.80	---
SCCAI component added:		
bowel frequency during the day	0.81	0.48
bowel frequency during the night	0.80	0.63
urgency of defecation	0.82	0.47
blood in the stool	0.80	0.71
general well-being	0.88	0.08
uveitis	---	---
pyoderma gangrenosum*	---	---
erythema nodosum*	---	---
arthritis	---	---
sum of all extra-intestinal manifestations	---	---

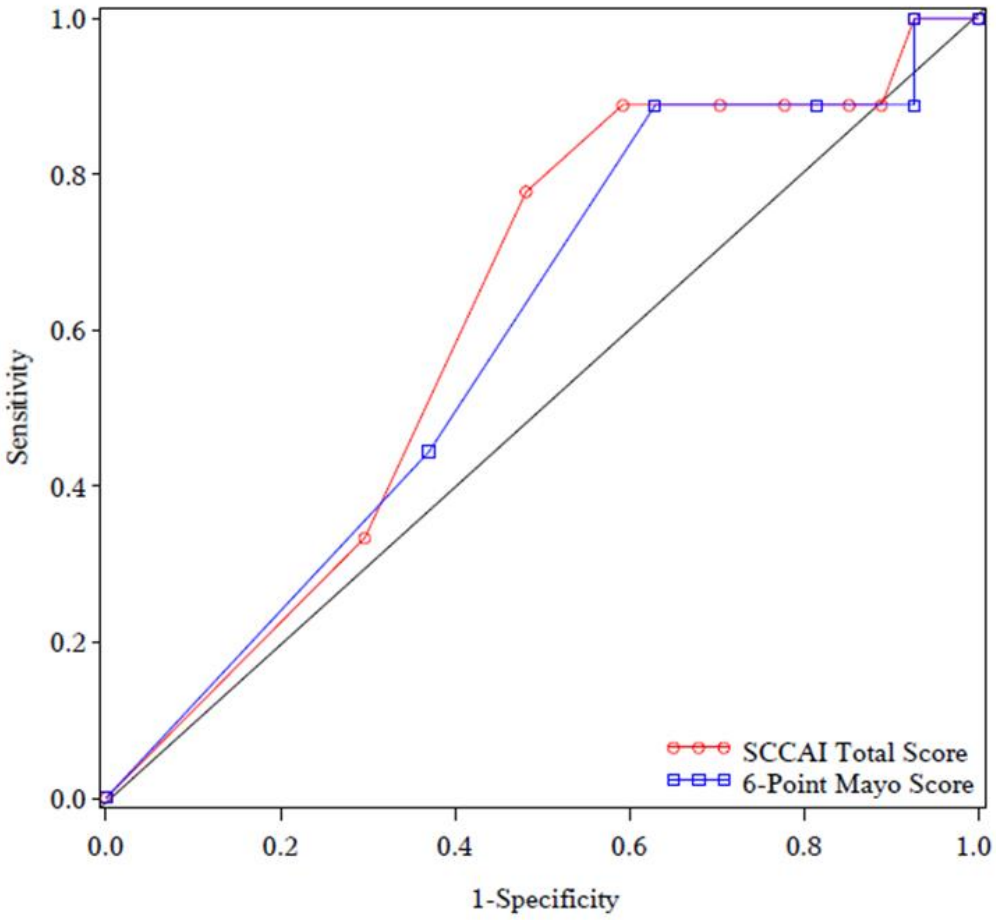
*unable to calculate due to insufficient numbers of patients reporting these conditions

Ulcerative Colitis Endoscopic Index of Severity

Of the 61 patients in the validation study, 36 had a colonoscopy performed. Three of the patients had an incomplete colonoscopy performed either due to a stricture or disease severity; these three patients were removed from the analysis. The remaining 33 patients had a complete colonoscopy that was retrospectively reviewed by an external gastroenterologist and scored according to the Ulcerative Colitis Endoscopic Index of Severity (UCEIS).[129,130] Correlations between the clinical disease activity indices and the UCEIS were overall poor: rho = 0.11, p = 0.54 (SCCAI and UCIS); rho = 0.18, p = 0.31 (6-Point Mayo and UCEIS); and rho = 0.33, p = 0.06 (single patient-driven

disease activity question and UCEIS). The SCCAI area under the curve was 0.62 and the 6-Point Mayo area under the curve was 0.59 (Figure 3.5).

Figure 3.5 ROC Curves for UC Endoscopic Index of Severity in the Validation Study



Discussion:

In this study, we have found and validated that the 6-Point Mayo score correlated strongly with the SCCAI and patient-reported disease activity, has a similar sensitivity and specificity as the SCCAI for patient-reported remission, and performs equally well in patients with more advanced disease (as defined by immunosuppressant drug exposure) as well as patients with varying UC disease extent (left-sided colitis versus pan-colitis). Prior studies have shown that the 6-Point Mayo score correlates well with

patient-driven disease activity as well as both the Partial- and Full-Mayo scores.[78,79] Our study is the first to correlate and validate the 6-Point Mayo with disease activity indices outside of the Mayo scoring system, and in patients on immunosuppression as well as patients with varying extent of UC. Furthermore, the 6-Point Mayo score avoided the use of cumbersome and potentially confusing questions regarding extra-intestinal manifestations of the IBD, and thus represents a simple, efficient and effective non-invasive disease severity measurement. We have also shown that addition of one or two questions from the SCCAI may improve prediction of the 6-Point Mayo score with patient-defined disease activity with minimal additional burden to patients or researchers.

In our initial study, patient-reported symptoms of urgency and general well-being, as collected by the SCCAI, led to discrepancies between a SCCAI-defined remission and a patient-defined remission. As these questions are not asked in the 6-Point Mayo, discrepancies between remission as defined in the scoring systems can be expected. It is possible that there may be points of confusion by the patients regarding each individual question and how it relates to their UC activity: urgency in the prior three days can be an important symptom of UC-disease; but it may also reflect irritable bowel syndrome. General well-being can be affected by many factors outside of UC disease activity. We also conducted additional analysis adding back these questions to the 6-Point Mayo and found that they do increase the accuracy of the 6-Point Mayo predicting patient-defined remission. Based on sequential assessment, the addition of general well-being appears to be sufficient, and may represent a very simple addition to the 6-Point Mayo.

The extra-intestinal manifestation questions in the SCCAI, specifically arthritis and uveitis, also led to discrepancies between SCCAI-defined remission and a patient-

defined remission in the initial study. Both arthritis and uveitis are difficult to describe to patients, and without direct physician assessment can be easily mistaken with non-IBD related symptoms such as osteoarthritis or allergic conjunctivitis. This illustrates a greater potential difficulty in eliciting the extra-intestinal IBD disease activity without direct physician contact. For example, in our initial study population, a high percentage of respondents stated they had uveitis (a relatively rare extra-intestinal complication of IBD) in the past 3 days. Despite these differences, the c-statistic for both scoring systems was very similar, indicating that overall, the remaining questions of stool frequency and bleeding accounted for much of the discriminative function in both indices. Furthermore, analysis adding back these extra-intestinal manifestations to the 6-Point Mayo did not result in improvements in the predictive ability of the scoring system, implying that these extra variables may be unnecessary in assessing active versus inactive disease.

Our validation study confirmed the correlation of the 6-Point Mayo score with the SCCAI and patient-defined disease remission. It is also the first study to validate the performance of the 6-Point Mayo score in both disease severity as well as UC disease extent, confirming the utility of the 6-Point Mayo across a broad range of clinical populations. Notably, in our validation population, while we did not find that the single addition of the SCCAI urgency or general well-being improved the accuracy of the 6-Point Mayo in predicting patient-defined remission, the addition of both components did improve the 6-Point Mayo score accuracy. It is possible that the validation study was simply underpowered to detect smaller differences at the individual component level, and certainly additional analysis exploring this should be performed.

Additionally, in our validation study, we did not find the high reported rates of extra-intestinal manifestations that we saw in our initial study. This may be the result of

differences in the study populations themselves: whereas the initial study was a mailed questionnaire, completed entirely by the patient outside of the clinical setting, the validation study was collected in the clinical setting and during enrollment within a larger prospective study. Unmeasured differences (recent exposure to a physician, willingness to enroll in a clinical study, etc) may have contributed to these variations, and stress the need for a simple, unambiguous patient-driven disease activity index.

There are potential limitations to our study. Both our initial and validation studies were carried out using patients at one of two tertiary care centers and thus may not be generalizable to other clinical settings. However, as such, they do represent a commonly-utilized UC population for clinical trials and therefore a population in whom a simple, patient-directed disease severity index would be most useful. Additionally, the majority had extensive experience with UC, thus lending to improved validity of our findings.

