# Predicting Disease Course in Inflammatory Bowel Disease using Health Administrative Data

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# ABSTRACT

**Background**: Investigators are often interested in using population-level health administrative data in inflammatory bowel disease (IBD) patients to study disease outcomes, risk factors and treatment effects to enhance knowledge, shape clinical practice and influence health care policy. A major limitation of using health administrative data for these purposes is the lack of detailed clinical data to adjust for the confounding effects of differential disease severity on observed associations. Methods to account for disease severity using administrative variables would offer a major advance to population-level studies in IBD patients. Thus, in this study we aimed to use a cohort of IBD patients from The Ottawa Hospital (TOH) to validate a model that was originally developed in Manitoba for estimating clinical disease course in IBD patients through healthcare utilization measures.

**Objectives**: The objectives of this thesis are: 1) To identify and characterize a reference cohort of IBD patients in the ambulatory clinics of four gastroenterologists from TOH on clinical disease course in the preceding year (reference cohort), based on a Manitoba definition of clinical disease course; 2) To fit a partial proportional odds (PPO) model for predicting IBD course, derived using Manitoba health administrative data, to the reference cohort of IBD patients using Ontario health administrative data; 3) To derive new PPO models of IBD disease course for the reference cohort using Ontario administrative variables and compare model performance; and 4) To apply the models to the Ontario Crohn's and Colitis cohort (OCCC) to estimate IBD course in Ontario, and compare the distribution to that of the Manitoba IBD population.

**Methods:** We first identified a reference cohort of IBD patients in Ontario from the outpatient clinics at TOH during fiscal year 2015. Through chart review, we classified these patients into one of four clinical

disease categories (remission, mild, moderate, or severe) using the Manitoba definition. We linked these patients to Ontario health administrative datasets. Given slight differences in data structure and coding between Manitoba and Ontario, we were unable to directly test the Manitoba model and instead fit a PPO model to the Ontario cohort using analogous administrative variables to those used in the final Manitoba model ("adapted model"). We subsequently derived new PPO models using unique Ontario administrative variables under three strategies: 1) Stepwise variable selection ("stepwise model"); 2) Forced fitting of all variables ("all-variables model"); and 3) Using a two-step modelling algorithm that considered IBD-related hospitalizations separate from other administrative variables ("two-step model"). We then compared model performance from the four strategies. Finally, we applied the models to the Ontario IBD population from 2004 to 2016 and compared model estimates to those from Manitoba.

**Results**: We identified 963 patients with IBD from TOH outpatient clinics, of which 52.3% (n=504) were males, 64.6% (n=622) had Crohn's Disease, and 89.2% (n=859) resided in an urban setting. Based on the Manitoba definition, 64.9% of patients within our reference cohort were classified as remission, while 11.4%, 14.1%, and 9.6% were classified as mild, moderate, and severe disease course, respectively. The adapted model (c-statistic 0.77, goodness-fit p-value 0.28) performed comparably to the other models: the stepwise model (c-statistic 0.77, goodness-fit p-value 0.50), the all-variables model (c-statistic 0.77, goodness-fit p-value 0.53), and the two-step model (c-statistic 0.78, goodness-fit p-value 0.75). The adapted model also resulted in overall similar estimates with regards to the disease course distribution among the Ontario IBD population. However, on closer inspection, our two-step model, in which individuals who had been hospitalized for an IBD-related indication within the past year were assumed to have severe disease, performed better with respect to accurately classifying individuals with moderate or severe disease, without sacrificing discriminative ability. Based on the

two-step model, from 2004 to 2016, 89.2-91.2% of the Ontario IBD population was in remission, 0% had mild disease, 2.4-3.2% had moderate disease, and 5.9-8.4% had severe disease. Distribution of disease course among IBD patients in Ontario differed considerably than that in Manitoba.

**Conclusion**: In the absence of clinical information within health administrative data, we present and compare four different models that can be used to partially account for the confounding effect of disease course among IBD patients in future population-based studies using Ontario health administrative data. Given that our models did not perform as originally expected, especially with regards to accurately identifying individuals with more active disease states, we advise researchers to use these models at their own discretion.

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# LIST OF ACRONYMS AND ABBREVIATIONS

AIC – Akaike information criterion

BIC – Bayesian Information Criterion

CCI – Canadian Classification of Health Interventions

CD – Crohn's Disease

CI – Confidence interval

DAD – Discharge Abstract Database

ED – Emergency department

FP/GP – General practitioner/ family physician

IBD – Inflammatory Bowel Disease

ICD – International Classification of Diseases

IPDB – ICES Physician Database

LHIN – Local Health Integration Network

NACRS – National Ambulatory Care Reporting System

NPV – Negative predictive value

OCCC – Ontario Crohn's and Colitis Cohort

OHIP – Ontario Health Insurance Plan

PPO – Partial proportional odds

PPV – Positive predictive value

RPDB – Registered Persons Database

SD – Standard deviation

TOH – The Ottawa Hospital

UC – Ulcerative Colitis

US – Ultrasound

# CHAPTER 1: INTRODUCTION

## 1.1 Rationale

Inflammatory bowel disease (IBD), comprised of Crohn's disease and ulcerative colitis, is a growing health problem worldwide, with Canada having among the highest prevalence and incidence rates in the world (2–5). Despite stabilizing incidence in Western countries, the prevalence of IBD continues to rise owing to an aging population that is living longer with the disease, which has led to substantial burdens on patients' quality of life, the healthcare system, and workplace productivity (3,4,6–9). In 2018, approximately 270,000 Canadians were living with IBD and this number is expected to rise to around 403,000 individuals (nearly 1% of the Canadian population) by the year 2030 (10). In 2018, direct health care costs for individuals with IBD were estimated at $1.28 billion (approximately $4,731 per person) and the indirect health-related costs relating to loss of productivity, medical absenteeism, premature death, and out-of-pocket expenses were estimated at $1.29 billion annually (11,12). In addition, with recent trends towards earlier initiation of biologic therapies, shifting of therapeutic targets from symptomatic remission to objective parameters, and an individualized management approach with tight monitoring, the costs associated with caring for persons with IBD are expected to rise significantly (13–17). Thus, real-world studies regarding IBD epidemiology, prognosis and treatment effectiveness are necessary to optimize treatment strategies and target scarce health care resources.

Routinely collected health administrative data are increasingly being used to conduct research in IBD patients in Canada as they are readily available, relatively inexpensive to use, involve large sample sizes, and capture information across different healthcare settings (18,19). However, a major limitation of using health administrative data is the lack of detailed clinical information which limits the ability of

researchers to account for disease severity among other clinical parameters in studies of patients with chronic health conditions such as IBD (19). Disease severity, which represents the presence and extent of a disease, is an independent contributor to health outcomes in individuals with IBD, is a confounder of exposure-outcome associations in observational studies, and is a known confounder in pharmacoepidemiology studies where it may result in confounding by severity where patient with higher severity are channeled to certain therapies (20–29). Disease severity is usually assessed through a combination of clinical, endoscopic, radiographic, and biochemical parameters (30). However, most of these parameters are not currently available within administrative datasets limiting our ability to accurately account for IBD severity in studies that use administrative datasets (18,19). Therefore, methods that account for disease severity using health administrative variables would offer a major advance to population-level studies in IBD patients as it could potentially allow researchers to adjust for and stratify patients across disease state categories in future population-based studies using health administrative datasets.

A group of researchers in Manitoba developed a predictive model that estimated clinical disease course (remission, mild, moderate, or severe) in the preceding year using healthcare utilization measures, disease characterizing factors, and sociodemographic indicators from health administrative datasets (1). Specific healthcare utilization measures used included: visits to a gastroenterologist for IBD and for non IBD indications, visits to a FP/GP for IBD and for non-IBD indications, non-IBD hospitalizations, endoscopic procedures, general radiologic procedures, and gastrointestinal related radiologic procedures. They ultimately concluded that clinical disease course in IBD patients can be predicted using healthcare utilization measures available within province-wide administrative datasets. Currently, there are no methods to account for disease severity in population-based studies using Ontario health administrative

datasets. Therefore, in this study we aimed to overcome that limitation by validating the Manitoba model in an established reference cohort of IBD patients from Ontario characterized on clinical disease severity. We also sought to derive new models to test the contribution of other potentially important administrative variables that were not included in the Manitoba model and to apply these models to estimate disease course in the Ontario IBD population over time and compare our estimates to those from Manitoba.

## 1.2 Thesis Objectives

The main purpose of this thesis was to validate an administrative model for predicting IBD course that was developed in Manitoba to estimate disease course in IBD patients in Ontario. Our aim was to develop a method to allow for partially adjusting for the confounding effects of differential disease severity in future IBD studies using Ontario health administrative data. Our specific objectives were:

1. To identify and characterize a consecutive cohort of IBD patients seen in the ambulatory clinics of four gastroenterologists from The Ottawa Hospital on clinical disease course in the preceding year (reference cohort), based on a Manitoba definition of clinical disease course
2. To fit a partial proportional odds (PPO) model for predicting IBD course, derived using Manitoba health administrative data, to the reference cohort of IBD patients using Ontario health administrative data
3. To derive new PPO models of IBD disease course for the reference cohort using Ontario administrative variables and compare model performance
4. To apply the models to the Ontario Crohn's and Colitis Cohort (OCCC) to estimate IBD course in Ontario, and compare the distribution to that of the Manitoba IBD population.

# CHAPTER 2: BACKGROUND

## 2.1 IBD

IBD includes a spectrum of diseases, with the two main subtypes being ulcerative colitis (UC) and Crohn's disease (CD). UC is defined by contiguous non-transmural inflammation, primarily in the colon and rectum, whereas Crohn's disease involves discontiguous and transmural inflammation that can affect any part of the digestive tract (31). Both diseases are chronic in nature, often with a relapsing-remitting pattern of inflammation and symptoms. To date, the precise etiology of IBD remains unclear but it is believed to result from a combination of genetic predisposition and environmental exposures resulting in a dysregulated intestinal microbiome and immune response (32,33).

The clinical presentation of IBD is highly variable depending on patients' age, IBD subtype, and extent of inflammation, ranging from an asymptomatic to a life-threatening presentation (34). Common symptoms and signs of IBD include abdominal pain, diarrhea, rectal bleeding, urgent bowel movements, reduced appetite, weight loss, fatigue, and anemia (35,36). Both conditions can become complicated by fulminant colitis, toxic megacolon and bowel perforation, and CD is often complicated by the development of intestinal strictures and both intestinal and perianal fistulas (37–39). Additionally, many patients with IBD experience symptoms resulting from extra-intestinal manifestations outside of the gastrointestinal tract due to the involvement of joints, eyes, bones, liver and skin, among other organs (40–45).

## 2.2 Epidemiology of IBD

The epidemiology of IBD has significantly changed throughout time and by geographical area (46). In the 20th century, IBD was mainly a disease of westernized countries (8,47). However, at the turn of the 21st century IBD became a global disease with stabilizing incidence yet high burden in Europe and North America and a rapidly rising incidence in areas with previously low incidence, including Eastern Europe and Asia (7,8,13,48). Canada has one of the highest prevalence rates of IBD world-wide (4,5,49). The prevalence of IBD in Canada in 2012 was estimated at around 233,000 (0.67%) with a higher prevalence reported for Crohn's disease compared to ulcerative colitis (129,000 vs 104,000 respectively) (50). In 2018, approximately 270,000 (0.7%) of Canadians were estimated to have IBD (135,000 individuals with CD and 120,000 with UC) out of a population of 36.71 million people, and this prevalence is expected steadily rise to approximately 403,000 patients (nearly 1% of the Canadian population) by 2030 (3,51). When broken down by province, the prevalence of IBD per 100,000 individuals in 2008 was as follows: 445 in Quebec (lowest), 507 in Ontario, 515 in British Columbia, 529 in Alberta, 555 in Saskatchewan, 567 in Manitoba, and 870 in Nova Scotia (highest) (51). In 2018, these numbers were estimated to rise ranging from approximately 652 per 100,000 individuals in Manitoba to 1,224 per 100,000 in Nova Scotia (51).

## 2.3 Disease Course in IBD

Typically recorded through long-term population-based cohort studies, the course of IBD can be relapsing-remitting or chronically progressive, with variable disease severity over time. For UC, a systematic review of 15,316 patients (from 17 population based cohorts) identified the disease course as mild-moderate in the majority of patients, with the greatest disease activity at diagnosis and with only 10-15% of patients experiencing a more aggressive disease course leading to frequent hospitalizations

and need for colectomy (7). Similarly, another systematic review of seven UC cohorts reported decreasing disease activity over time (52). For CD, before the introduction of immunosuppressive medications, a systematic review of six Crohn's disease cohorts reported that the majority of patients experienced disease progression in the form of complications such as strictures, fistulas, and abscesses (53). In the biologics era, an Australian prospective population-based study of incident cases of IBD during 2007-2008 and 2010-2013 reported that a quarter of UC patients and a third of CD patients experienced a disabling disease course, which they defined based on the number of hospitalizations after diagnosis, surgeries including intestinal resection, use of medications such as steroids, and the presence of chronic disabling symptoms (54).

Disease severity as approximated by disease course is a critical factor influencing IBD patient outcomes as was previously demonstrated in numerous studies (23–29,55). It is also a confounder of exposure-outcome associations in observational studies, and is a known confounder in pharmacoepidemiology studies where it may result in confounding by severity where patient with higher severity are channeled to certain therapies (20–22). In the absence of a well-established classification system of IBD severity, Melesse et al. (1) applied a clinical definition of IBD course developed using a review of the existing literature, general consensus, and expert consultation to stratify their cohort. This definition used patient and physician report of symptoms and/or flares, immunosuppressive medication uses and IBD related hospitalizations over a one-year look-back period to classify individuals into four disease states: Remission, mild, moderate, and severe (Table 2.1).

**Table 2.1:** Clinical definition for IBD course used by Melesse et al. (1).

| Disease course category | Description |
|---|---|
| Remission | • minimal or no IBD symptoms; AND<br>• no change in medication in the preceding year |
| Mild | • one symptom flare in the year prior to enrollment that required a change in medication, but no introduction of corticosteroids or anti-tumour necrosis factor [anti-TNF] therapy; OR<br>• a single change in dosing of immunosuppression or anti-TNF therapy that facilitated remission<br>• did not meet criteria for moderate or severe disease |
| Moderate | • two distinct symptom flares in the year prior to study enrollment; OR<br>• at least one flare requiring the use of corticosteroids or anti-TNF therapy; OR<br>• chronic low-level symptoms of IBD without remission<br>• did not meet criteria for severe disease |
| Severe | • more than one course of corticosteroids in the year prior to study enrollment; OR<br>• IBD-related hospitalization; OR<br>• in remission for <3 months of the year prior to study enrollment; OR<br>• chronic moderate symptoms |

## 2.4 IBD Studies Using Health Administrative Data

In Canada, health administrative data capture comprehensive health care utilization information for all residents with a valid healthcare registration. These databases include acute care hospitalizations, emergency department visits, ambulatory physician visits (through billing claims), complex chronic care and prescription drug claims, among other health service encounters for each individual within a specific jurisdiction and are linked together through unique encrypted identifiers (56,57). However, as healthcare in Canada is mostly administered at the provincial or territorial level, each jurisdiction collects its own healthcare utilization data within its individual unique databases. These databases often tend to slightly differ in between the jurisdictions due to differences in physician billing practices within each province in addition to different variable coding techniques and data structures (58). Therefore, models developed in one healthcare jurisdiction might not be directly applicable to another jurisdiction without

first being validated. In Ontario, health administrative data are maintained by ICES, a non-profit research institute that facilitates the linkage of medical records of individuals across databases, registries, and healthcare encounters through unique encrypted identifiers (57).