Most of the patients surveyed in both studies were in a clinically-defined disease remission. Despite this, we did have a broad range of UC disease severity, as evidenced by the high numbers of UC patients using immunosuppressant therapy as well as the variations in disease extent. It is possible that the indices examined in this study would perform differently among patients with more severe or active disease.

The indices examined in this study were for clinical remission, specifically patient-defined remission, only. We found that none of the clinical disease activity indices assessed (SCCAI, 6-Point Mayo or a single Likert-scale of patient-defined disease activity) correlated well with a purely endoscopic assessment of disease severity. Prior work has shown a good correlation with the SCCAI and an invasive index of disease severity, the Powell-Tuck (or St. Mark's) Index.[127] However, the Powell-Tuck Index, like many of the scoring indices in UC, is a composite of clinical, biochemical, and

sigmoidoscopic evaluations of the patient, which may lend a greater correlation with a clinical index (such as the SCCAI or 6-Point Mayo) compared to a purely endoscopic evaluation. Endoscopic and histologic disease activity measures have been correlated with important outcomes including colectomy, colorectal cancer and quality of life.[75,131-134] However, in many studies, invasive disease assessment may be infeasible or serve as a deterrent to patient enrollment. Even in studies which employ invasive disease methods, more frequent follow-up measurements may be more easily obtained via mail, email, or phone, without direct physician contact. Furthermore, patient-perceived assessment of disease activity is arguably paramount in assessing quality of life which, in turn, has effects on adherence to medical therapy. In these settings, the utility of a simple patient-driven disease assessment tool can be appealing to researchers and patients alike.

In conclusion, we have demonstrated that the 6-Point Mayo score, comprised of only two questions regarding stool frequency and the presence of blood, was highly correlated with the SCCAI and performed comparably to the SCCAI in identifying patient-perceived clinical remission. We have further shown that addition of either the SCCAI general well-being and/or urgency components increased the predictive value of the 6-Point Mayo with minimal additional survey burden. Finally, we have validated our findings in a separate UC population, and further evaluated and validated our findings in patients of varying disease extent. Therefore, the 6-Point Mayo score represents a simple and reproducible patient-driven disease severity index for use in observational studies or in clinical trials without direct physician assessment.

CHAPTER 4: Patient-Preferences for Surgical versus Medical Therapy in Ulcerative Colitis

Short Title: UC Patient Preferences: Medical vs Surgical Therapy

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Abbreviations: Inflammatory bowel disease (IBD); ulcerative colitis (UC); serious adverse events (SAE); maximum acceptable risk (MAR); discrete-choice experiments (DCE)

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Angie Fairchild: data interpretation; statistical analysis; critical revision of manuscript

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BACKGROUND: Therapy options for mesalamine-refractory ulcerative colitis (UC) include immunosuppressive medications or surgery. Chronic immunosuppressive therapy increases risks of infection and cancer, whereas surgery produces a permanent change in bowel function. We sought to quantify the willingness of patients with UC to accept the risks of chronic immunosuppression to avoid colectomy.

METHODS: We conducted a state-of-the-art discrete-choice experiment among 293 patients with UC who were offered a choice of medication or surgical treatments with different features. Random parameters logit was used to estimate patients' willingness to accept tradeoffs among treatment features in selecting surgery vs medical treatment.

RESULTS: A desire to avoid surgery and the surgery type (ostomy versus J-pouch) influenced patients' choices more than a specified range of 10 y mortality risks from lymphoma or infection, or disease activity (mild vs remission). To avoid an ostomy, patients were willing to accept a greater than 5% 10-year risk of dying from lymphoma or infection from medical therapy, regardless of medication efficacy. However, data on patients' stated-choice indicated perceived equivalence between J-pouch surgery and incompletely effective medical therapy. Patient characteristics and disease history influenced patients' preferences regarding surgery vs medical therapy.

CONCLUSIONS: Patients with UC are willing to accept relatively high risks of fatal complications from medical therapy to avoid a permanent ostomy and to achieve durable clinical remission. However, patients' view J-pouch surgery, but not permanent ileostomy, as an acceptable therapy for refractory UC in which medical therapy is unable to induce a durable remission.

Keywords: inflammatory bowel disease, IBD, DCE, maximum acceptable risk

INTRODUCTION:

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that can be severely debilitating, and has no medical cure. Historically, UC was treated with mesalamine and corticosteroids; and if these failed, surgical resection of the colon. Because UC is limited to the colon, surgery offers a theoretical "cure" and eliminates the risk of colon cancer. The two most common operations performed are a total proctocolectomy with end ileostomy and restorative ileal pouch anal anastomosis (IPAA). The former entails a permanent ileostomy while the latter avoids this but is associated with frequent bowel movements and the risk of fecal incontinence.

The demonstrated efficacy of thiopurine analogues and antibodies against tumor necrosis factor α has improved our ability to induce and maintain remission. However, at least one-third of patients will fail to produce a durable remission.[41,135,136] These patients will often be exposed to repeated or chronic corticosteroid therapy which is associated with increased morbidity and mortality.[20,21,23] Furthermore, chronic immunosuppressant maintenance therapy risks serious and opportunitistic infections,[21,26,137] and an increased the risk of certain cancers including lymphoma[30,31] and hepatosplenic T-cell lymphoma.[138,139]

If surgery for UC resulted in a completely normal quality of life, the choice between medical and surgical therapy would be obvious. Because this is not the case, physicians and their patients are willing to accept risks of medical therapies, often with the presumption that the patient's foremost desire is to avoid surgery. However, for some patients this may not be the case; and in an era that places an increasing premium on patient autonomy and shared decision making, quantifying UC patients risk

preferences includes their voice in an increasingly complex decision process. Furthermore, quantifying patients' risk threshold can help physicians, drug manufacturers and regulators when contemplating appropriate indications for existing and new medical therapies. Prior studies evaluating UC patients' preferences have been few and employed methodologies that make numerous uncertain or inaccurate assumptions about patient preferences.[50,61] In this study, we used an innovative patient-preference methodology called discrete-choice experiment (DCE) to quantify the UC patients' tolerance for life-threatening serious adverse events (SAEs) in exchange for specific treatment benefits. We estimated the mean maximum acceptable risk (MAR) for SAEs associated with immunosuppressant therapy in UC that patients are willing to accept to avoid colectomy with ostomy, IPAA or IPAA complicated by fecal incontinence. We also evaluated how clinical characteristics affect tolerance for medical therapy risks in preference to surgery.

MATERIALS AND METHODS:

DCEs, also known as choice-format conjoint analysis, quantify strength of preferences for features of products, services, or health-care interventions and are increasingly being applied in the health sciences.[67,140,141] Interventions, such as medical or surgical treatments, derive value from their specific attributes, features or outcomes including treatment efficacies and potential SAE risks. Each of these attributes can occur at varying levels, such as remission rates or SAE incidence. DCEs recognize that patients have preferences of varying strengths for different attributes and are willing to accept tradeoffs among various levels. By systematically eliciting tradeoffs among constructed outcome combinations, DCEs generate choice data to quantify implicit decision weights indicating relative utility or satisfaction that patients have for both

individual attributes of a treatment (such as the specific risks and benefits) as well as the treatment as a whole. Because DCEs measure the rate at which patients accept tradeoffs among different treatment attributes, it is possible to use these trade-off rates to scale a change in one attribute to equivalent units of another attribute. It is thus possible to calculate time equivalents, money equivalents, and risk equivalents of a given change in treatment options. In this study, we used estimated trade-off rates to calculate the MAR as an indication of patients' willingness to accept medication-related SAE risks to avoid surgery.

Survey Development

A DCE survey instrument was developed using best-practice methods[142] to elicit patients' willingness to accept tradeoffs among therapeutic options regarding medical and surgical interventions for UC. The survey instrument assessed respondents' baseline demographics, current disease activity (using the Simple Clinical Colitis Activity Index (SCCAI) and 6-point Mayo score),[79,126] medication use history and knowledge of colectomy surgery. Numeracy was assessed using test questions.