Originally captured for administrative and reimbursement purposes, health administrative data present researchers with robust, cost-effective, and unique opportunities to conduct population-based observational studies to examine disease outcomes, risk factors and treatment effects as well as to enhance knowledge, shape clinical practice and influence health care planning and policy development (18,59–62). They also provide excellent opportunities to examine trends in disease epidemiology and for chronic disease surveillance as patients can be followed longitudinally through multiple health encounters (60–62). Nonetheless, a significant limitation of administrative data is their lack of detailed clinical information about disease severity, course, phenotype, and medication use which limits the ability to make valid inferences from observational studies that utilize them (63,64). Thus, methods that count for disease severity would greatly advance the conduct of observational studies conducted using health administrative data. To overcome this limitation, a group of researchers in Manitoba developed a prediction model that uses healthcare utilization measures over the previous year as proxies of disease course in IBD patients in Manitoba (1).

### 2.5 Derivation of a Predictive Model of IBD Course using Manitoba Administrative Data

Melesse et al. prospectively identified an IBD cohort of 407 consecutive patients from the clinic of a single gastroenterologist practicing at an academic hospital over one fiscal year from 2009-2010 (1). They then applied a clinical definition of IBD course as described in Table 2.1 above over a one-year look-back period to classify their reference cohort into four disease states: Remission, mild, moderate,

and severe. They then linked this cohort to Manitoba health administrative data and retrieved healthcare utilization measures and control measures defined as over a one-year look-back period that would potentially approximate clinical disease course. Analyses were controlled for the following variables: age at time of enrollment, gender, residential area at diagnosis and socioeconomic status, disease type and disease duration. IBD course over a pre-defined period, incorporating subjective and objective parameters reflecting major IBD health states, was felt to present a better construct of overall disease severity influencing future patient outcomes as compared to cross-sectional measures of disease severity that have been used in other indices (1).

The investigators subsequently used ordinal regression to derive a partial proportional odds model that predicted IBD course using their chosen administrative variables. They chose a partial proportional odds modelling strategy because some of the predictors included in their model violated the proportional odds assumption of standard ordinal logistic regression (1,65). The list of candidate predictors and final model predictors, along with parameter estimates, are provided in Table 2.2 (1). Using this model, they stratified the Manitoba IBD population, identified using the University of Manitoba IBD Epidemiology Database and found that from 1995-2013, 43.6-59.9% of the Manitoba IBD population were in remission, 21.5-28.2% had mild disease, 10.9-17.1% had moderate disease, and 6.9-10.0% had severe disease (1,66).

**Table 2.2:** Final Multivariable Partial Proportional Odds Model from Manitoba for Predicting IBD Course (1)

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Visits to Gastroenterologist for IBD †** | 0-2 | Ref | Ref | Ref |
| | >=3 | 3.33*** [2.03–5.54] | 4.70*** [2.78–8.04] | 11.27*** [4.82–29.09] |
| **Visits to a Gastroenterologist for non-IBD** | 0 | Ref | Ref | Ref |
| | 1-2 | 1.33 [0.81–2.18] | 1.33 [0.81–2.18] | 1.33 [0.81–2.18] |
| | >=3 | 2.26** [1.23–4.15] | 2.26** [1.23–4.15] | 2.26** [1.23–4.15] |
| **Visits to a FP/GP for IBD †** | 0 | Ref | Ref | Ref |
| | 1-2 | 0.51 [0.88–1.52] | 1.71 [0.95–3.09] | 1.61 [0.68–3.69] |
| | >=3 | 2.97** [1.44–6.37] | 4.39*** [2.17–8.97] | 5.16*** [2.16–12.26] |
| **Visits to a FP/GP for non-IBD** | 0-2 | Ref | Ref | Ref |
| | 3-5 | 1.31 [0.81–2.14] | 1.31 [0.81–2.14] | 1.31 [0.81–2.14] |
| | >=6 | 1.23 [0.74–2.03] | 1.23 [0.74–2.03] | 1.23 [0.74–2.03] |
| **Hospitalizations for non-IBD** | 0 | Ref | Ref | Ref |
| | >=1 | 3.13*** [1.58–7.04] | 3.13*** [1.58–7.04] | 3.13*** [1.58–7.04] |
| **Endoscopic procedures †** | 0 | Ref | Ref | Ref |
| | >=1 | 2.83** [1.33–6.41] | 1.47 [0.73–2.95] | 1.25 [0.54–2.81] |
| **General radiologic procedures †** | 0 | Ref | Ref | Ref |
| | >=1 | 2.22** [1.31–3.80] | 2.41** [1.44–4.02] | 2.36** [1.19–4.72] |
| **Gastrointestinal related radiologic procedures** | 0 | Ref | Ref | Ref |
| | >=1 | 1.06 [0.59–1.90] | 1.06 [0.59–1.90] | 1.06 [0.59–1.90] |

This model is adjusted for sex, age at diagnosis, disease duration, disease type, and rural vs. urban status
**p-values from Wald $\chi 2$ test [**p < 0.01, ***p < 0.001].** † non-proportional predictor
IBD = inflammatory bowel disease; FP/GP = general practitioner/ family physician; GIT-related radiologic procedures includes US/CT/barium studies or MRI procedures reported as a single combined variable because of small cell sizes in each procedure

## 2.6 Validating the Manitoba Model Using Ontario Administrative Data

Population-level research in IBD patients in Ontario is possible using the OCCC, which was developed through validated case ascertainment algorithms of health care contacts for IBD (67,68). While allowing for accurate identification of IBD patients, differentiation of UC from CD, and separation of prevalent from incident cases there is no method currently available to estimate IBD disease course from administrative data in Ontario. This is a significant weakness of population-based studies of IBD

patients in Ontario (and other provinces), because exposure-outcome associations could be confounded due to differential disease severity across exposure groups. Indeed, disease severity, as approximated by disease course over time in this study, is a critical factor influencing IBD patient outcomes as was previously demonstrated in numerous studies (23–29,55). Thus, the ability to partially adjust for this confounding influence would be of major benefit for future studies. The Manitoba model presents an opportunity to estimate disease course among IBD patients in Ontario using administrative variables. Given potential differences in administrative variable definitions, database structure and clinical practice in Ontario as compared to Manitoba, it is important to validate the Manitoba disease course model using Ontario health administrative data before using it in future Ontario population-based studies. It was also important to test the contribution of other potentially important administrative variables that were not included as part of the Manitoba model, to determine whether model performance could be improved in Ontario.

## 2.7 Ordinal Logistic Regression Modelling

### *2.7.1 The Need for Ordinal Logistic Regression*

While ordinal outcomes (outcomes with more than two discrete levels that follow a natural ordering) are commonly encountered in medical research, many of them are converted into other formats for the purpose of modeling and analysis (69). This includes collapsing adjacent categories together to create dichotomous outcomes, considering them as continuous variables, or maintaining the separate categories and analyzing them as nominal variables (70). Consequences of converting ordinal outcomes to other formats include loss of information, which may result in a reduced statistical and exploratory power, and misinterpretation of observed associations (71). The inherent structuring of ordinal outcomes can be

preserved by utilizing ordinal logistic regression, which is an extension of binary logistic regression and provides a parsimonious option for modeling and analyzing ordinal outcomes (72).

### *2.7.2 Overview of Ordinal Logistic Regression*

There are various types of ordinal models, with the most popular and most used variant being the cumulative logits, also known as the cumulative odds, model. It models the cumulative probability of an individual's outcome being equivalent to, or above (or below), a given category, in either an ascending or a descending order (72–74). This model simultaneously examines the effect of the predictors across all cumulative logit splits and provides an average association for each predictor across all potential logit splits (74).

### *2.7.3 Common Subtypes of the Cumulative Logit Model*

There are several subtypes within the cumulative logit model, including:

1) The proportional odds model

   Developed by McCullagh in 1980, this is the most commonly used subtype of ordered logit models and the most parsimonious (73). It is the most parsimonious ordinal regression modelling strategy but constrains all the predictors across response levels to a single set of parameter estimates, even if a given predictor has a differential association across different cumulative logit splits. Therefore, a single coefficient and a single odds ratio would be produced for each predictor across the number of cumulative logit splits of the outcome. This odds ratio would represent an overall summary measure of the predictor effect. This model can be executed using the Proc Logistic procedure in SAS 9.4. By default, if the outcome has more than two levels, then Proc Logistic fits the proportional odds model (75). For this model to be used, the

proportional odds assumption, as described below must be satisfied, otherwise the model can generate invalid results.

2) The non-proportional cumulative odds model

   Also known as the generalized ordered logit model (76). This is the least restrictive of the three subtypes as it does not constrain any of the predictors across the response levels. Therefore, if this subtype is used, each predictor would have a different parameter estimate for each cumulative logit split. The difference between this model and nominal regression analysis is that this model maintains the ordinal nature of the outcome.

3) The partial proportional odds model

   This model was first described by Peterson and Harrell in 1990 and offers a more parsimonious option than the non-proportional odds model (77). It represents an extension of the proportional odds model that allows for constraining some predictors to have the same estimate across response levels while other predictors are allowed to have varying estimates across response levels (72,78).

The choice of the specific subtype depends on whether or not the predictors meet an underlying assumption known as the proportional odds assumption (79).

### *2.7.4 The Proportional Odds Assumption*

The proportional odds assumption, also known as “equal slopes” or “parallel lines” or “parallel slopes” assumption, is a key assumption in cumulative logits models that must be satisfied in order to use the

proportional odds model (79). The assumption states that the effects of the predictors are proportional or consistent across each level of the response variable. In other words, the odds of the response are constant or are the same across all cumulative logit splits for a given predictor, irrespective of the specific categories. Therefore, one coefficient can be produced for each predictor no matter how the outcome is dichotomized within the cumulative logit model and a single odds ratio represents an overall summary measure of each predictor effect (80,81).

This assumption can be tested using several methods. Some of these methods allow for simultaneous adjustment for the effect of other variables while testing the assumption whereas others only allow for proportionality testing without adjusting for other variables. In order for these tests to be accurate, a cross tabulation of the predictors against the outcome should have a minimum count of five values (78). If a cross-tabulation reveals a cell count of $< 5$, then it is suggested that it might be more appropriate to collapse adjacent categories together and then check for proportionality (78).

### *2.7.5 Methods for Testing the Proportional Odds Assumption*

There are several ways to assess whether variables to be included in a model meet the proportional odds assumption:

1) Score test for overall model (proc logistic)

   This is a test for the proportional odds assumption for all variables included within a model. This test is automatically provided in the SAS output when modeling a dependent variable with more than two outcomes (65,73,77). A non-significant score ($p > 0.05$) indicates that the proportional odds assumption is met for all variables included within the model. If the assumption is met, then the proportional odds model represents an appropriate model choice for the outcome. However,

if the score test is significant ($p<0.05$), it indicates that one or more variables in the model do not meet the proportional odds assumption. Therefore, constricting all variables to a single odds ratio across response levels might not be appropriate for some of the variables within the model and additional testing is needed to identify the specific variables that violate the assumption. However, this test often inappropriately rejects the proportionality assumption, especially for large datasets or if there are many independent variables (65,70,81,82). Therefore, other methods for assessing proportionality should be used in conjunction with the score test.

2) Individual score tests from univariate models (proc logistic)

   If univariate models with an ordinal outcome are modelled using proc logistic, then individual score tests are produced for each predictor. Different levels of significance (e.g. $p<0.05$ or a more conservative cut-off of $p<0.1$) can be used to identify possible non-proportional predictors.

3) Wald test from a non-proportional cumulative model

   This involves fitting all variables in a non-proportional cumulative model which allows predictors to go up or down across the different splits and then performing Wald tests for each parameter to assess whether the effects of the parameters are the same (83). The Wald test can be used to examine for significance between the different splits using different levels of significance (e.g. $p<0.05$, $p<0.1$, $p<0.2$)

4) Graphical methods (empirical logit plots and mosaic plots)

   Empirical plots which are based on observed counts of the dependent variable involves plotting individual predictors versus empirical logit (84). This allows for a way to visually assess

proportional odds by examining whether the separate plotted levels are parallel to each other. Empirical plots do not allow for adjustment of other variables when testing proportionality. Mosaic plots present a visual representation of the observed proportions of each level in the explanatory variable against the ordinal outcome variable (85). In other terms, they plot the cross-tabulation frequencies of the variables where the width depends on the number of patients in each category against the outcome. If a variable is proportional, the plots would go up or down in a proportional fashion. Mosaic plots also do not adjust for other variables.

5) Plotting separate cumulative binary models to see how the estimates differ

   Although the ordinal model does not represent an average of the cumulative binary models, plotting separate cumulative binary models allows for a crude assessment of how the predictors act together.

6) Letting SAS test for the proportionality assumption as part of model building

   It is also possible to let SAS test proportionality through automated selection procedures (e.g. Stepwise, forward, or backward). This allows for testing of proportionality of statistically significant variables as they are about to enter the model, thereby allowing them to enter as proportional or non-proportional depending on the prespecified cut off level for proportionality. If a variable enters the model as non-proportional, it cannot enter the model as proportional later, whereas if the variable enters the model as proportional, it can enter the model at a later step as non-proportional with one less degree of freedom (76). Therefore, a single model might end up with a proportional and a non-proportional version of the same variable where one can be used to adjust for the effect of the other.

### *2.7.6 Steps to Take if the Proportional Odds Assumption is Violated*

If the proportionality assumption is not met for a predictor variable then there are several options that can be considered. If there were cumulative logit levels with small numbers for a given predictor's categories, then one or more of these categories can be collapsed. If there is a desire to maintain ordinality of the outcome then partial proportional odds models, non-proportional cumulative odds models, or other less commonly used variants of ordinal logistic models can be used. Alternatively, the outcome ordering can be ignored, and multinomial regression (generalized logistic model) can be used instead.

### *2.7.7 Assessing the Performance of Ordinal Logistic Regression Models*

Model discrimination and calibration are two key elements that are frequently used for assessing the performance of logistic regression models. Discrimination refers to the model's ability to differentiate in between concordant and discordant pairs of individuals while calibration represents the agreements between predicted and observed outcomes (86,87). The c-statistic, also known as the c-index or the concordance statistic and generally equivalent to the area under the receiver operating characteristic curve, represents one of the most commonly used measures for evaluating the discriminative ability of binary logistic regression models (88). Several extensions exist for the application of the c-statistic to ordinal response models (69,89). Models with perfect discrimination have a c-statistic of 1, whereas those with no discriminative ability have a c-score of 0.5 (86). Furthermore, c statistic values of 0.5 and 0.7 indicate poor discrimination, those 0.7 to 0.8 show acceptable discrimination, those 0.8 to 0.9 indicate excellent discrimination, and ≥0.9 show outstanding discrimination (90). Model calibration is most commonly tested through the Hosmer-Lemeshow goodness of fit test, which also has an extension

for ordinal logistic regression models where a non-significant value at $p>0.05$ indicates good model calibration (91–94).