For the DCE scenarios, attributes were determined from a literature review, IBD expert consultation, focused interviews with IBD patients and a pilot study in 127 UC patients. On the basis of this information, a decision frame was developed in which respondents assume a moderate-to-severe UC flare and must select either a new medication or surgery as treatment for the flare (Table 4.1). Medication treatment attributes included efficacy with levels of remission and incomplete response resulting in

mild disease activity for 10 years, described using text from the Mayo score.[128]

Table 4.1: Treatment Attributes and Levels

Treatment Attribute	**Levels**
Disease activity *All patients were asked to assume a constant reference condition of a moderate-severe disease flare defined as:* *3-4 stools more than normal per day* *Obvious blood with stool most of the time* *Abdominal pain (with or without bowel movements* *Generally feeling unwell most of the time* *Difficulty going to work or carrying out normal activities most of the time*	Remission Surgical (permanent; see Surgery attribute) Medical (for 10 years) *Normal number of stools per day* *No blood seen* *No abdominal pain* *Generally feeling well* *No interference with work or normal daily activities* Mild disease activity (medication only; for 10 years) *1-2 stools more than normal per day* *Streaks of blood with stool less than half the time* *Having abdominal pain (with or without bowel movements) a few times each day* *Generally feel unwell 25% of the time* *Having difficulty going to work or carrying out normal activities 3 days per month*
Surgical outcomes (surgery option only)	IPAA IPAA with incontinence during day or night Permanent ostomy bag
Increased chance of dying from colorectal cancer within 10 years	Medication 0.3% Surgery: 0%
Increased chance of dying from lymphoma within 10 years	Medication 0%, 0.5%, 2%, 5% Surgery 0%
Increased chance of dying from serious infection within 10 years	Medication 0%, 0.5%, 2%, 5% Surgery 0%, 0.5%, 2%, 5%

Surgery was described as a one- or two-step process with a resultant permanent surgical remission. A permanent ostomy (single stage operation) was described as having a surgical remission with no blood, abdominal pain, fatigue or interference with job/daily activities and having bowel movements through the ostomy. Pictures of female and male patients with ostomy bags were shown. Two-stage (IPAA) surgery was described as resulting in an average 5 bowel movements per day but otherwise having similar disease-activity symptoms as those having an ostomy. Incontinence also was described. All surgery was described as carrying a one-in-three chance of having

difficulty becoming pregnant for female patients. Pilot testing indicated good understanding of the medical and surgical outcomes.

For non-surgical options, a 0.3% risk of dying from colon cancer within 10 years was included.[143] Two SAEs were additionally considered. The risk of dying from lymphoma was only associated with selection of medication therapy; the risk of dying from a serious infection was associated with both medication therapy and surgery. Colorectal cancer, lymphoma and serious infections were described using layman terms based in part on descriptions from the American Cancer Society patient information[144]. For each of the SAEs, hypothetical risk levels ranged from 0% to 5% for experiencing the event within the next 10 years. Pretest interviews and pilot data indicated that this range yielded trade-off information required to quantify MAR. The 10-year time frame was determined to be appropriate during piloting and data collection/analysis from conceptual, methodological and patient-cognitive perspectives. Pretests of the instrument found that 10 years allowed for magnification of annual risks to levels that could be described graphically and were sufficiently salient to induce tradeoffs among other attributes.

To limit cognitive burden and numeracy concerns, all treatment benefits were described as certain and all treatment risks were described as known probabilities. To avoid measurement error in preference elicitation and analysis, specific risk levels (rather than ranges) were presented in keeping with best practice methods.[142] To further aid respondents understanding of quantitative risks, the SAE probabilities were presented in three ways: graphically as a risk grid of shaded circles indicating the number of patients out of a full grid of 1000 circles who would die from the SAE; and numerically as fractions (counts out of 1000) and percentages (Figure 4.1).

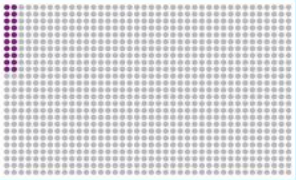
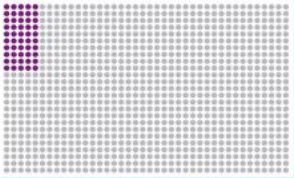
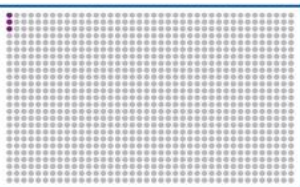
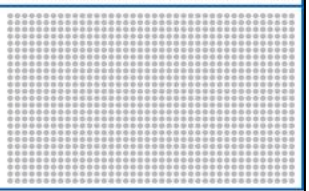
Treatment Results	Medicine	Surgery
Symptoms	No symptoms for 10 years	Permanent remission
Ostomy	None	No bag (ostomy) after second operation
Increased chance of dying from lymphoma within 10 years	20/1,000 (2%) 	No increased chance
Increased chance of dying from serious infection within 10 years	No increased chance	50/1,000 (5%) 
Increased chance of dying from colon cancer within 10 years	3/1,000 (0.3%) 	0/1,000 (0%) 
Which treatment would you choose if these were your only choices?	**Medicine** (No symptoms for 10 years)	**Surgery** (Permanent remission)

Figure 4.1: Example of conjoint scenario comparing medication and surgical therapy for UC flare

The DCE questions in the final survey instrument asked patients to choose between a medication resulting in either complete remission or incomplete remission (i.e. mild disease activity) for 10 years or surgical therapy for their UC disease flare. Figure 1 is an example of the DCE question format. We used a variation of a commonly used algorithm in SAS to construct a D-efficent experimental design resulting in 48 pairs of treatment options.[145-149] To reduce respondent burden, the trade-off scenarios were blocked into 6 sets of 8 questions. Each participant was randomly assigned to receive 1 of the 6 sets of questions. Surveys were mailed using the Dillman method to maximize response rates.[150]

Survey Validation

The design of the DCE survey included tests for numeracy and an internal test for subject-level validity through logic testing. To assess numeracy, subjects were shown a series of numerical examples of risk, presented as percentages, fractions and an illustrative risk grid, and subsequently tested on their understanding of these numeric concepts. Logic testing was assessed to evaluate if respondents understood the question-choice format sufficiently to indicate a preference for a visibly better therapy through an additional trade-off scenario in which medication treatment dominated the surgical treatment for every attribute. The model was tested to evaluate the statistical influence of respondents who failed one or both of these tests.

Survey Sample

Patients were eligible if they were ≥ 18 years of age with an ICD-9 code for UC (556.0-556.6 and 556.8-556.9) and an outpatient gastroenterology clinic visit at participating institutions within the prior two years. Patients with any ICD-9 code for Crohn's disease (555.0-555.2, 555.9) were ineligible. In the survey, patients were asked if they considered themselves to have UC; only respondents who further self-identified as having UC were included in the survey sample. All patients received a small financial compensation for their time and effort.

Statistical Analysis

In DCE studies, the pattern of choices by respondents observed reveals the implicit decision or preference weights respondents used to evaluate the hypothetical treatment tradeoffs. Multivariate random-parameters logit was used to estimate preference weights for each attribute level while avoiding potential estimation bias in choice models from unobserved variation in preferences not accounted for by the variables in the model.[151,152] Both a mean value and taste-distribution standard-deviation

parameter are estimated for each preference weight. A flexible correlation structure also accounts for within-sample correlation in the question sequence for each participant.

Effects coding was used so that the mean effect of each attribute is normalized at zero instead of setting all the omitted categories to zero. The omitted-category parameter is the negative sum of the included-category parameters for each attribute. This provides a parameter estimates for every attribute-level preference weight, avoids confounding the grand mean with marginal effects, and facilitates subsequent calculations. T-statistics thus are interpreted relative to the mean effect rather than the omitted category.

The resulting mean preference weights are used to estimate the MAR, the maximum acceptable risk, defined as the specific increase in treatment risk that exactly offsets the therapeutic benefit of a given improvement in treatment outcomes. For example, consider a medication A that has a measured therapeutic benefit $\beta_1 = 0.5$ (versus surgery); and a value of $\beta_i = -0.025$ for each 1% increase in infection risk. The MAR for medication A is the increased risk of infection that exactly offsets the increase in satisfaction from preserving one's colon. Since offering medication A increases patients' satisfaction by 0.5 versus surgery, if medication A increases the risk of infection by 0.5/0.025 = 20%, then the increased infection risk exactly offsets patients' perceived satisfaction from avoiding surgery. However, if medication A increases the risk of infection by <20%, then patients would be better off with medication A than with surgery. In practice, risk levels are fit to a generalized nonlinear function to utilize all information regarding the shape of the response gradient when determining the level of risk that makes the mean preference weight = 0 between categorical risk-level parameters.

In our model, certain attributes were applicable only to the medication or surgical therapy option. Furthermore, the surgical therapy option was inherently different from the medication therapy option. Interaction terms and constraints in the model account for and measure the effect of surgery versus medical therapy in choice preferences for attributes. The goal of the survey instrument was to calculate respondents' willingness to trade off risk of SAE for improvements in UC symptoms through either medical or surgical therapy by calculating the MAR which respondents were willing to accept from a given medical therapy of specified efficiency to avoid a specific surgical outcome. Comparisons were made of the MARs for the lymphoma and serious infection SAEs in exchange for treatment efficacy to avoid surgical outcomes of an ostomy, a J-pouch with incontinence and a perfectly functioning J-pouch. When computation of MAR required extrapolation beyond the upper level of risk presented in the survey, we report risk tolerance as greater than the level of risk shown.