Other methods for assessing model performance include the Cohen's kappa and the weighted kappa statistics which compare the agreement between observed and predicted outcomes with the weighted kappa taking into consideration the closeness of agreement between the categories (95,96). A Kappa value of 1 indicates perfect agreement, values greater than 0.75 indicate excellent agreement, those between 0.4 and 0.75 indicate fair to good agreement, and those less than 0.4 indicate poor agreement (97). In addition, the Akaike information criterion (AIC) and Bayesian Information Criterion (BIC) which are based on the log-likelihood values with additional penalties for the inclusion of unnecessary predictors can be used to compare models with lower values indicating more preferred models (98).

# CHAPTER 3: METHODS

## 3.1 Overview of Study Methodology

This study aimed to externally validate a predictive model of IBD clinical course that was derived using Manitoba health administrative data in a cohort of IBD patients from The Ottawa Hospital as outlined in figure 3.1.

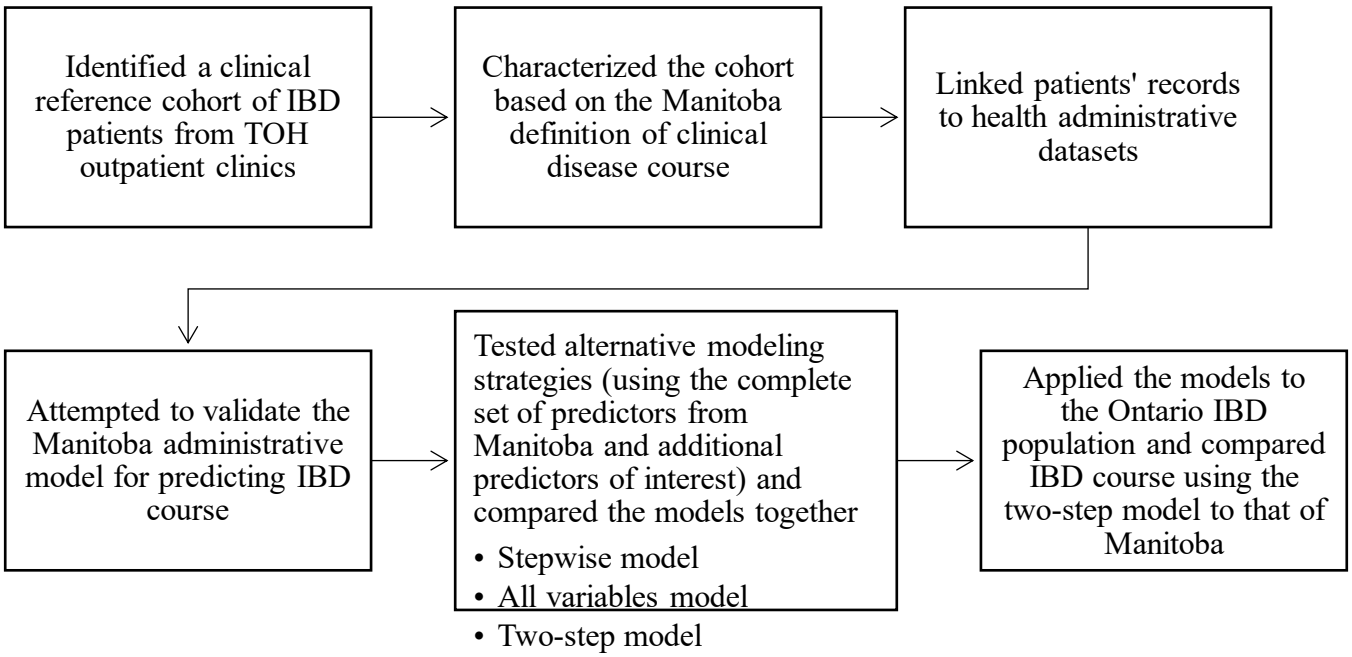



**Figure 3.1:** Study overview

Consecutive IBD patients seen over a one-year period in the ambulatory care clinics of four IBD specialists were retrospectively reviewed. These patients were characterized on clinical disease course by the Manitoba definition using a one-year lookback window (1). These patients were then linked, using unique identifiers, to Ontario health administrative datasets to ascertain relevant health care utilization variables that would be used to test the performance of the Manitoba model in the Ontario

cohort and to derive new models for comparison. Given differences in variable coding and structure in Ontario and Manitoba administrative datasets, a model using Ontario administrative variables that were analogous to the Manitoba variables was fit to the Ontario cohort. Performance measures from this "adapted model" were compared to those of models derived using unique Ontario administrative variables. Each Ontario model was then used to stratify the Ontario IBD population, identified from the OCCC, annually on disease distribution between 2004 and 2016 (67,68). Disease distribution in the Ontario IBD population using the two-step model was then compared to that of Manitoba.

For each modelling strategy, we tested the proportionality assumption for the overall model using the score test and for each variable using individual score tests from univariate models (using a cut-off of $p < 0.1$), Wald tests from the non-proportional cumulative model (with a cut off of $p < 0.2$), through graphical methods in the form of empirical logit plots and mosaic plots to visualize proportionality, and by examining the differences in the individual odds ratios for each binary split after plotting separate cumulative binary models. PPO logistic regression models were developed using the candidate administrative variables and the models were compared using the c-statistic, Hosmer-Lemeshow goodness of fit test, and simple and weighted kappa, in addition to AIC and BIC statistics. We also generated a cross-tabulation of predicted vs observed disease course. Lastly, we applied the models to the OCCC to stratify predicted disease course in the Ontario IBD population annually between 2004 and 2016 and compared our findings to those from Manitoba. Results were displayed as odds ratios with 95% confidence intervals (CI). All statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

## 3.2 Ethical Considerations and Privacy

This study was approved by the Ottawa Health Sciences Network Research Ethics Board (OHSN-REB), and by ICES Privacy. The clinical cohort from the Ottawa Hospital (TOH) was linked through encrypted unique identifiers to the administrative data at ICES. All cell sizes < 10 were supressed to protect patient privacy.

## 3.3 Study Populations and Data Sources

IBD patients included in our reference cohort were retrospectively identified from the outpatient practices of four gastroenterologists at The Ottawa Hospital, based on the latest encounter during the fiscal year 2015 (April 1, 2015 – March 31, 2016) (index visit). Their clinical disease course, as per the Manitoba definition, was determined through chart review over the preceding year (electronic medical records and outpatient paper charts at the Ottawa Hospital). Individuals without at least one year of follow-up with one of the four gastroenterologists leading up to the index visit were excluded.

Health care utilization variables were obtained by linking the IBD reference cohort from TOH to Ontario health administrative databases housed at ICES using unique encrypted personal identifiers. Specific health administrative databases used in this study included: 1) The Ontario Health Insurance Plan (OHIP) claims database which contains billing claims from health care providers for insured services; 2) The Discharge Abstract Database (DAD) which contains clinical and administrative data and information on patient demographics for each hospitalization; 3) The National Ambulatory Care Reporting System (NACRS) which contains information on emergency department visits and ambulatory care; 4) The Registered Persons Database (RPDB) which collects demographic information

on all Ontario health card holders; and 5) The ICES Physician Database (IPDB) which contains information on physicians such as their demographics, location, and speciality.

We further identified IBD patients in Ontario through the OCCC which is a validated ICES derived cohort of IBD patients living in Ontario (67,68). The algorithms used to derive and validate this cohort for individuals 18-64 years of age have a sensitivity of 76.8% - 92.3%, a specificity of 96.2% - 99.1%, a positive predictive value (PPV) of 81.4% and negative predictive value (NPV) of 95.0% (67). Whereas, the algorithms used to derive and validate this cohort for individuals aged 65 year or older have a sensitivity of 59.3% - 86.4%, a specificity of 98.5% - 98.2%, a positive predictive value (PPV) of 64.0% and negative predictive value (NPV) of 98.2% (67).

We excluded: 1) individuals with missing or invalid unique identifiers as we were not able to link their records to the administrative databases; 2) those lacking continuous OHIP eligibility during the 12 months prior to the index visit date, since their healthcare utilization data that would be needed to ascertain candidate variables would not have been captured within the databases; 3) individuals residing in the South East Local Health Integration Network (LHIN), as many physicians practicing in this region are paid through an alternate funding model and did not submit re-imbursement claims, which were necessary to ascertain certain candidate variables in the OHIP database; and 4) individuals with "IBD type unclassifiable" subtype in the OCCC, which means that their disease phenotype as CD or UC could not be elucidated using health administrative data as disease subtype was one of the categories in the models.

### 3.4 Variable Definitions

We retrieved a combination of diagnostic, procedural, and billing codes from Ontario health administrative data that were analogous to the variables included in the final partial proportional odds regression model (PPO model) in the Manitoba study. Differences in data availability and administrative variable definitions between Ontario and Manitoba precluded directly replicating the Manitoba variables. We used the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10) to identify diagnostic codes, the Canadian Classification of Health Interventions (CCI) for procedural codes, and billing claims to identify ambulatory visits (63–66). Variables from the Manitoba study included in the models include the following (see Table S.1 in the Appendix for full definitions):

1. **Age at IBD diagnosis** in years
2. **Sex,** reported as male versus female
3. **Mean neighbourhood household income quintile**, a measure for socioeconomic status (SES) which ranges from 1-5 as provided through Census Canada reports where 1 represents the lowest and 5 represents the highest income quintile.
4. **Region of residence** as rural versus urban, based on Census population distribution and using an established ICES definition to define rural and urban status
5. **Disease type** as CD vs. UC, based on an established variable within the OCCC
6. **IBD duration** in years
7. **Hospitalizations for non-IBD indications,** which represented the number of hospitalizations within the past year in which the most responsible, comorbid or transfer discharge diagnosis was not UC or CD
8. **Visits to a gastroenterologist for IBD,** which included the number of visits to a gastroenterologist in the preceding year with billing claims for UC or CD

9. **Visits to a gastroenterologist for non-IBD reasons,** which included the number of visits to a gastroenterologist in the preceding year with billing claims other than for UC or CD
10. **Visit to a general practitioner (FP/GP) for IBD,** which included the number of visits to a FP/GP within the past year with a billing claim for UC or CD
11. **Visit to a FP/GP for non-IBD reasons,** which included the number of visits to a FP/GP or a family physician within the past year with a billing claim other than for UC or CD
12. **General radiological procedures,** which included the number of billing codes for over 100 radiological procedures as outlined in the appendix
13. **Endoscopic procedures,** which included the number of billing codes for numerous endoscopic procedures as outlined in the appendix
14. **Gastrointestinal related radiologic procedures** which is a single combined variable with the number of billing codes for US, CT scan, Barium studies, or MRI procedures as outlined in the appendix

Additional variables considered in this study included the following (see Table S.1 in the Appendix):

1. **Emergency department visits for IBD without hospitalization,** which included the number of ED visits within the past year for UC or CD that did not result in a hospital admission
2. **Emergency department visits for a non-IBD indication without hospitalization,** which included the number of ED visits within the past year for anything other than UC or CD that did not result in a hospital admission
3. We also considered **hospitalizations for IBD indications** which represented the number of hospitalizations within the past year in which the most responsible, comorbid or transfer discharge diagnosis was either UC or CD as part of our two-step model.

## 3.5 Objective 1: Identifying and Characterizing a Reference Cohort of IBD Patients from Ontario Based on a Manitoba Definition of Clinical Disease Course

### *3.5.1 Overview*

To meet objective 1, we first identified a reference cohort of IBD patients at The Ottawa Hospital and characterized them on disease course over the preceding year through chart review based on the Manitoba definition. We then linked these patients to their health administrative records at ICES to retrieve similar predictors to those in the final Manitoba model and adapt the variables as closely as possible to the Manitoba variables.

### 3.5.2 *Reference cohort identification, characterization and linkage to administrative records*

We identified individuals that attended the ambulatory IBD clinics of four gastroenterologists practicing at The Ottawa Hospital in fiscal year 2015. We then identified the latest visit for each individual within the study period and assigned it as the index visit. Using the same definition as the Manitoba study, two independent abstractors reviewed the clinical data of each individual for the year preceding the index visit using a chart review (electronic medical records and outpatient paper charts at the Ottawa Hospital) and classified patients by disease course into four distinct categories: remission, mild, moderate, and severe (Table 2.1, above). After applying the pre-defined exclusion criteria, we linked the eligible cohort to Ontario health administrative databases at ICES using unique encrypted identifiers and applied additional administrative exclusion criteria to arrive at our "gold standard" cohort, against which we tested our model's performance.

### *3.5.3 Structuring the Healthcare Utilization Measures*

For our cohort, we retrieved relevant health utilization measures within administrative databases corresponding to the year preceding the index outpatient visit. We structured the predictors as closely as possible to the Manitoba predictors. While the Manitoba study used the socioeconomic factor index (SEFI), we opted for the mean neighbourhood household income quintiles as our measure for SES because it is more commonly used and readily available in Ontario and can be easily obtained through an established ICES macro (1). Furthermore, it is a validated proxy for individual level socioeconomic status (103). For visits to a gastroenterologist for non-IBD reasons, we collapsed two of the three categories together due to small numbers from (0, 1-2, and ≥3 visits) to (0, ≥1 visits). Additionally, several key variables had slight differences in administrative coding definitions as compared to their Manitoba counterparts, including general radiological procedures, endoscopic procedures, and gastrointestinal related radiologic procedures (CT/ MRI/ ultrasound (US), or barium studies) (Table S.2 in the Appendix)

## 3.6 Objective 2: Fitting the Manitoba PPO model to Ontario Health Administrative Data

### *3.6.1 Overview*

There were some differences in variable structure, coding definitions, and data availability for several variables between Manitoba and Ontario. As a result, we were unable to directly apply the original Manitoba model to Ontario data using their exact parameter estimates. Therefore, we opted to develop a new PPO model using the same variables as those used in Manitoba (with slightly different coding definitions for some predictors) using the Ontario data structure to produce an adapted model, rather than directly validate the Manitoba model.

### *3.6.2 Fitting the Adapted PPO Model*

We first tested the overall model, comprising all variables adapted from the Manitoba model, for proportionality using the score test. Our model violated this assumption, indicating that at least one of the variables included in the model was non-proportional. In the Manitoba model, only certain healthcare utilization predictors were tested for proportionality whereas other variables were forced to enter the model as proportional predictors. Following their strategy, we only tested the following healthcare utilization measures for proportionality without examining other variables: visits to gastroenterologist for IBD, visits to a gastroenterologist for non-IBD, visits to a family physician (FP) or general practitioner (GP) for IBD, visits to a FP/GP for non-IBD, hospitalizations for non-IBD, endoscopic procedures, general radiologic procedures, and gastrointestinal related radiologic procedures.

To test the predictors for proportionality we ran individual score tests from univariate models (using a cut-off of $p < 0.1$), examined the Wald tests from the non-proportional cumulative model (with a cut off of $p < 0.2$) and used graphical methods in the form of empirical logit plots and mosaic plots. In addition, we plotted the separate cumulative binary models and examined into individual odds ratios for each binary split to see how much the estimates differed. A summary of proportionality testing is presented in Table S.3, and Figures S.1, S.2, and S.3 in the appendix. Variables that consistently violated the proportionality assumption (i.e. visits to a gastroenterologist for IBD), were entered into the model as non-proportional predictors and the rest were entered as proportional.

We then fit a multivariable PPO model using the adapted Ontario variables. Modeled probabilities were cumulated over the lower ordered values. The model results were reported as odds ratios with 95% confidence intervals (see Table S.1 in the appendix for complete variable definitions).

## 3.7 Objective 3: Developing New PPO Models Using Ontario Health Administrative Variables and Comparing Model Performance Against the Adapted PPO Model

### *3.7.1 Overview*

To evaluate whether more discriminant models could be derived than the adapted Manitoba model, we derived new PPO models in our cohort, under several different strategies, using a set of candidate administrative variable predictors. These included the complete set of adapted predictors included in the adapted Manitoba model as well as additional predictors of potential relevance. The latter included emergency department (ED) visits without hospitalization for IBD-related indications and ED visits without hospitalization for non-IBD indications. We also tested different operational definitions of some variables, including testing age at diagnosis as a continuous variable, testing gastroenterologist visits for IBD as a 3-category variable (0-1, 2-3, ≥4 visits) and testing FP/GP visits for IBD as a 3-category variable (0, 1, ≥2 visits).

We tested all the predictors for proportionality. A summary of proportionality testing is presented in Table S.4 in the appendix. We then derived the following three models: A) Derived Parsimonious PPO model through stepwise selection (Stepwise model); B) Forced fitted full PPO model (All-Variables Model) and C) Derived PPO model through a two-step algorithm using IBD hospitalizations (Two-step model).

### *3.7.2 Derived Parsimonious PPO Model Through Stepwise Selection (Stepwise Model)*

This was a partial proportional odds model that was developed through stepwise automated selection, using a model entry criterion of $p < 0.2$ and a model exit criterion of $p < 0.1$, and pre-specification of

variables as non-proportional or proportional. Modeled probabilities were cumulated over the lower ordered values. The model results were reported as odds ratios with 95% confidence intervals.

### *3.7.3 Forced Fitted Full PPO Model (All-Variables Model)*

This was a partial proportional odds model that included all of the variables from the adapted PPO model along with the two additional identified predictors: ED visits without hospitalization for IBD-related indication and ED visits without hospitalization for non-IBD indication. Modeled probabilities were cumulated over the lower ordered values. The model results were reported as odds ratios (OR) with 95% confidence intervals (CIs).

### *3.7.4 Derived PPO Model Through a Two-Step Algorithm Using IBD hospitalizations (Two-step Model)*

This was a two-step algorithm in which we first categorized all patients within the cohort who had an IBD-related hospitalization within the prior year as having a severe disease course. We then fitted an all-variables model to the remaining individuals (those without an IBD hospitalization) to predict their disease course using their previous year's healthcare administrative data. Because IBD-related hospitalization is identifiable as an administrative variable and, by definition, defines a severe disease course, this strategy allowed us to determine whether overall predicted probability could be refined by excluding these individuals from the model. Modeled probabilities were cumulated over the lower ordered values. The model results were reported as ORs with 95% CIs.

### *3.7.5 Comparing the models*

The adapted and newly derived models were compared in several ways. First, we assessed their discriminative ability based on the c-statistic value (104). We considered c statistic values of 0.5 to 0.7 as having poor discrimination, those 0.7 to 0.8 as acceptable discrimination, those 0.8 to 0.9 as excellent discrimination, and those ≥0.9 as outstanding discrimination (90). For the two-step model, the c-statistic was manually calculated, whereas for the other models it was automatically produced through SAS. We also examined the models' calibration using the Hosmer-Lemeshow goodness-of-fit test and considered non-significant values at $p > 0.05$ as an indication of good model calibration (91). We also calculated the simple and weighted Kappa statistics for each of the observed vs expected disease course categories for our IBD reference cohort considering a value of 1 as perfect agreement, values greater than 0.75 as excellent agreement, those between 0.4 and 0.75 as fair to good agreement, and those less than 0.4 as poor agreement (97). For nested models, we compared their AIC and BIC values with lower values indicating more preferred models.

## 3.8 Objective 4: Applying the Models to the OCCC to Estimate IBD Course in Ontario and Comparing the Distribution to that of the Manitoba IBD Population

In order to apply the models to the Ontario IBD population, we first retrieved the same administrative variables for all individuals in the OCCC for each fiscal year (April 1$^{st}$ to March 31$^{st}$) from 2004-2016. We excluded all data prior to 2004 due to the change in coding from ICD-9 to ICD-10 that was introduced in 2002/2003. At the time of analysis, 2016 was the latest year for which administrative records were available for all of our predictors.

We then applied the same inclusion and exclusion criteria as for our reference cohort. We identified the index visit as the latest visit within each fiscal year and used a one-year look-back period to define predictors. Subsequently, we applied the above models to each individual in the OCCC and obtained their predicted probability for being in each of the four specified disease states (remission, mild, moderate, severe) from 2004-2016. We assigned each individual's disease course based on the category that had the highest predicted probability for each fiscal year from 2004 to 2016 and used this information to estimate the annual predicted percentage of each disease course. We compared our estimates of disease course for the Ontario IBD population to those reported in the Manitoba study for the Manitoba IBD population (1).

# CHAPTER 4: RESULTS

## 4.1 Objective 1: Identifying and Characterizing a Reference Cohort of IBD Patients from Ontario Based on a Manitoba definition of Clinical Disease Course

### *4.1.1 Overview and Descriptive Statistics of Our Reference Cohort*

Our final cohort included 963 of 1038 patients seen at The Ottawa Hospital. Reasons for exclusion were: residence in the South East LHIN (n=39), lack of continuous OHIP eligibility during the preceding year (n=14), "undefined IBD" subtype (n=12), and duplicate records and individuals not found in the OCCC (n =10).

Just over half of the individuals were male 52.3% (n=504) and 64.6% (n=622) of individuals had Crohn's disease. The mean age at IBD diagnosis was 32.7 years (SD=15.3) and the mean disease duration was 11.4 years (SD=6.8). The majority of patients resided in an urban setting (89.2%, n=859). The lowest proportion of patients fell into the first mean neighbourhood household income quintile (11.4% of patients) and the highest proportion were in the fourth- and fifth-income quintiles (25.3% of patients) in each, which was similar to other population-based cohorts of IBD patients in Ontario (105,106). Based on the Manitoba definition of clinical disease course ascertained through chart review, 64.9% (n=625) of patients were in remission, 11.4% (n=110) had a mild disease course, 14.1% (n=136) had a moderate disease course, and 9.6% (n=92) had a severe disease course in the year preceding the index visit.

With regards to healthcare utilization within our reference cohort, only 5% (n= 48) of patients were hospitalized for non-IBD reasons within the past year, 43.2% (n= 416) had an endoscopy, 42.8% (n=

412) had a general radiological procedure, and 39.0% (n= 376) had a gastrointestinal related radiologic procedure in the preceding year. In looking into physician visits, 40.4% (n=389) of the patients had three or more visits to a gastroenterologist for IBD as compared to 59.6% (n=574) with two or less visits. Around 40.5% (n=390) of patients had at least one visit to a gastroenterologist for non-IBD reasons. The majority of patients, 59.7% (n=575) did not have a recorded visit for IBD with their FP/GP within the past year, whereas 30.6% (n=295) of the patients had 1-2 visits to their FP/GP regarding IBD, and 9.7% (n=93) had three or more visits to their FP/GP regarding IBD. Approximately 36.7% (n=353) of patients had less than three visits to their FP/GP for non-IBD reasons, 28.3% (n=272) had three to five visits, and 35.1% (n= 338) had ≥six visits to their FP/GP for non-IBD reasons.

When broken down by disease course, there was no difference with regards to the distribution of IBD severity and gender, area of residence, or age at diagnosis. However, there was a higher percentage of severe disease amongst individuals with a shorter disease duration as compared to those with longer disease duration (17.2% for individuals with IBD for less than 4 years versus 7.2% for those with IBD for more than 15 years). There was also more severe disease among individuals with a greater number of visits to a gastroenterologist or a FP/GP for IBD and for non-IBD indications as compared to those with fewer physician visits. Similarly, there was more severe disease amongst patients with non-IBD hospitalizations and amongst those with at least one endoscopic, general radiologic or gastrointestinal related radiological procedure as compared to those without any of the above. Disease severity also tended to increase as socioeconomic status decreased as only 6.2% of patients in the 5$^{th}$ income quintile had experienced a severe disease course as compared to 22.7% of patients in the 1$^{st}$ income quintile. See Table 4.1 for the descriptive statistics of our cohort, overall and by clinical disease course.

**Table 4.1:** Characteristics of the IBD reference cohort, overall and by disease course

| Characteristic | | Overall Freq (%) | Disease course | | | | P value * |
|---|---|---|---|---|---|---|---|
| | | | Remission % (n=625) | Mild % (n=110) | Moderate % (n=136) | Severe % (n=92) | |
| **Age at diagnosis (years)** | ≤ 20 | 240 (24.9) | 61.3 | 11.7 | 17.5 | 9.6 | 0.46 |
| | 21-34 | 325 (33.8) | 65.2 | 11.1 | 12.3 | 11.4 | |
| | ≥ 35 | 398 (41.3) | 66.8 | 11.6 | 13.6 | 8.0 | |
| **Sex** | Male | 504 (52.3) | 63.5 | 11.9 | 14.5 | 10.1 | 0.80 |
| | Female | 459 (47.7) | 66.5 | 10.9 | 13.7 | 8.9 | |
| **Mean neighbourhood household income quintile** | 1 (poorest) | 110 (11.4) | 52.7 | 10.9 | 13.6 | 22.7 | <0.001 |
| | 2 | 167 (17.3) | 59.3 | 11.4 | 17.4 | 12.0 | |
| | 3 | 198 (20.6) | 64.1 | 12.1 | 15.7 | 8.1 | |
| | 4 | 244 (25.3) | 68.0 | 12.7 | 12.7 | 6.6 | |
| | 5 (richest) | 244 (25.3) | 71.7 | 9.8 | 12.3 | 6.2 | |
| **Area of residence** | Rural | 104 (10.8) | 67.3 | 8.7 | 14.4 | 9.6 | 0.83 |
| | Urban | 859 (89.2) | 64.6 | 11.8 | 14.1 | 9.6 | |
| **Disease type** | UC | 341 (35.4) | 69.5 | 9.4 | 14.4 | 6.7 | 0.05 |
| | CD | 622 (64.6) | 62.4 | 12.5 | 14.0 | 11.1 | |
| **Disease duration (years)** | ≤ 4 | 151 (15.7) | 53.6 | 15.2 | 13.9 | 17.2 | 0.002 |
| | 5-9 | 297 (30.8) | 69.0 | 11.8 | 11.1 | 8.1 | |
| | 10-14 | 223 (23.2) | 69.5 | 8.5 | 12.6 | 9.4 | |
| | ≥ 15 | 292 (30.3) | 63.0 | 11.3 | 18.5 | 7.2 | |
| **Visits to a Gastroenterologist for IBD** | 0-2 | 574 (59.6) | 80.7 | 6.8 | 9.8 | 2.8 | <0.000 |
| | ≥ 3 | 389 (40.4) | 41.7 | 18.3 | 20.6 | 19.5 | |
| **Visits to a Gastroenterologist for non-IBD** | 0 | 573 (59.5) | 74.0 | 8.6 | 10.8 | 6.6 | <0.000 |
| | ≥ 1 | 390 (40.5) | 51.5 | 15.6 | 19.0 | 13.8 | |
| **Visits to a FP/GP for IBD** | 0 | 575 (59.7 | 73.2 | 11.8 | 10.6 | 4.4 | <0.000 |
| | 1-2 | 295 (30.6) | 59.3 | 9.8 | 18.0 | 12.9 | |
| | ≥ 3 | 93 (9.7) | 31.2 | 14.0 | 23.7 | 31.2 | |
| **Visits to a FP/GP for non-IBD** | 0-2 | 353 (36.7) | 68.6 | 9.9 | 15.0 | 6.5 | 0.008 |
| | 3-5 | 272 (28.3) | 68.8 | 11.0 | 12.1 | 8.1 | |
| | ≥ 6 | 338 (35.1) | 58.0 | 13.3 | 14.8 | 13.9 | |
| **Hospitalizations for non-IBD** | 0 | 915 (95.0) | 65.9 | 11.4 | 13.9 | 8.9 | 0.004 |
| | ≥ 1 | 48 (5.0) | 45.8 | 12.5 | 18.8 | 22.9 | |
| **Endoscopic procedures** | 0 | 547 (56.8) | 75.9 | 9.0 | 9.7 | 5.5 | <0.000 |
| | ≥ 1 | 416 (43.2) | 50.5 | 14.7 | 20.0 | 14.9 | |
| **General radiologic procedures** | 0 | 551 (57.2) | 72.8 | 12.0 | 11.4 | 3.8 | <0.000 |
| | ≥ 1 | 412 (42.8) | 54.4 | 10.7 | 17.7 | 17.2 | |
| **Gastrointestinal Related radiologic procedures** | 0 | 587 (61.0) | 75.0 | 10.9 | 10.4 | 3.8 | <0.000 |
| | ≥ 1 | 376 (39.0) | 49.2 | 12.2 | 20.0 | 18.6 | |

IBD = inflammatory bowel disease; FP/GP = family physician/general practitioner; CD = Crohn's disease; UC = ulcerative colitis; n= number of visits. *P-values were obtained from $\chi 2$ test of each individual predictor against disease course.

### *4.1.2 Comparison of Our IBD Reference Cohort to the Manitoba IBD Reference Cohort*

In comparing our IBD reference cohort from Ontario to the Manitoba reference cohort, the Ontario cohort had an overall higher percentage of patients in remission, and lower percentage of patients with clinically severe, moderate, and mild IBD course as compared to Manitoba (see Table 4.2 below).

**Table 4.2:** Disease course status in Ontario vs Manitoba reference cohorts based on clinical definition

| **Disease course status** | **Ontario reference cohort (n=963)** Frequency (%) | **Manitoba reference cohort (n=407)** Frequency (%) |
|---|---|---|
| Remission | 625 (64.9) | 167 (41.0) |
| Mild | 110 (11.4) | 104 (25.6) |
| Moderate | 136 (14.1) | 79 (19.4) |
| Severe | 92 (9.6) | 57 (14.0) |

In looking into healthcare utilization factors, there were substantial differences between the two reference cohorts with a considerably higher percentage of patients receiving procedural and/or imaging studies in Manitoba as compared to Ontario (85.5% vs 43.2% for endoscopic procedures, 66.3% vs 42.8% for general radiologic procedures, and 83.8% vs 39% for gastrointestinal related radiologic procedures, for Manitoba vs Ontario respectively). Similarly, non-IBD hospitalizations, which were defined in the Manitoba study as not having an IBD diagnosis within the first 3 diagnoses fields of the discharge summary, were higher in Manitoba as compared to Ontario, (12% vs 5%, respectively). Conversely, the number of visits to a gastroenterologist for IBD were comparable among the two cohorts and there were only minor differences with regards to the number of FP/GP visits for IBD. As for the sociodemographic and disease characterizing factors, the mean age at diagnosis, mean disease duration, and disease type were similar between the Ontario and Manitoba clinical cohorts. However, the Ontario reference cohort had slightly higher male patients than Manitoba (52.3% vs 45.7%, respectively), and a higher urban population than in Manitoba (89.2% vs 67.6%, respectively). See Table 4.3 for a comparison of the descriptive characteristics between the two reference cohorts.