Overall joint tests of parameter differences employed the scale-controlled likelihood-ratio test for choice models.[153] Tests of differences of MARs used 2-tailed z-tests for differences of means for independent, normally distributed random variables. Statistical differences between individual parameter estimates were tested using maximum-likelihood asymptotic 2-tailed tests at the 95% confidence level. Subgroup analysis was performed utilizing an effects-coded model that included an interaction term with the most preferred parameter to maximize the statistical power of the subgroup models. SAS 9.2 was used for data management and tables. Limdep/NLOGIT 7.0 was used for statistical modeling.

ETHICAL CONSIDERATIONS:

The study and final survey instrument were approved by the Institution Review Boards at participating institutions.

RESULTS:

Survey Population

Survey instruments were mailed to 662 patients and responses were received from 374 patients (56% response rate). We had limited information on non-responders, but men were less likely to respond (data not shown). Eight respondents (3%) answered the numeracy questions correctly but failed a test scenario in which there was a clearly-dominated treatment choice. Given the small number and their appropriate response to the numeracy questions, these patients remained in the analyzed final sample. After applying the exclusion criteria and excluding patients with missing answers to conjoint questions, 293 respondents were included in the final analysis (Fi

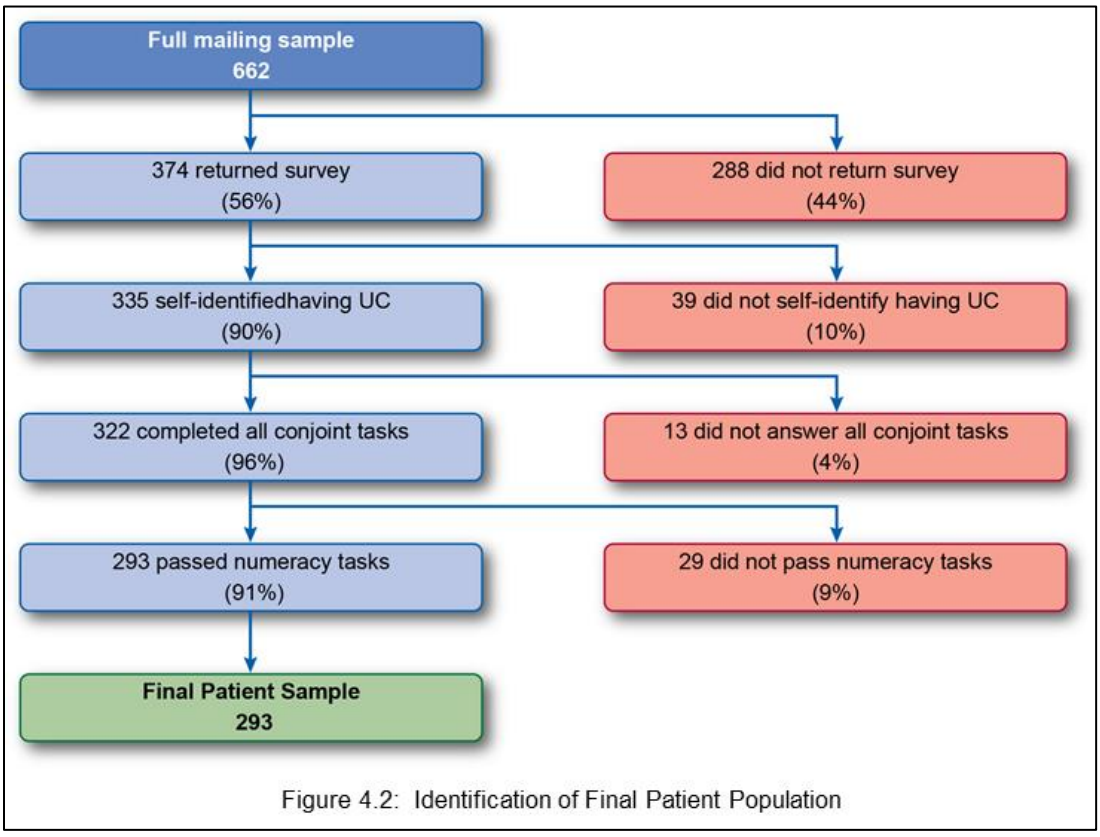


Figure 4.2: Identification of Final Patient Population

gure 4.2). Baseline demographics are shown in Table 4.2. Notably, the majority of respondents was highly educated and had a long-standing history of UC. Over half were in a remission as defined using the SSCAI or 6-point Mayo score. The majority of respondents had previously or was currently taking an immunosuppressant medication, inclusive of thiopurine analog, calciurin inhibitor, methotrexate and/or anti-TNFα (Table 4.2).

Table 4.2: Summary of Patient Characteristics*

Characteristic	Patients (N = 293)
Gender, n (%)	
Female	166 (57)
Male	127 (43)
Age	
Median	45 years
Mean	47 years
Site n(%)	
Dartmouth-Hitchcock Medical Center	20 (7)
Hospital of the University of Pennsylvania	273 (93)
Ethnicity/Race n(%)	
Caucasian	256 (87)
African-American	17 (6)
Asian	9 (3)
Latino	2 (1)
Other	4 (1)
Highest level of completed education, n (%)	
Less than high school	1 (<1)
High school or equivalent	32 (11)
Less than four years of college	59 (21)
4-year college degree (e.g., BA, BS)	91 (32)
Post-graduate studies	99 (35)
Marital status, n(%)	
Single/Divorced/Widowed	94 (33)
Married	189 (67)
Desire for children, n(%)	
Would like to have children in future	80 (28)
No desire/plans to have children in future	202 (72)
Smoking status, n (%)	
Current smoker	15 (5)
Past smoker	105 (38)
Never smoked	160 (57)
Length of time with UC	
1+ years, n (%)	293 (100)
Mean, years	13
Median, years	10
Currently having active UC symptoms, n(%)	75 (27)
When last active UC symptoms were experienced, n(%)	

Currently or within last 3 months	70 (25)
3-6 months ago	38 (14)
6 months to one year ago	41 (15)
Greater than one year ago	131 (47)
Simple Clinical Colitis Activity Index < 2.5	56%
6-point Mayo score < 1.5	64%
5-ASA (oral and/or rectal)	
Current use	57%
Past use	83%
Corticosteroids (oral and/or rectal)	
Current use	10%
Past use	70%
Azathioprine/6-MP	
Current use	16%
Past use	29%
Cyclosporine and/or tacrolimus	
Current use	2%
Past use	2%
Methtrexate	
Current use	<1%
Past use	3%
Anti-TNF therapies (infliximab, adalimumab, certolizumab)	
Current use	15%
Past use	22%
Current or past immunosuppressant use (azathioprine, 6-MP, cyclosporine, tacrolimus methotrexate, anti-TNF)	54%
Personal history of serious infection requiring hospitalization	19%
Knew family member and/or friend with serious infection requiring hospitalization	23%
Personal history of colorectal cancer	1%
Knew family member or friend with colorectal cancer	36%
Personal history of lymphoma	2%
Knew family member or friend with lymphoma	19%
Personally had history of bowel surgery with ostomy	13%
Knew family member or friend with ostomy bag	17%
Never discussed surgical options with medical or surgical physician	51%
Believe colonoscopies will prevent colorectal cancer	74%

*Missing data excluded for each category

Preference Weights

Analysis of respondents' preference weights for the varying levels of mortality from lymphoma or serious infection over 10 years indicated a relatively steep decrease in DCE utility for all attributes when going from 0% to 0.5% risk compared to equivalent increments in levels of risk beyond 0.5% (Figure 4.3A). This result is inconsistent with

the conventional preference-elicitation methods which assume linear preferences across probabilities; and indicate that participants perceived a much larger decrease in utility from going from “no risk” to “some risk” (such as 0.5%) than they did from moving from “some risk” to “some additional risk” (such as 2% or 5%). Other researchers have identified similar risk-preference nonlinearities in non-health and health applications.[61,62]

Figure 4.3B shows the relative preference-weight estimates for the risk attributes and medication efficacy. The estimated preference weights for risks and efficacies are consistent with the natural ordering of the levels. The largest effect on DCE utility was for the difference between a J-pouch and ostomy when the participant selected the surgery option: no other change in risk levels was comparable to the perceived benefit of avoiding an ostomy when surgery was chosen as the preferred therapy for a UC flare. This difference in surgery type—J-pouch versus ostomy—influenced patients’ choices more than the risk of dying from lymphoma or serious infection, or medication efficacy over the ensuing 10 years when the medical therapy was chosen. At the other extreme was medication efficacy: the difference between a medication-induced remission and an incompletely effective medication that only improves disease activity to a mild state was roughly equivalent only to the difference between a 0% risk of lymphoma and a 0.5% risk. Thus, on average, patients were willing to accept a 0.5% increase in risk of dying from lymphoma over 10 years if the medication put them in a complete remission. However, if the risk of lymphoma mortality over 10 years were higher, patients preferred a less effective medication with 0% risk of lymphoma.

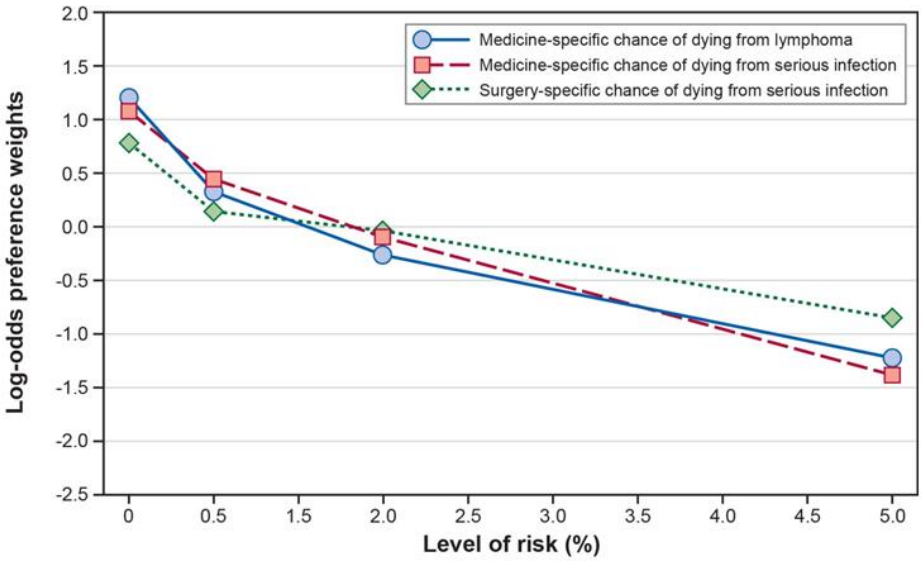


Figure 4.3A: Preference weights for varying levels of mortality from lymphoma or serious infection over 10 years

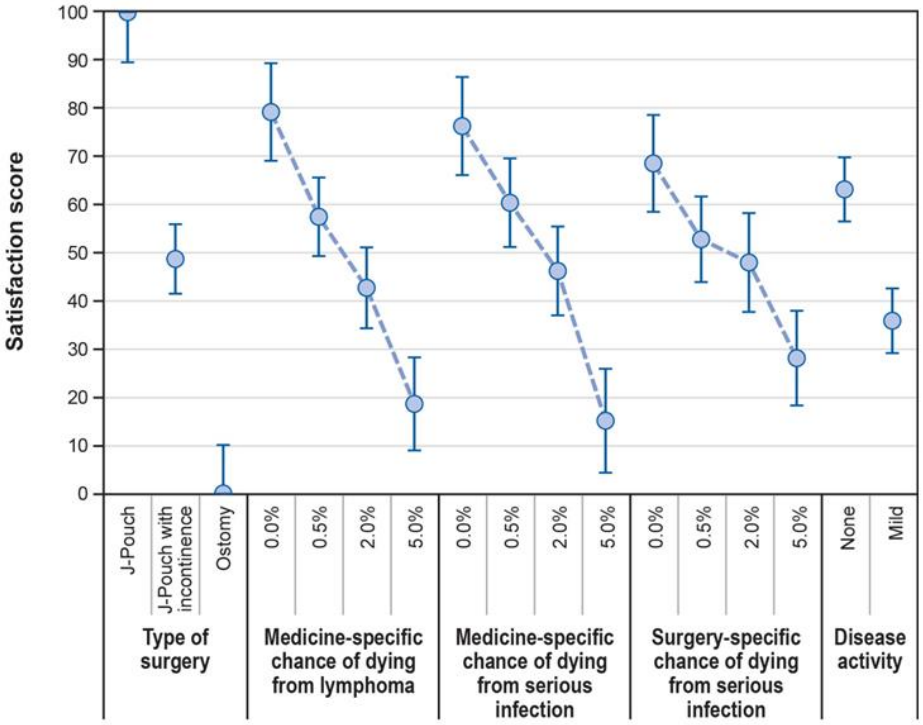


Figure 4.3B: Relative preference utility for risk attributes and medication efficacy. The vertical axis shows relative utility/satisfaction (scores scaled between 0 and 100, with 0 corresponding to the smallest satisfaction score across treatment attributes and 100 corresponding to the largest satisfaction score) and the horizontal axis the varying levels of the attributes. Illustrated satisfaction scores at each level of risk take into account the significantly increased preference utility associated with selecting medical therapy in preference of any type of surgery (for example, satisfaction scores for J-pouch without incontinence are conditional on selecting surgery).

The mean MAR estimates of tolerance for SAE mortality risks respondents were willing to accept for better surgical or medication outcomes are shown in Table 4.3. To avoid having an ostomy, patients were willing to accept more than 5% risk of dying from lymphoma over 10 years even if the medication was incompletely effective. In contrast, patients were willing to accept only a 1-1.6% risk of death from lymphoma or serious infection for improved medication efficacy. Patients were less tolerant of medication risk if the surgical outcome was a J-pouch; and remarkably, patients were equally satisfied with J-pouch surgery as with an incompletely effective medical therapy that left them with mild disease symptoms over 10 years (Table 4.3).

Table 4.3. Maximum Acceptable 10-Year Serious Adverse Event Risk (MAR) for Selected Treatment Benefits to Avoid Surgery

Initial Health State	Final Health State	Lymphoma† Mean MAR (lower bound, upper bound)	Serious Infection† Mean MAR (lower bound, upper bound)	To avoid**:
Moderate	Medicine with Remission	1.04% (0%, 4%)††	1.61% (0%, 4%)††	J-pouch
Moderate	Medicine with Mild Symptoms	0.00% (0%, 1%) ††	0.00% (0%, 1%) ††	J-pouch
Moderate	Medicine with Remission	>5%* (4%, >5%)	>5%* (4%, >5%)	J-pouch with incontinence
Moderate	Medicine with Mild Symptoms	3.73% (1%, >5%)	3.93% (2%, >5%)	J-pouch with incontinence
Moderate	Medicine with Remission	>5%* (>5%, >5%)	>5%* (>5%, >5%)	Ostomy
Moderate	Medicine with Mild Symptoms	>5%* (>5%, >5%)	>5%* (>5%, >5%)	Ostomy

* All MARs >5% indicate extrapolations outside the range of risks evaluated in the trade-off questions
† 10-year risk of death from lymphoma/infection
** Surgical options assume a mean 10-year surgery-associated infection mortality risk of 1.87%
†† Lower bounds could not be less than 0%, indicating non-significant findings

Effect of Covariates on Benefit-Risk Tradeoff Preferences

Subgroup analysis was performed utilizing an effects-coded model and implementing an interaction on the most preferred parameter (Figure 4.4). Disease duration, time from last flare (< 3 months) and disease activity overall had no impact on preferences for surgical versus medical therapy. There was a small subgroup of patients currently on immunosuppressant therapy who reported current active disease symptoms

(n=23), thus representing a compelling sample of patients facing possible surgery. Compared to those not on immunosuppressant therapy, these patients were less willing to accept ostomy surgery (p=0.04), but also less willing to accept the risk of lymphoma with medical therapy (p=0.03). These findings are consistent with our overall findings of equivalent satisfaction with J-pouch surgery (but not ostomy) in the face of ineffective medical therapy and seem to indicate an influence of disease history on risk tolerance.

Desire to have children did not influence the preference for surgical versus medical therapy; but females were significantly less willing to accept ostomy surgery (p=0.03). Prior knowledge of the attributes did influence preferences: patients with either personal or first-hand knowledge of colectomy surgery were more willing to accept surgery overall (p=0.002) and less willing to accept ineffective medical therapies (p=0.007). Those first-hand knowledge of serious infection, colon cancer or lymphoma were also more willing to accept surgery overall (p=0.006), although they were also less willing to accept ostomy as an outcome (p=0.02). Additionally, those patients who had discussed surgery with a surgeon or physician were significantly more willing to accept surgery overall (p=0.03).