**Table 4.3:** Descriptive characteristics of the Ontario and Manitoba reference cohorts

| Characteristic | | Ontario cohort [n=963] | Manitoba cohort [n=407] |
|---|---|---|---|
| | | Percentage, % | Percentage, % |
| **Age at diagnosis (years)** | ≤ 20 | 24.9 | 30.7 |
| | 21-34 | 33.8 | 36.9 |
| | ≥ 35 | 41.3 | 32.4 |
| **Sex** | Male | 52.3 | 45.7 |
| | Female | 47.7 | 54.3 |
| **Mean Neighbourhood Household Income Quintile** | 1 | 11.4 | 32.7 (low) |
| | 2 | 17.3 | |
| | 3 | 20.6 | 34.4 (middle) |
| | 4 | 25.3 | |
| | 5 | 25.3 | 32.9 (high) |
| **Area of residence** | Rural | 10.8 | 32.4 |
| | Urban | 89.2 | 67.6 |
| **Disease type** | UC | 35.4 | 35.6 |
| | CD | 64.6 | 63.4 |
| **Disease duration (years)** | ≤ 4 | 15.7 | 23.8 |
| | 5-9 | 30.8 | 25.5 |
| | 10-14 | 23.2 | 20.0 |
| | ≥ 15 | 30.3 | 30.7 |
| **Visits to a Gastroenterologist for IBD** (n) | 0-2 | 59.6 | 57.7 |
| | ≥ 3 | 40.4 | 42.3 |
| **Visits to a Gastroenterologist for non-IBD** (n) | 0 | 59.5 | 58.5 (0 visit) |
| | ≥ 1 | 40.5 | 24.8 (1-2 visits) |
| | | | 16.7 (>=3 visits) |
| **Visits to a FP/GP for IBD** (n) | 0 | 59.7 | 61.7 |
| | 1-2 | 30.6 | 22.1 |
| | ≥ 3 | 9.7 | 16.2 |
| **Visits to a FP/GP for non-IBD** (n) | 0-2 | 36.7 | 27.5 |
| | 3-5 | 28.3 | 39.1 |
| | ≥ 6 | 35.1 | 33.4 |
| **Hospitalizations for non-IBD** (n) | 0 | 95.0 | 88.0 |
| | ≥ 1 | 5.0 | 12.0 |
| **Endoscopic procedures** (n) | 0 | 56.8 | 14.5 |
| | ≥ 1 | 43.2 | 85.5 |
| **General radiologic procedures** (n) | 0 | 57.2 | 33.7 |
| | ≥ 1 | 42.8 | 66.3 |
| **Gastrointestinal related radiologic procedures** (n) | 0 | 61.0 | 16.2 |
| | ≥ 1 | 39.0 | 83.8 |

IBD = inflammatory bowel disease; FP/GP = general practitioner/ family physician; CD = Crohn's disease; UC = ulcerative colitis; n= number of visits. *P-values were obtained from $\chi 2$ test of each individual predictor against disease course

## 4.2 Objective 2: Fitting the Manitoba PPO model to Ontario Health Administrative Data

Our first model, the adapted model, contained a total of fourteen predictors encompassing healthcare utilization measures and socio-demographic characteristics (Table 4.4).

**Table 4.4:** The adapted model

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Visit to a gastroenterologist for IBD†** | 0-2 | *Ref* | *Ref* | *Ref* |
| | ≥3 | **4.34*** (3.11- 6.07)** | **3.05*** (2.13- 4.38)** | **4.58*** (2.53- 8.27)** |
| **Visit to a gastroenterologist for non-IBD** | 0 | *Ref* | *Ref* | *Ref* |
| | ≥1 | 0.71 (0.44- 1.14) | 0.71 (0.44- 1.14) | 0.71 (0.44- 1.14) |
| **Visit to a FP/GP for IBD†** | 0 | *Ref* | *Ref* | *Ref* |
| | 1-2 | **1.90*** (1.37- 2.66)** | **2.57*** (1.78- 3.71)** | **2.97*** (1.71- 5.16)** |
| | ≥3 | **3.24*** (1.87- 5.63)** | **3.25*** (1.90- 5.55)** | **3.97*** (2.07- 7.60)** |
| **Visit to a FP/GP for non-IBD** | 0-2 | *Ref* | *Ref* | *Ref* |
| | 3-5 | 0.78 (0.54- 1.13) | 0.78 (0.54- 1.13) | 0.78 (0.54- 1.13) |
| | ≥6 | 0.87 (0.61- 1.28) | 0.87 (0.61- 1.28) | 0.87 (0.61- 1.28) |
| **Hospitalization for non-IBD** | 0 | *Ref* | *Ref* | *Ref* |
| | ≥1 | 1.26 (0.67- 2.34) | 1.26 (0.67- 2.34) | 1.26 (0.67- 2.34) |
| **Endoscopic procedures** | 0 | *Ref* | *Ref* | *Ref* |
| | ≥1 | **1.80* (1.11- 2.91)** | **1.80* (1.11- 2.91)** | **1.80* (1.11- 2.91)** |
| **General radiologic procedures†** | 0 | *Ref* | *Ref* | *Ref* |
| | ≥1 | **1.59** (1.15- 2.21)** | **2.17*** (1.51- 3.11)** | **3.02*** (1.74- 5.24)** |
| **Gastrointestinal related radiologic procedures** | 0 | *Ref* | *Ref* | *Ref* |
| | ≥1 | **1.82*** (1.32- 2.50)** | **1.82*** (1.32- 2.50)** | **1.82*** (1.32- 2.50)** |
| **Sex** | Male | *Ref* | *Ref* | *Ref* |
| | Female | 1.24 (0.93- 1.66) | 1.24 (0.93- 1.66) | 1.24 (0.93- 1.66) |
| **Age at diagnosis** | ≤ 20 | *Ref* | *Ref* | *Ref* |
| | 21-34 | 0.85 (0.59- 1.24) | 0.85 (0.59- 1.24) | 0.85 (0.59- 1.24) |
| | ≥ 35 | **0.67* (0.46- 0.97)** | **0.67* (0.46- 0.97)** | **0.67* (0.46- 0.97)** |
| **Disease Duration** | ≤ 4 | *Ref* | *Ref* | *Ref* |
| | 5-9 | 0.71 (0.46- 1.09) | 0.71 (0.46- 1.09) | 0.71 (0.46- 1.09) |
| | 10-14 | 0.80 (0.51- 1.27) | 0.80 (0.51- 1.27) | 0.80 (0.51- 1.27) |
| | ≥ 15 | 0.79 (0.51- 1.20) | 0.79 (0.51- 1.20) | 0.79 (0.51- 1.20) |

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Disease type** | UC | *Ref* | *Ref* | *Ref* |
| | CD | 0.85 (0.62- 1.16) | 0.85 (0.62- 1.16) | 0.85 (0.62- 1.16) |
| **Location of residence** | Rural | *Ref* | *Ref* | *Ref* |
| | Urban | 1.28 (0.79- 2.09) | 1.28 (0.79- 2.09) | 1.28 (0.79- 2.09) |
| **Mean neighborhood household income quintile** | 1 | **1.99** (1.20- 3.29)** | **1.99** (1.20- 3.29)** | **1.99** (1.20- 3.29)** |
| | 2 | 1.41 (0.90- 2.22) | 1.41 (0.90- 2.22) | 1.41 (0.90- 2.22) |
| | 3 | 1.24 (0.81- 1.90) | 1.24 (0.81- 1.90) | 1.24 (0.81- 1.90) |
| | 4 | 1.10 (0.73- 1.67) | 1.10 (0.73- 1.67) | 1.10 (0.73- 1.67) |
| | 5 | *Ref* | *Ref* | *Ref* |

This model adjusted for sex, age at diagnosis, disease duration, disease type, location of residence, and Mean neighborhood household income quintile**.** IBD = inflammatory bowel disease; FP/GP = general practitioner/ family physician; gastrointestinal related radiologic procedures include US/CT/barium or MRI studies reported as a single combined variable because of small cell sizes in each procedure, visits to a gastroenterologist for non-IBD was recoded into a binary variable due to small cell sizes. **p-values from Wald $\chi 2$ test [*p<0.05, **p < 0.01, ***p < 0.001].** † non-proportional predictor
c-statistic = 0.7664**.** Hosmer and Lemeshow Goodness-of-Fit Test p value= 0.2760

All 963 patients from our reference cohort were used to develop the adapted PPO model using a one-year look-back period in administrative health data (Table 4.4). In this model, the proportional odds assumption was violated by three variables (visits to a gastroenterologist for IBD, visit to a FP/GP for IBD, and general radiologic procedures). For these variables, separate odds ratios were obtained for each of the three splits (mild/moderate/severe vs remission, moderate/severe vs remission/mild, and severe vs remission/mild/moderate) whereas for the rest of the variables the odds ratio was constant across the different splits. The c-statistic for the model was 0.7664. indicating an acceptable model discriminatory capacity. The Hosmer-Lemeshow test p-value was 0.2, which was not significant, confirming good model calibration.

The adapted model demonstrated that IBD patients with one or more endoscopic procedures over the past year had 1.8 times greater odds of having a more severe disease course as compared to patients with no endoscopic procedures over the past year (95% CI 1.11-2.91). Similarly, patients with at least one

gastrointestinal related radiologic procedure within the past year had 1.82 greater odds of being in a higher disease course category in comparison to those without any of those procedures over the past year.

Individuals with ≥3 visits to a gastroenterologist for IBD had approximately three to four times higher odds of having a more severe disease course as compared to those with 0-2 visits in the last year. In addition, individuals with more visits to a FP/GP for IBD and those with more than one general radiological procedure had significantly higher odds of having a more severe disease course compared to those with no FP/GP visits for IBD and those with no general radiological procedures in the past year, respectively. However, there was no statistically significant effect of the number of visits to gastroenterologists for a non-IBD indication, the number of visits to a FP/GP for non-IBD reasons, and hospitalizations for non-IBD reasons on disease course in IBD patients.

## 4.3 Objective 3: Developing New PPO Models Using Ontario Health Administrative Variables and Comparing Model Performance Against the Adapted PPO Model

### *4.3.1 Overview*

Before developing the new PPO models, we first identified additional predictors of interest and then carried out an exploratory data analysis of all the variables to find the most useful way to operationalize them. Additional predictors that we identified were emergency department (ED) visits without a hospitalization for IBD-related indications and ED visits without a hospitalization for non-IBD indications. Within our reference cohort 6.2% (n=60) of the patients had at least one ED visit for IBD without a matching admission, and 26.1% (n=251) had at least one ED visit for non-IBD without being admitted. We also tested different operational definitions of some variables. As a result of our

exploratory data analysis, we included age as a continuous variable and changed the categorization of FP/GP visits for IBD from a two-level variable (0-2, ≥3 visits) to a three-level variable (0-1, 2-3, ≥4 visits) and of gastroenterologists visits for IBD from (0, 1-2, ≥3 visits) to (0, 1, ≥2 visits). Consequently, the mean age at IBD diagnosis was 32.7 years (SD=15.3), 17.9% (n=172) of patients had two or more visits to a FP/GP for IBD, 22.4% (n=216) of patients had one FP/GP visit for IBD and 59.7% (n=575) of patients did not have a FP/GP visit for IBD. Also, about a third of patients had each of 1 visit, 2-3 visits, and ≥4 visits to a gastroenterologist for IBD, respectively.

### 4.3.2 *Derived Parsimonious PPO Model Through Stepwise Selection (Stepwise Model)*

The stepwise model (Table 4.5) included nine out of the sixteen variables that were considered for entry, two of which entered the model as non-proportional (visits to a gastroenterologist for IBD and general radiological procedures) and the rest were proportional. This model had a c-statistic of 0.7664 indicating an acceptable discriminatory capacity and a Hosmer Lemeshow test of p=0.5030 which was not significant, confirming good calibration.

**Table 4.5:** Derived Parsimonious PPO model through stepwise selection (Stepwise model)

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Visit to a gastroenterologist for IBD†** | 0-1 | Ref | Ref | Ref |
| | 2-3 | **2.52*** (1.64-3.88)** | **1.66* (1.02- 2.72)** | **1.81 (0.75-4.36)** |
| | ≥4 | **5.86**** (3.82- 9.00)** | **3.57**** (2.25- 5.67)** | **4.93**** (2.26- 10.80)** |
| **Visit to a FP/GP for IBD** | 0 | Ref | Ref | Ref |
| | 1 | **1.97*** (1.37- 2.85)** | **1.97*** (1.37- 2.85)** | **1.97*** (1.37- 2.85)** |
| | ≥2 | **2.76**** (1.90- 4.01)** | **2.76**** (1.90- 4.01)** | **2.76**** (1.90- 4.01)** |
| **Endoscopic procedures** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.49* (1.10- 2.01)** | **1.49* (1.10- 2.01)** | **1.49* (1.10- 2.01)** |
| **General radiologic procedures†** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.54** (1.12- 2.12)** | **2.12**** (1.49- 3.02)** | **3.11**** (1.81- 5.35)** |

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Gastrointestinal related radiologic procedures** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.73*** (1.27- 2.35)** | **1.73*** (1.27- 2.35)** | **1.73*** (1.27- 2.35)** |
| **ED visits without hospitalization for IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.84* (1.09- 3.13)** | **1.84* (1.09- 3.13)** | **1.84* (1.09- 3.13)** |

This model adjusted for age at diagnosis, sex, and mean neighborhood household income quintile
IBD = inflammatory bowel disease; FP/GP = general practitioner/ family physician; CD = Crohn's disease; UC = ulcerative colitis**. p-values from Wald χ2 test [**p < 0.01, ***p < 0.001, ****p < 0.0001]**. † non-proportional predictor**.** c-statistic = 0.7664. Hosmer-Lemeshow Goodness-of-Fit Test p value= 0.5030

This model demonstrated that individuals with four or more visits to a gastroenterologist for IBD had 3.57 to 5.86 higher odds of being in a more severe disease course as compared to those with 0-1 visit to a gastroenterologist for IBD in the preceding year. However, a similar effect was not consistently observed when comparing individuals with 2-3 gastroenterologists visits for IBD versus those with 0-1 visits. Furthermore, individuals with two or more FP/GP visits for IBD and those with one visit had a 2.76 (95% CI 1.90-4.01) and a 1.97 (95% CI 1.37-2.85) higher odds of having a more severe disease course as compared to those without any FP/GP visits for IBD in the past year, respectively.

### *4.3.3 Forced Fitted Full PPO Model (All-Variables Model)*

The all-variables model (Table 4.6) included a total of 16 predictors: all 11 variables from the adapted model, 3 restructured variables, and 2 new variables. Visits to a gastroenterologist for IBD and general radiological procedures were entered as non-proportional and the remaining variables were included as proportional. This model had a c-statistic of 0.770 indicating an acceptable discriminatory capacity and a Hosmer-Lemeshow Goodness-of-Fit Test p-value of 0.5315, which was not significant confirming good model calibration.