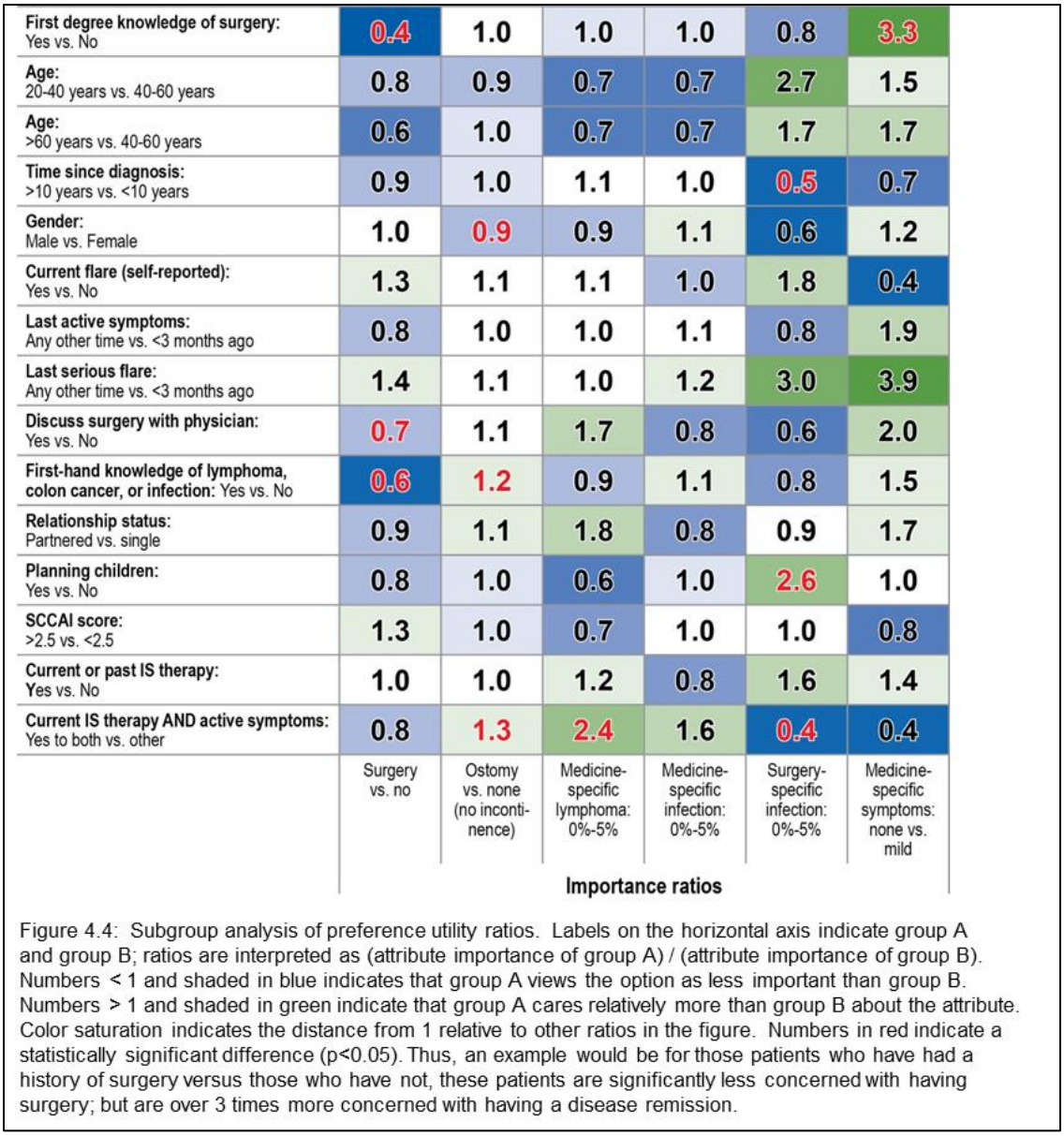


Figure 4.4: Subgroup analysis of preference utility ratios. Labels on the horizontal axis indicate group A and group B; ratios are interpreted as (attribute importance of group A) / (attribute importance of group B). Numbers < 1 and shaded in blue indicates that group A views the option as less important than group B. Numbers > 1 and shaded in green indicate that group A cares relatively more than group B about the attribute. Color saturation indicates the distance from 1 relative to other ratios in the figure. Numbers in red indicate a statistically significant difference ($p<0.05$). Thus, an example would be for those patients who have had a history of surgery versus those who have not, these patients are significantly less concerned with having surgery; but are over 3 times more concerned with having a disease remission.

Impact of numeracy skills on results

Twenty-nine patients (9%) failed one or more of the numeracy tests. These patients were excluded from the overall sample of 293 and assessed separately. This group was significantly older than the baseline sample (median age 70 years), and 21% were African-American or described their race/ethnicity as "other." 54% had a high-school/GED education or less; only 22% had a 4-year college or higher education. More were prior smokers (58%) and fewer (39%) had never smoked. Finally, a large

percentage (83%) stated they had never discussed surgical options for their UC with a surgeon or physician; and this low-numeracy group expressed a stronger preference to avoid surgery compared to the remainder of the population (p=0.02, data not shown).

DISCUSSION:

To our knowledge, this is the first study utilizing DCE to quantify patients' trade-off preferences for life-threatening adverse medication risks, surgical options and symptom relief in UC. Using DCE, we found that patients were willing to accept high levels of serious adverse risk from medical therapy to avoid an ostomy. However, patients also valued medication efficacy; indeed, if a durable clinical remission could not be achieved with medical therapy, patients were equally satisfied with J-pouch surgery. To our knowledge, this is the first empirical demonstration that UC patients without prior surgery view a well-functioning J-pouch as equivalent to persistent mild disease activity.

Our results have several important implications. First, patients expressed a willingness to accept tradeoffs among treatments of varying efficacies, risks of associated SAEs and surgical options in their responses to the DCE scenarios. As expected, patients' choices indicated a systematic preference for lower risk of SAEs and improved medication efficacy. However, the preference to avoid surgery or SAEs outweighed concerns regarding medication efficacy. During piloting, one-on-one interviews elicited a repeated sentiment that a disease flare associated with corticosteroid use was "acceptable" because it was a previously experienced risk, whereas the risks of a lymphoma, serious infection or surgery were much less familiar. The sentiment that rarer or poorly-understood risks are worse than more familiar risks is a well-studied phenomenon and the consistency of our results with this literature supports the face validity of our findings.[154]

Second, patients expressed a willingness to accept extremely high risks of SAEs to avoid a permanent ostomy or complications of a J-pouch. However, not all surgical options were so strongly disregarded in preference for medical therapy: UC patients were equally satisfied with an uncomplicated J-pouch surgery as they were with medical therapy, especially if that medical therapy was incompletely effective in maintaining a sustained remission (normal number of daily stools without blood or abdominal pain; and a good functional status without interference with work/daily activities) for 10 years. To the best of our knowledge, this is the first documentation of such a finding in UC.

Our study's finding that UC patients are willing to accept surgery as a treatment option for their disease is novel and has several important implications. First, it highlights that patient preferences can vary significantly from providers' assumptions regarding these preferences. Current treatment algorithms have rested on the assumption of UC patients' aversion to all surgical options; and indeed, prior conventional risk-assessment in UC supported this finding.[50-54] Our findings underline the need for rigorous methodologies to accurately measure patient-preferences, and present several potential areas for further inquiry regarding UC patient preferences' for their disease. As noted below, these findings and our methodological approach also have implications for diseases beyond UC, where physicians often make assumptions about patient preferences for risks and therapies in the absence of guiding data.

Second, our study illustrates a critical unmet need in treatment discussions with UC patients. Shared decision-making and informed consent have increasing importance in the changing treatment algorithms for IBD.[155] The majority of GI providers will escalate medical therapy for their UC patients due to failure of mesalamine to ensure a durable remission.[8,14] However, our survey indicated that approximately 50% of patients with UC had never discussed surgical options for their UC with either a medical or

surgical physician, including 39% of patients with current or past immunosuppressant therapy use (data not shown). Despite this, nearly 75% of our population indicated they felt they understood their surgical options very well or had minimal questions regarding surgery for UC (data not shown), indicating attainment of information from sources outside of their IBD care providers. Therefore, our findings that UC patients overall were willing to accept J-pouch surgery when faced with incompletely effective medical therapy clearly indicates a potential unmet need in treatment discussions with UC patients by all providers. Given the low surgery-discussion rate in our sample, our findings could also under-estimate UC preferences regarding surgical therapy, which may further bolster the importance of both discussions with patients and the acceptability of surgical options.