The all-variables model demonstrated that there was no statistically significant difference with regards to disease course in IBD patients and the number of visits to gastroenterologists for non-IBD reasons, the number of visits to a FP/GP for non-IBD reasons, non-IBD hospitalizations and non-IBD ED visits. However, IBD patients with ≥2 gastroenterologist visits for IBD had greater odds of having a more severe disease course than those with 0-1 visits. Likewise, individuals with a higher number of FP/GP visits for IBD and those with at least 1 ED for IBD in the past year had a greater odds of having a more severe disease course. Moreover, patients with at least 1 endoscopic or general radiologic procedure, or gastrointestinal related radiologic procedures in the preceding year had a greater odds of having a worse disease course in comparison to those without any of those procedures over the past year.

**Table 4.6:** All-variables model

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Visit to a gastroenterologist for IBD†** | 0-1 | Ref | Ref | Ref |
| | 2-3 | **2.52**** **(1.63-3.89)** | **1.65* (1.01-2.70)** | 1.79 (0.74-4.35) |
| | ≥4 | **6.00**** **(3.89-9.26)** | **3.61**** **(2.26-5.76)** | **4.89**** **(2.22-10.75)** |
| **Visit to a gastroenterologist for non-IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | 0.74 (0.46-1.20) | 0.74 (0.46-1.20) | 0.74 (0.46-1.20) |
| **Visit to a FP/GP for IBD** | 0 | Ref | Ref | Ref |
| | 1 | **2.06*** **(1.42-2.98)** | **2.06*** **(1.42-2.98)** | **2.06*** **(1.42-2.98)** |
| | ≥2 | **2.98**** **(2.04-4.37)** | **2.98**** **(2.04-4.37)** | **2.98**** **(2.04-4.37)** |
| **Visit to a FP/GP for non-IBD** | 0 | Ref | Ref | Ref |
| | 3-5 | 0.82 (0.56-1.20) | 0.82 (0.56-1.20) | 0.82 (0.56-1.20) |
| | ≥ 6 | 0.93 (0.64-1.36) | 0.93 (0.64-1.36) | 0.93 (0.64-1.36) |
| **Hospitalization for non-IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | 1.23 (0.65-2.32) | 1.23 (0.65-2.32) | 1.23 (0.65-2.32) |
| **Endoscopic procedures** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.77* (1.09-2.87)** | **1.77* (1.09-2.87)** | **1.77* (1.09-2.87)** |
| **General radiologic procedures†** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.61** (1.15-2.25)** | **2.19**** **(1.52-3.17)** | **3.12**** **(1.79-5.45)** |
| **Gastrointestinal related radiologic procedures** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.78*** **(1.29-2.45)** | **1.78*** **(1.29-2.45)** | **1.78*** **(1.29-2.45)** |
| **ED visits without hospitalization for IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.83* (1.07-3.14)** | **1.83* (1.07-3.14)** | **1.83* (1.07-3.14)** |

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **ED visits without hospitalization for non IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | 0.96 (0.68-1.36) | 0.96 (0.68-1.36) | 0.96 (0.68-1.36) |

This model adjusted for sex, age at diagnosis, disease duration, disease type, location of residence, and mean neighborhood household income quintile**.** IBD = inflammatory bowel disease; FP/GP = general practitioner/ family physician; **p-values from Wald χ2 test [**p < 0.01, ***p < 0.001].** † non-proportional predictor
c-statistic = 0.770
Hosmer and Lemeshow Goodness-of-Fit Test p value= 0.5315

### *4.3.4 Derived PPO model through a two-step algorithm using IBD hospitalizations (Two-step model)*

The two-step model (Table 4.7) first identified and categorized all patients with an IBD-related hospitalization as having a severe disease course. This included a total of 89 individuals within our reference cohort. We then fitted the all-variables model to the remaining individuals (those without an IBD hospitalization). This model had a c-statistic of 0.7841 indicating acceptable discrimination and a Hosmer-Lemeshow Goodness-of-Fit Test p-value of 0.7516 which was not significant confirming a good calibration.

The two-step model demonstrated that IBD patients with ≥4 gastroenterologist visits for IBD in the preceding year had a significantly higher odds of experiencing a more severe disease course than those with 0-1 visits (odds ratio ranging from 3.41 to 5.89). Furthermore, individuals with one FP/GP visit for IBD had a greater odds of having a mild, moderate, or severe disease course versus remission than those with no FP/GP visits for IBD (OR 2.04, 95% CI 1.38-3.01). Similarly, IBD patient with ≥2 FP/GP visits for IBD had a 2.35 (95% CI 1.52-3.63) odd of having a higher disease course than those with no visits, and individuals with ≥1 ED visits for IBD had a 2.13 (95% CI 1.15-3.95) greater odds of experiencing a more severe course than those without ED visits for IBD in the prior year. There was no difference with

regards to disease course category and visits to a gastroenterologist for non-IBD reasons, visits to a FP/GP for non-IBD reasons, non-IBD hospitalizations, non-IBD ED visits, and gastrointestinal related radiologic procedures. There were marginally significant results with regards to having endoscopic or general radiologic procedures and the odds of having a more severe disease course.

**Table 4.7:** Two-step model

| | *Number of visits* | *Mild/ moderate/ severe vs remission OR (95% CI)* | *moderate/ severe vs remission/ mild OR (95% CI)* | *Severe vs remission/ mild/ moderate OR (95% CI)* |
|---|---|---|---|---|
| **Visit to a gastroenterologist for IBD†** | 0-1 | Ref | Ref | Ref |
| | 2-3 | **2.59**** (1.65-4.08)** | 1.67 (0.98-2.87) | 2.20 (0.66-7.34) |
| | ≥4 | **5.89**** (3.71-9.36)** | **3.41**** (2.03-5.73)** | **4.01* (1.32-12.22)** |
| **Visits to a gastroenterologist for non-IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | 0.81 (0.47-1.39) | 0.81 (0.47-1.39) | 0.81 (0.47-1.39) |
| **Visits to a FP/GP for IBD** | 0 | Ref | Ref | Ref |
| | 1 | **2.04*** (1.38-3.01)** | **2.04*** (1.38-3.01)** | **2.04*** (1.38-3.01)** |
| | ≥2 | **2.35*** (1.52-3.63)** | **2.35*** (1.52-3.63)** | **2.35*** (1.52-3.63)** |
| **Visits to a FP/GP for non-IBD** | 0-2 | Ref | Ref | Ref |
| | 3-5 | 0.87 (0.58-1.29) | 0.87 (0.58-1.29) | 0.87 (0.58-1.29) |
| | ≥ 6 | 0.94 (0.63-1.41) | 0.94 (0.63-1.41) | 0.94 (0.63-1.41) |
| **Hospitalization for non-IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | 1.45 (0.69-3.05) | 1.45 (0.69-3.05) | 1.45 (0.69-3.05) |
| **Endoscopic procedures** | 0 | Ref | Ref | Ref |
| | ≥1 | **1.75* (1.01-3.05)** | **1.75* (1.01-3.05)** | **1.75* (1.01-3.05)** |
| **General radiologic procedures†** | 0 | Ref | Ref | Ref |
| | ≥1 | 1.32 (0.92-1.89) | **1.63* (1.08-2.46)** | 1.71 (0.81-3.59) |
| **Gastrointestinal related radiologic procedures** | 0 | Ref | Ref | Ref |
| | ≥1 | 1.35 (0.96-1.90) | 1.35 (0.96-1.90) | 1.35 (0.96-1.90) |
| **ED visits without hospitalization for IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | **2.13* (1.15-3.95)** | **2.13* (1.15-3.95)** | **2.13* (1.15-3.95)** |
| **ED visits without hospitalization for non IBD** | 0 | Ref | Ref | Ref |
| | ≥1 | 1.11 (0.76-1.62) | 1.11 (0.76-1.62) | 1.11 (0.76-1.62) |

This model adjusted for sex, age at diagnosis, disease duration, disease type, location of residence, and mean neighborhood household income quintile**.** IBD = inflammatory bowel disease; FP/GP = general practitioner/ family physician; **p-values from Wald $\chi 2$ test [**p < 0.01, ***p < 0.001].** † non-proportional predictor. c-statistic = 0.7841. Hosmer and Lemeshow Goodness-of-Fit Test p value= 0.7516

### *4.3.5 Comparing the Models*

#### *4.3.5.1 Comparing the Structure of the Models*

The main differences with regards to the included predictors are presented in Figure 4.1 and Table 4.8.

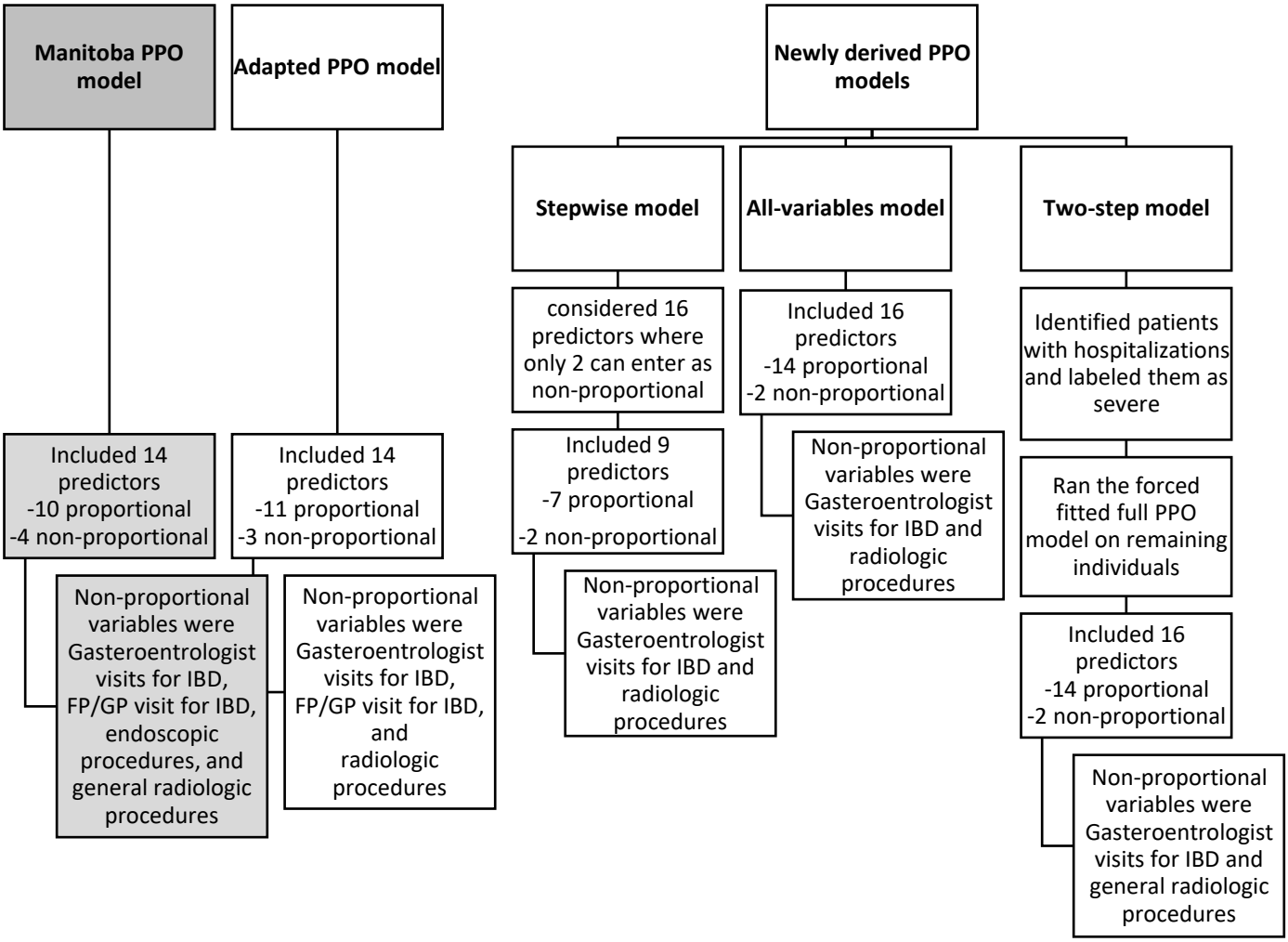



**Figure 4.1**: A Comparison of the structure of the models

**Table 4.8:** Comparison between the original Manitoba model and the adapted and three derived models

| | Manitoba PPO model $ | Adapted model | Stepwise model | All-variables model | Two step model |
|---|---|---|---|---|---|
| **Visits to a gastroenterologist for IBD** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Visits to a gastroenterologist for non-IBD** | ✓ | ✓ | × | ✓ | ✓ |
| **Visits to a FP/GP for IBD** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Visits to a FP/GP for non-IBD** | ✓ | ✓ | × | ✓ | ✓ |
| **Non-IBD Hospitalization** | ✓ | ✓ | × | ✓ | ✓ |
| **Endoscopic procedures** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **General radiologic procedures** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Gastrointestinal related radiologic procedures** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Age at diagnosis (years)** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Disease duration (years)** | ✓ | ✓ | × | ✓ | ✓ |
| **Disease type** | ✓ | ✓ | × | ✓ | ✓ |
| **Sex** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Location of residence** | ✓ | ✓ | × | ✓ | ✓ |
| **Socioeconomic status** (Mean neighborhood household income quintile) | ✓ | ✓ | ✓ | ✓ | ✓ |
| **ED visits without hospitalization for IBD** | | | ✓ | ✓ | ✓ |
| **ED visits without hospitalization for non-IBD** | | | × | ✓ | ✓ |

$This is the actual model that was used by Melesse et al. in the original Manitoba study

**✓ = variable retained in final model** **× = variable not retained in final model**

### *4.3.5.2 Comparing the Performance Characteristics of the Models*

A comparison of the performance of the four models from our study is presented in Table 4.9. Overall, the four models had a similar acceptable discriminative capacity with very minor variations in the actual value of the c-statistic. All models had a non-significant Hosmer-Lemeshow Goodness-of-Fit Test with $p > 0.05$ which indicated a good fit. In the two nested models, the stepwise model and the all-variables model, the stepwise model had lower AIC and BIC values, without sacrificing discriminatory capacity. With regards to the weighted Kappa, it was also very similar between the adapted model, the stepwise model and the all-variables model and it was even lower in the two-step model.

**Table 4.9:** Comparing the performance characteristics of the four models

| | Adapted model | Stepwise model | All-variables model | Two step model |
|---|---|---|---|---|
| **c-statistic** | **0.7657** | **0.7664** | **0.770** | **0.7841** |
| **Hosmer-Lemeshow Goodness-of-Fit Test p value** | 0.2760 | 0.5030 | 0.5315 | 0.7516 |
| **AIC intercept only** | | 1988.176 | 1988.176 | |
| **AIC Intercept and covariates** | | **1713.415** | **1722.453** | |
| **BIC intercept only** | | 2002.787 | 2002.787 | |
| **BIC intercept and covariates** | | **1825.427** | **1883.165** | |
| **Simple Kappa (95% CI)** | **0.2354** (0.1884-0.2824) | **0.2337** (0.1865-0.2809) | **0.2412** (0.1941-0.2883) | **0.1548** (0.1078-0.2017) |
| **Weighted Kappa (95% CI)** | **0.4083** (0.3386-0.478) | **0.4050** (0.3346-0.4753) | **0.4117** (0.3418-0.4815) | **0.2542** (0.1833-0.3252) |

#### *4.3.5.3 Comparing the Models by Cross-Tabulating the Observed and Predicted Disease Course States*

We applied the models to our reference cohort and obtained predicted disease course for each individual within our cohort by assigning the disease state with the highest predicted probability as the predicted course for each individual. We then compared the performance of the four models (the adapted model and all three newly derived models) by cross-tabulating the observed clinical disease course obtained through chart review and the predicted disease course as assigned by the models (Table 4.10 below). The cross-tabulations showed that the overall distribution of the different disease course categories was comparable across all models with remission being predicted far more than any other categories across the different modelling strategies. Moreover, all models fairly accurately classified individuals observed to be in remission. However, despite the acceptable c statistic across the models which ranged from

0.7657 to 0.7841, cross-tabulating observed and predicted disease course states showed that all four models performed very poorly with regards to predicting more active disease states. In fact, all individuals that met our clinical definition of mild disease course were misclassified by the models into other disease course categories (83.6-87.3% of the patients with clinically mild disease were misclassified as remission and 12.7-16.4% were misclassified to either a moderate or severe disease course). Similarly, the models misclassified many individuals observed to have moderate-to-severe disease as being in remission (53.5 - 67.1%). Therefore, our c-statistic might have possibly been heavily weighted by the accurate classification of patients within remission, which comprised the majority of our cohort.

**Table 4.10** Cross tabulating the observed and predicted disease course states frequencies from 4 models in our reference cohort of 963 IBD patients

| | | Predicted disease course | | | |
|---|---|---|---|---|---|
| | | **Remission** | **Mild** | **Moderate or Severe*** | **Total** |
| **Observed disease course** | ***Adapted model*** | | | | |
| | Remission | 605 | 0 | 20 | 625 |
| | Mild | 96 | 0 | 14 | 110 |
| | Moderate | 105 | 0 | 31 | 136 |
| | Severe | 45 | 0 | 47 | 92 |
| | ***Stepwise model*** | | | | |
| | Remission | 606 | 0 | 19 | 625 |
| | Mild | 96 | 0 | 14 | 110 |
| | Moderate | 109 | 0 | 27 | 136 |
| | Severe | 44 | 0 | 48 | 92 |
| | ***All-variables model*** | | | | |
| | Remission | 606 | 0 | 19 | 625 |
| | Mild | 93 | 0 | 17 | 110 |

| | Predicted disease course | | | |
|---|---|---|---|---|
| | **Remission** | **Mild** | **Moderate or Severe*** | **Total** |
| Moderate | 107 | 0 | 29 | 136 |
| Severe | 44 | 0 | 48 | 92 |
| ***Two-step model*** | | | | |
| Remission | 596 | 0 | 29 | 625 |
| Mild | 92 | 0 | 18 | 110 |
| Moderate | 100 | 0 | 36 | 136 |
| Severe | 22 | 0 | 70 | 92 |

* Rates for moderate and severe disease are reported together due to small numbers

## 4.4 Objective 4: Applying the Models to the OCCC to Estimate IBD Course in Ontario and Comparing the Distribution to That of the Manitoba IBD Population

### *4.4.1 Applying the Models to the Ontario Crohn's and Colitis Cohort*

To estimate the course of IBD at a population level, we applied our models (the adapted model, and the three derived models) to a total of 82,483 patients in the OCCC in 2016. After applying the above noted exclusion criteria, we then assigned the highest predicted probability of being in each of the four disease course categories as the predicted disease course for each individual within the OCCC. Subsequently, we extended the models to estimate disease course for each fiscal year from 2004 to 2016 (see Figure 4.2 and Figure 4.3).

According to our models, the estimated percentages of individuals in remission, moderate, and severe disease course categories have largely remained uniform from 2004 to 2016 with minor variations each year. Overall, across all models from 2004 to 2016, 89.2% to 95.7% of the IBD population were in remission, 0.8-3.2% had a moderate disease course, and 3.4-8.4% had a severe disease course

(Figure 4.2 and Figure 4.3). However, all models failed to classify any of the individual within the OCCC to a mild disease course.

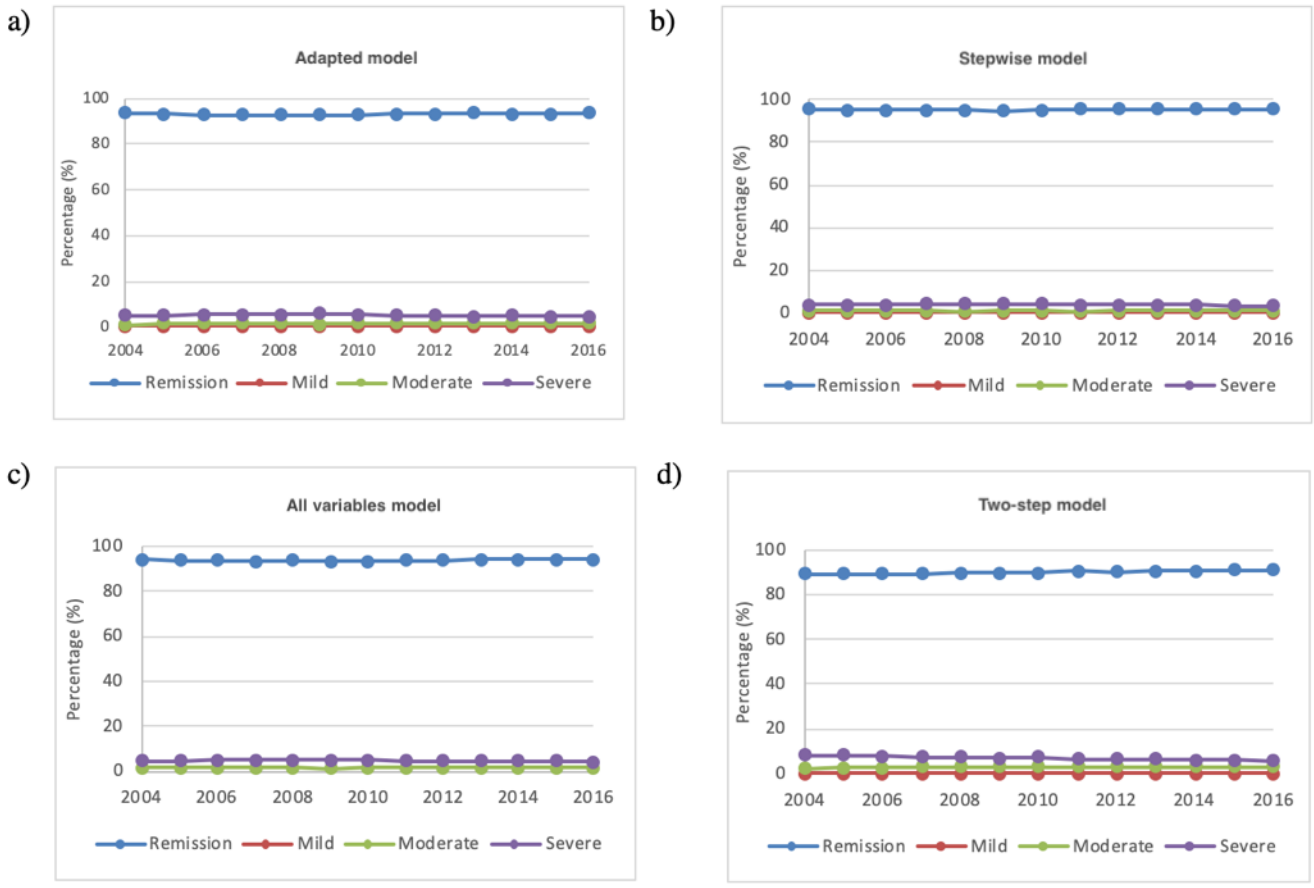



**Figure 4.2:** Predicted IBD course in the OCCC from 2004 to 2016 by model

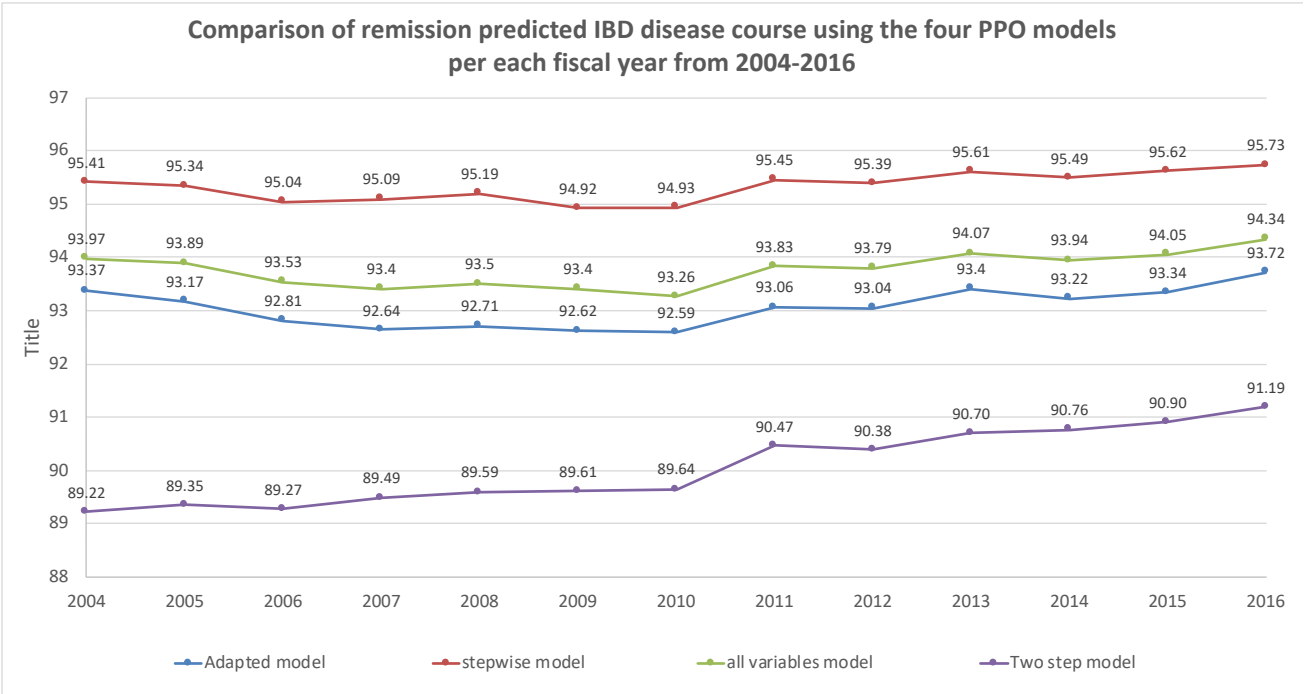
When broken down by the specific models, the percentage of individuals in remission was estimated to range approximately from 92.6-93.7% in the adapted model, from 94.9-95.7% in the stepwise model, from 93.3-94.3% in the all-variables model, and from 89.2-91.2% in the two-step model. Similarly, the estimated percentage of individuals with a moderate disease course range from 1.5-1.8% based on the adapted model, from 0.8-1.0% based on the stepwise model, from 1.4-1.6% based on the all-variables model, and from 2.4-3.2% based on the two-step model. Likewise, severe disease

course estimates ranged from 4.6-5.8% according to the adapted model, from 3.4-4.3% according to the stepwise model, from 4.2-5.2% according to the all-variables model, and from 5.9-8.4% according to the two-step model (Table 4.11 and Figure 4.3).

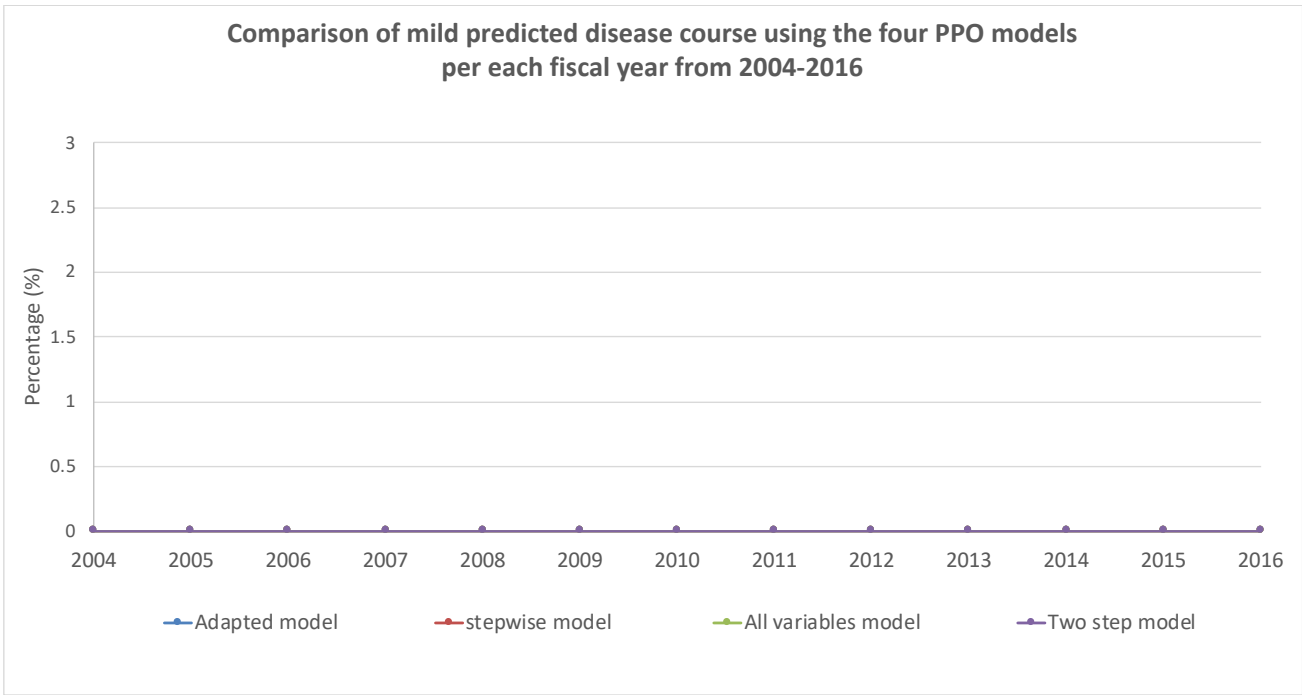
**Table 4.11** Estimated Range of the percentage of individuals is each of the four disease course categories in the Ontario IBD cohort based on the four models from 2004 to 2016

| Predicted disease course category | Estimated Range of each of the four disease course categories by model (in percentage) | | | |
|---|---|---|---|---|
| | Adapted Model | Stepwise model | All-variables model | Two-step model |
| Remission | 92.6-93.7% | 94.9-95.7% | 93.2-94.3% | 89.2-91.2% |
| Mild | 0% | 0% | 0% | 0% |
| Moderate | 1.5-1.8% | 0.8-1.0% | 1.4-1.6% | 2.4-3.2% |
| Severe | 4.6-5.8% | 3.4-4.3% | 4.2-5.2% | 5.9-8.4% |