Finally, this finding has important implications for testing efficacy of novel therapies. These data suggest that for a medication to be preferred over J-pouch surgery, it needs to achieve sustained remission, not just a clinical response. As such, remission may be the preferred outcome for testing efficacy of new therapies.

We also found that clinical history did influence preferences for therapies, including current and prior disease course, gender, knowledge of the attributes and discussion of surgery with a care provider. It is important to note, however that the study design was not powered for precise sub-group analysis (as indicated by some large but non-significant ratios in the subgroup analysis Figure 4.4). Given variable distribution of potential clinical characteristics, it is possible that other meaningful differences could not be discerned.

DCE has significant advantages over other approaches to preference assessment. Simple survey instruments which ask patients for their willingness to take medications fail to take into account alternative therapies or outcomes if the therapy is not taken. Simple Likert-scale questions on the importance of separate interventions or

outcomes do not provide data on clinically relevant trade-off evaluations required in actual treatment decisions. DCE mimics such actual decision-making by requiring respondents to evaluate tradeoffs in a realistic, although hypothetical, choice context. Alternative techniques such as standard gamble or time trade off elicit preferences for clinically unrealistic tradeoffs and assume that preferences are linear in time, linear in probabilities and identical across groups of patients, not allowing for health history or current health state to affect the relative importance of outcomes. Our current study has shown that such assumptions are inaccurate for UC patients.

Our results are subject to several potential limitations and qualifications. DCE is a simulated decision-making experience using hypothetical therapeutic options and therefore do not have the same medical, emotional and financial consequences of actual therapeutic decisions. Therefore, patients may be more or less willing to accept risks in an actual clinical setting. We sought to minimize this limitation with a series of patient-level interviews and intense piloting to make the DCE trade-off scenarios as realistic as possible.

The exercise of evaluating tradeoffs among multiple therapy options with multiple endpoints may be congnitively challenging. However, we assessed the validity in participant responses through numeracy and logic tests, and the majority of our respondents (over 90%) passed these evaluations. In particular, our study population had extensive experience with UC, was overall well-educated, and included a large proportion with personal knowledge of many of the attributes, thus strengthening the validity of their preferences of choice options in the DCE survey. However, in our study, those participants who failed the numeracy exams had essentially uninterpretable results. Therefore, extrapolation of our results to low-numeracy populations should be done with caution.

Our patients were seen by a variety of physicians from tertiary-care centers; and the majority had escalated medical therapy. While this may limit generalizability, our sample would seem to typify the UC patient who has exhausted 5-ASA therapies and now faces decisions regarding immunosuppressant use versus surgery for further UC flares. Many of these patients are seen by community and local practices; thus, our findings have applicability beyond referral centers.

Both SAEs associated with medical therapies and surgical outcomes are probabilistic in the real clinical setting. However, in piloting, including conditional probabilities (the probability of an SAE conditional on the probability of having the outcome) led to significant patient confusion. This was likely related to known difficulties with conditional-probability numeracy skills in the general population. Therefore, to minimize this bias, we presented surgical outcomes as certain and presented SAEs as mortality associated with the SAEs. Our estimates therefore cannot be interpreted as MARs for uncertain benefits or outcomes at the individual patient level, and therefore must be interpreted with caution. However, we sought to evaluate the MARs over the a plausible distribution of potential SAEs related to medical therapy, or over the potential distribution of surgical outcomes, so that despite these simplifying assumptions, these aggregate estimations may be informative for decisions regarding benefit-risk tradeoffs for populations of UC patients.

Similarly, the outcome of pouchitis is a conditional outcome of J-pouch surgery; and is further conditional in its chronicity with some having an isolated episode while others have a more chronic course. To avoid such complicated calculations, we chose not to include the risk of pouchitis as an attribute. However, we did include incontinence which may serve as a surrogate for some of the clinical symptoms of pouchitis (including bowel frequency and incontinence). To the extent that fear of pouchitis might dissuade

patients from having pouch surgery, the MAR for infection and lymphoma relative to pouch surgery could be viewed as underestimates. However, for these patients, incontinence would be expected to be a worse outcome than pouchitis, and therefore the estimated MAR for J-pouch surgery with pouchitis can be extrapolated to fall between incontinence and a perfectly-functioning J-pouch.

Our attributes were within a 10 year time horizon for both risks and efficacy. This helped to avoid requiring respondents to interpret extremely small probabilities. Furthermore, when medical therapies such as thiopurines or anti-TNF therapy are initiated, the plan typically calls for chronic therapy as long as the medication remains effective. Similarly, colectomy is irreversible. Although assuming that UC would remain in remission or mildly active for a full 10 years is an over-simplification of the natural history of medically treated UC, one can view these results as if the average disease activity was mildly active or inactive for the 10 year period. Thus, the 10 year time horizon presented in this discrete choice model provided for improved patient understanding and was consistent with the time frame appropriate for the clinical decision.

In conclusion, we have applied a novel methodology to quantify UC patients' treatment preferences with striking findings. Patients preferences are most strongly impacted by the type of surgical outcome: patients are willing to accept medications that have relatively high risks of fatal complications to avoid a permanent ostomy or incontinence. Our findings therefore lend quantifiable evidence that support current treatment paradigms that involve pursuance of medical therapies to avoid these surgical outcomes. This rigorous methodology also can aid regulators in understanding patients' evaluation of the risk of SAEs for future medical therapies in the context of potential therapeutic benefit.

Even more striking, however, UC patients are equally satisfied with an uncomplicated J-pouch as they were with a medication that has very small risks of fatal complications or a medication that is incompletely effective at sustaining a durable clinical remission. Traditionally, clinical trials of new therapies have evaluated two endpoints--clinical response and clinical remission. Our findings indicate that when evaluating new therapies or therapeutic algorithms, the primary outcome should be a clinical remission rather than a clinical response. Given that patients are equally satisfied with surgery as with mild disease activity, and the goal of medical therapy is to achieve greater patient satisfaction than with surgery, our findings also indicate a critical unmet need to improve physician-patient communication regarding realistic expectations of medical and surgical therapies.

CONCLUSIONS

UC represents a unique type of IBD in which there is the potential for a cure; however, this is a surgical cure with an imperfect quality of life. The past few decades have seen an increasing array of immunosuppressive medical therapies for UC, and the upcoming years bring promise of additional such therapies. Inherent in the development of these therapies, and in current treatment paradigms, is the assumption that UC patients' prefer to avoid colectomy surgery at all costs. However, as medical therapy in UC has continued to progress, so has the appreciation for the SAEs associated with these therapies as well as the inconsistent durable efficacy of these therapies for a lifelong disease. This begs the question, "What if medical therapy is not right for everyone? At what point are UC patients unwilling to accept chronic medical therapies for their UC, and more willing to accept a surgical cure?"

To address this question, traditional patient risk tolerance studies have been conducted with results that would support the notion that UC patients view colectomy surgery as an option of last resort. However, these traditional methods for measuring risk tolerance have inherent flaws that may bias their estimates of patient preferences. While economic theory has advanced the methodologies used to quantify utility estimation and risk-benefit tolerance, these advanced methodologies have not been applied to the question of medical versus surgical therapies in UC. We recognized that such studies are critical in this field, where current treatment guidelines rest solely on such assumptions of patients' intolerance for surgery; and where the risks of chronic medical therapy can have life-threatening consequences. We therefore sought to apply DCE to accurately quantify UC patients' risk-tolerances for medical and surgical therapy in their disease.

We began by defining all-cause and cause-specific mortality in UC in the most comprehensive meta-analysis performed to date. Our findings are the first to demonstrate an increased all-cause mortality rate relative to the general population, a finding that itself is worthy of additional investigation. We also found increased cause-specific mortality from CRC, pulmonary disease and nonalcoholic liver disease in UC. Further investigation is warranted to elucidate specific causes of these elevated mortality rates. To this end, we have conducted initial analysis in the area of overall mortality with a study comparing relative survival of UC patients with moderate-severe disease pursuing chronic medical therapy versus elective colectomy surgery. Our finding of an increased mortality in UC patients with moderate-severe disease pursuing chronic medical therapy supports earlier limited studies addressing this question, and raises important questions about the two treatment strategies, especially in the setting of the findings from our DCE work.[38,39,156]

Additional studies are also needed aimed at evaluating pulmonary-related and liver-related mortality. It is interesting to note that CD patients in particular also had an elevated liver-related mortality. Traditionally, liver-related disease in IBD was believed to be secondary to primary sclerosing cholangitis (PSC), a rare disease most commonly associated with UC. It is possible that the elevated liver-related mortality is not exclusively due to PSC but perhaps due to other causes of liver disease. Those with IBD are also at risk for liver diseases that affect the general population. The most common of these conditions is that of non-alcoholic fatty liver disease;[121] and recently there has been an intriguing association between visceral fat and IBD, specifically CD activity.[157,158] These findings raise the question of whether fatty liver disease is a cause or a consequence in IBD. Specifically, it is possible that active IBD increases visceral

and hepatic fat. We are currently conducting analysis to investigate underlying rates of non-alcoholic fatty liver disease in IBD and correlate it with disease activity and increased visceral adiposity. Pulmonary-related mortality in IBD may be related to lack of tobacco cessation in this population; or related to increased pulmonary-related infections, especially in the setting of increased immunosuppressant use. Results from further studies investigating these potential causes of elevated mortality in CD and UC could inform improved interventions such as vaccines, dietary therapies, or even improved informed consent for IBD patients when making decisions regarding therapy options for their disease.

While not the primary purpose of our meta-analysis, our study also demonstrated that inception-based cohorts and population-based studies yielded very similar overall mortality estimates in IBD. It has been widely believed that inception-based cohorts were superior to population-based studies in evaluating mortality. Our findings suggest the potential for greater inclusion of population-based studies in these investigations, which may allow for data enrichment from cohorts not otherwise utilized.

Assessing disease severity in UC without direct physician contact was critical to our DCE study. Non-invasive clinical disease assessment has been a challenge, due to cumbersome and complicated patient-driven disease activity indices such as the SCCAI. We evaluated a simple 2-question patient-driven non-invasive disease activity index, the 6-Point Mayo, and found it to have good correlation, sensitivity, specificity and predictive value compared to the SCCAI. We further validated this in a separate cohort of UC patients and found similar results even when stratified by varying disease extent (pancolitis versus left-sided colitis). Finally, we conducted analysis adding back components of the SCCAI to determine if the 6-Point Mayo could be improved with any

single SCCAI component. We found that the components of urgency and general well-being improved the 6-Point Mayo's predictive value. Overall, these supplemental SCCAI components contribute very little additional burden to the 6-Point Mayo, thus allowing clinical investigators a simple non-invasive tool to assess disease activity without direct physician contact. With the increasing number of clinical studies in UC, this promises to be a very important tool for researchers.

In our study, we did find a poor correlation between the non-invasive patient-driven indices and a purely endoscopic evaluation of UC disease activity. It is well-known that endoscopic, and even histologic, active disease is often found in patients who are asymptomatic. With an increasing awareness of the importance of mucosal healing in IBD, this disconnect between patient symptoms and endoscopic activity leads to important future questions. It is likely that different parameters govern patients' willingness to accept additional medical therapy risks to improve mucosal healing and presumably prevent future disease relapses, especially in the setting of asymptomatic clinical disease. We are currently conducting DCE analysis evaluating patients' risk tolerances in this setting. The findings of this study will have important impact in therapy algorithms for IBD patients, including defining potential thresholds for therapy efficacy and SAEs to achieve mucosal healing.

Finally, we have conducted the first DCE study evaluating UC patient risk tolerances for medical therapy SAEs to avoid colectomy surgery with varying treatment efficacy. We have shown, for the first time, that when facing incomplete durable clinical remission with medical therapy, UC patients are equally willing to accept J-pouch surgery. Additionally, this study illustrates that UC patients do value the difference

between remission and clinical response, and suggests that the former should be the preferred outcome when evaluating therapies in UC.

Our work emphasizes that UC patient preferences for disease therapy can vary significantly from providers' assumptions regarding their preferences; and questions the traditional therapy algorithm in UC of exhausting all medical therapy before considering colectomy surgery. Taken together with increasing evidence that elective colectomy may have a survival benefit in moderate-severe UC,[38,39,156] the current work supports early discussion regarding surgical options for UC patients. In our current work, the majority of UC patients indicated a lack of discussion regarding surgical options for their UC in their current medical care, a finding previously supported by other studies.[159-161] There are several possible reasons for this. UC patients may reject considering surgery as a valid option due to pre-formed notions regarding surgery in general. Gastroenterologists may not have time to discuss surgical options for their patients, and may make it a low priority in therapy discussions. This may be especially true given the traditional view held by gastroenterologists that UC patients want to avoid surgery at all costs. Finally, gastroenterologists may not sufficiently or accurately depict surgery in a way that makes UC patients comfortable with their discussion. In our prior work, we examined what factors were associated with UC patients reporting that they "felt very comfortable with their understanding of the surgical options for their UC and had no further questions regarding surgery." The only statistically significant variable associated with UC patients reporting satisfactory understanding with UC surgery was discussion with a surgeon—not a gastroenterologist.[159]

Our work has therefore illustrated a critical unmet need for improved surgical education and discussion in UC. If UC patients are averse to the risks of medical

therapy, but lack sufficient knowledge about the surgical options for their UC, educational interventions are crucial to facilitate shared decision-making and informed consent. One of the most important roles of education is to help patients weigh medical therapy risks against the risks of surgical therapy. This informed decision-making has even greater value in the setting of incompletely effective medical therapy that risks continued active disease. Education could alter patients' readiness to choose colectomy instead of medical therapy. This takes on even greater impact given the potential for improved survival with elective colectomy compared to chronic ineffective medical therapy, which entails continued risks of active symptoms and/or need for corticosteroid therapies. For example, given the low surgery-discussion rates in our current work, our findings could under-estimate UC preferences regarding surgery therapy: it is possible that UC patients may be more willing to accept ostomy surgery; and may even prefer J-pouch surgery to chronic ineffective medical therapy.

We are currently working on an online patient-driven educational tool for UC patients with a dedicated surgery component. We have also designed a DCE-based study to evaluate the impact of this tool on UC patient risk tolerances. Rigorous methodologies to assess the effect of educational interventions on decision-making by UC patients have not previously been performed, and thus the impact of such educational interventions is unknown. This information can enhance and validate our proposed educational tool in UC. It can also set metrics for future educational tools in UC (or in IBD) as well as establish a rigorous methodology to assess efficacy and impact of future tools in IBD.

Our current work in UC patient risk tolerance assessment also highlights the need for rigorous assessment of patient preferences. The findings of our DCE study are

in contrast to the findings from more traditional—but methodologically flawed—systems for assessing patient risk preferences. However, DCE is not without potential limitations including one inherent to its approach, namely that it remains a simulated decision-making experiment. Patients may be more or less likely to accept risks in actual clinical settings. Revealed-preference (RP) is a method of obtaining measured utilities based upon actual decision-behaviors. However, because RP data is based on actual choices, large numbers of observations are needed and data quality is limited: data only reflects existing therapy options, and may reflect mixed preferences including those of patient, physician and payer.

While many studies have shown good concordance between DCE and RP measured risk preferences and the successful ability to merge these data in transportation and environmental research,[162-165] to date only one study has evaluated such joint estimation in health care.[166] UC represents a unique opportunity for health-care based joint DCE-RP data enrichment. Treatment decisions regarding medical versus surgical therapy are dominated by UC patient preferences regarding surgery. Understanding external forces that shape these preferences can inform measured patient preferences. We have currently proposed a study to utilize our existing I3 database to combine DCE with RP decisions made in real clinical settings. This joint estimation of preference choice data will have several significant impacts: this will allow for real-world statistical discrimination of UC patient risk tolerance; it can allow for the identification of new attributes affecting UC patients' risk tolerance; it will allow refinement of DCE measured tolerances to be reflective of revealed behavior; and it can inform DCE data-enrichment methodology in other chronic diseases and treatment preferences. Fundamentally, patient preferences play a key role in their satisfaction and

willingness to accept and adhere to therapies, which in turn influences clinical outcomes. Thus, improved methodologies in risk estimation can help answer the question, “Why are UC patients not having surgery, and what can be done to improve medical and surgical therapy options for UC patients?”

In summary, we have completed a set of experiments that challenges and changes the way we view the prognosis of UC, how we measure UC disease activity, the methodologies used to quantify UC patient risk preferences, and the way we view treatment algorithms in UC. We have determined all-cause and cause-specific mortality in UC, and investigated methodological tools used to measure these outcomes. We have investigated and validated a simple patient-driven tool for assessing UC disease severity. Finally, we have challenged the traditional view that UC patients wish to avoid colectomy surgery at all costs as well as the conventional methods used to quantify UC patient preferences for medical and surgical therapies in UC. Our work has immediate direct impact for UC patients, providers and health-care administers; and it further informs many important future research questions regarding UC therapies, treatment algorithms, and patient decision-making.

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