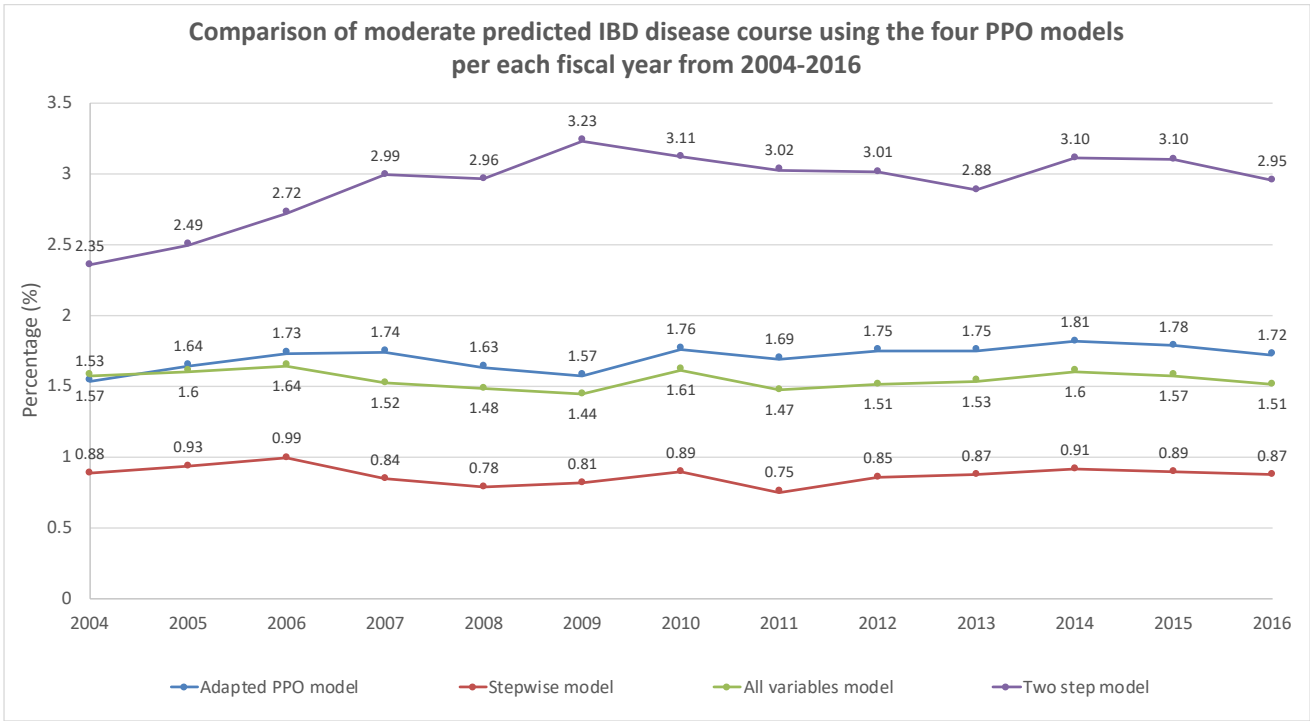
a)



b)


Comparison of mild predicted disease course using the four PPO models per each fiscal year from 2004-2016
Percentage (%)
3
2.5
2
1.5
1
0.5
0
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Adapted model
stepwise model
All variables model
Two step model

c)


Comparison of moderate predicted IBD disease course using the four PPO models per each fiscal year from 2004-2016
Percentage (%)
3.5
3
2.5
2
1.5
1
0.5
0
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2.35
2.49
2.72
2.99
2.96
3.23
3.11
3.02
3.01
2.88
3.10
3.10
2.95
1.53
1.64
1.73
1.74
1.63
1.57
1.76
1.69
1.75
1.75
1.81
1.78
1.72
1.57
1.6
1.64
1.52
1.48
1.44
1.61
1.47
1.51
1.53
1.6
1.57
1.51
0.88
0.93
0.99
0.84
0.78
0.81
0.89
0.75
0.85
0.87
0.91
0.89
0.87
Adapted PPO model
Stepwise model
All variables model
Two step model

d)

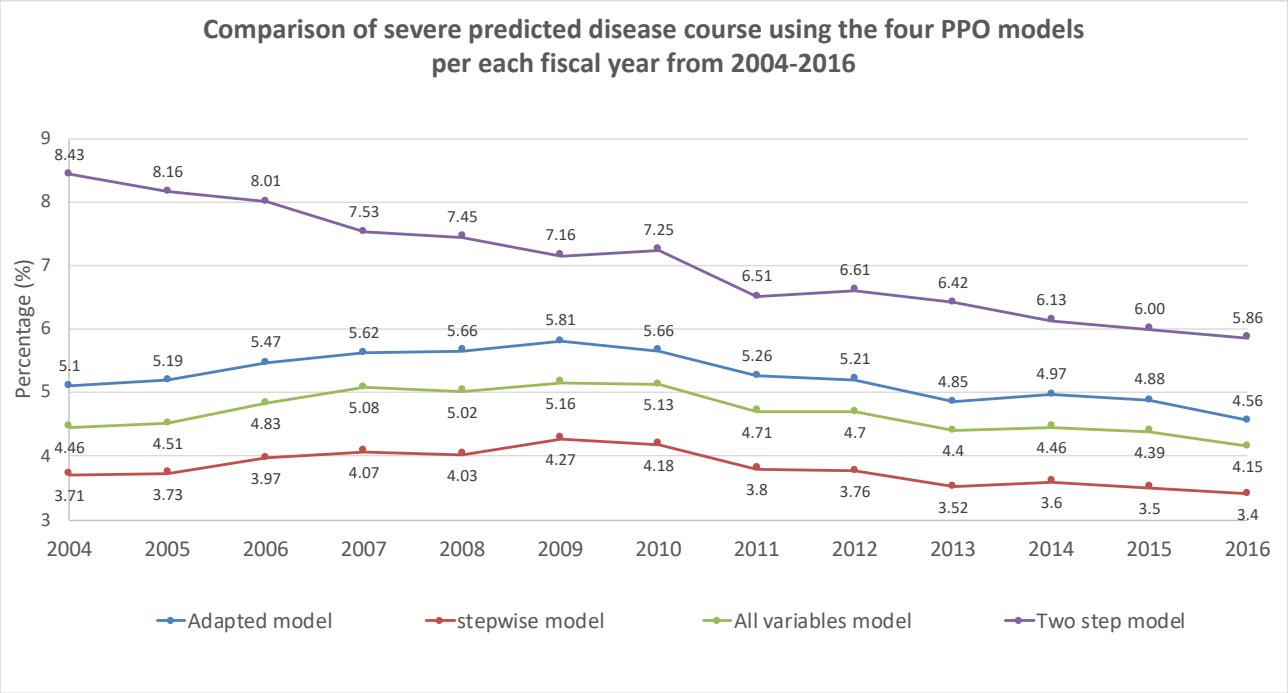



**Figure 4.3:** Application of the four models to the Ontario Crohn's and Colitis Cohort from 2004-2016 broken down by disease course

### *4.4.2 Comparing Disease Course Estimates for the Ontario IBD Population Based on the Two-step Model to the Manitoba IBD Population Estimates*

We present a comparison of the predicted disease course distribution for the Ontario IBD population based on the two-step model to the estimates for the Manitoba IBD population. From 2004 to 2016, the overall predicted percentages for each of the four disease course categories among the Ontario IBD population according to the two-step model has remained stable with around 89.2-91.2% of individuals in remission, 2.4-3.2% with moderate disease, and 5.9-8.4% with severe disease. In contrast, in the Manitoba study the authors estimated a rise in remission rates among the Manitoba IBD population from 43.6% in 1995 to 60.0% in 2013 and a drop in the other three disease course

categories with around 21.5-28.2% with mild disease, 10.9-17.1% with moderate disease, and 6.9-10.0% with severe disease (Figures 4.2- 4.4 and Table 4.12).

**Table 4.12:** Comparison of the estimated range of percentage of each of the four disease course categories among the Ontario and Manitoba IBD populations

| Predicted disease course category | Estimated range of the percentage of individuals within the Ontario IBD population using the two-step model from 2004-2016 | Estimated range of the percentage of individuals within the Manitoba IBD population from 1995-2013 |
|---|---|---|
| Remission | 89.2-91.2% | 43.6 to 60.0% |
| Mild | 0% | 21.5 to 28.2% |
| Moderate | 2.4-3.2% | 10.9 to 17.1% |
| Severe | 5.9-8.4% | 6.9 to 10.0% |

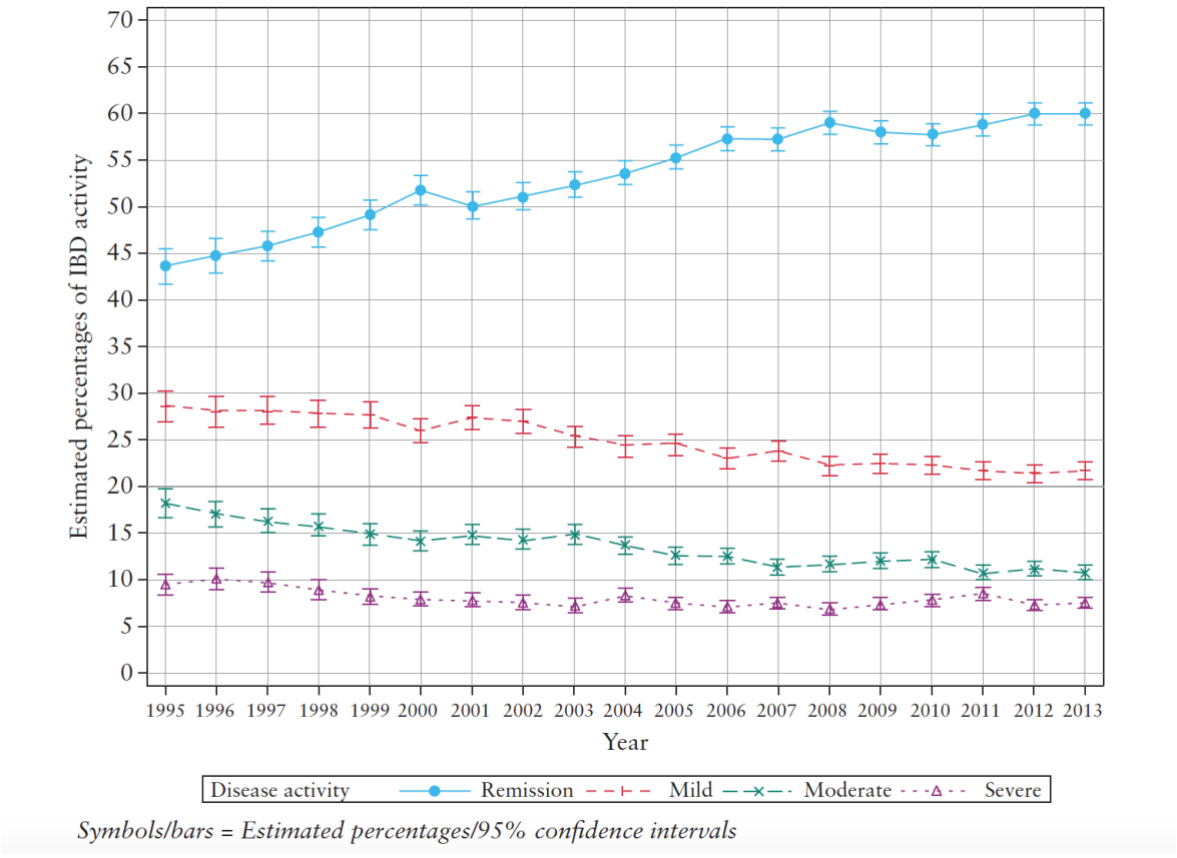



**Figure 4.4:** Estimated percentages of disease course for the Manitoba IBD population from 1995 to 2013 as reported by Melesse et al. (1)

# CHAPTER 5: DISCUSSION

## 5.1 Overview

Population-based health administrative data is increasingly being used to conduct observational research in IBD patients. However, the current lack of clinical information to adjust for the confounding effects of disease severity on observed exposure-outcome associations severely limits our ability to make valid inferences within those studies as severity is an important independent contributor to health outcomes in persons with IBD (23–29,55). Disease severity indices using claims data have already been developed for several other diseases including stroke (107), rheumatoid arthritis (108), and asthma (109). Thus, in this study we intended to overcome this limitation for IBD by exploring several algorithms that can potentially be used to adjust for the confounding effect of disease severity in future observational studies using health administrative data in Ontario. Our specific aims were 1) to identify and characterize a reference cohort of IBD patients in the ambulatory clinics of four gastroenterologists from The Ottawa Hospital on clinical disease course in the preceding year (reference cohort), based on a Manitoba definition of clinical disease course, 2) to fit a PPO model for predicting IBD course, derived using Manitoba health administrative data, to the reference cohort of IBD patients using Ontario health administrative data, 3) to derive new PPO models of IBD disease course for the reference cohort using Ontario administrative variables and compare model performance, and 4) to apply the models to the OCCC to estimate IBD course in Ontario, and compare the distribution to that of the Manitoba IBD population.

## 5.2 Summary of the Study Results and Comparison to the Manitoba study

Using a cohort of 963 IBD patients with known clinical disease course status from TOH outpatient clinics, our study demonstrated that a straightforward adaptation of the Manitoba model for predicting IBD course to Ontario health administrative data (c-statistic 0.77, goodness-fit p-value 0.28) produced a comparable overall performance to newly derived models from Ontario: the stepwise model (c-statistic 0.77, goodness-fit p-value 0.50), the all-variables model (c-statistic 0.77, goodness-fit p-value 0.53), and the two-step model (c-statistic 0.78, goodness-fit p-value 0.75). Furthermore, across all four models, individuals with higher number of visits to a gastroenterologist for IBD, those with more visits to a FP/GP for IBD, and those with at least one endoscopic, general radiologic, and gastrointestinal related radiologic procedures had significantly higher odds of having a more active disease course compared to individuals with fewer number of visits and procedures.

In looking into the performance measures, all models were able to reasonably discriminate individuals with greater versus lesser disease severity (based on the c-statistic value and using disease course as a construct for disease severity) and had overall acceptable calibration (based on the Hosmer-Lemeshow goodness-of-fit test). However, when evaluated more closely across strata of disease course, our models were highly specific but less sensitive for predicting greater disease course categories. In fact, all of our models performed very poorly for predicting individuals with mild, moderate or severe disease and in particular all four models failed to capture individuals with a mild disease course both within our reference cohort and when projected to the Ontario IBD population. In comparison to the other models, the two-step model, where individuals who had been hospitalized for an IBD-related indication within the past year were assumed to have severe disease, performed slightly better with respect to accurately classifying individuals with moderate or severe disease, without sacrificing the overall model specificity.

On further examination of individuals within our reference cohort, 83.6-87.3% of the patients that met our clinical definition of mild disease were misclassified as being in remission by our models, and 12.7-16.4% were misclassified to either a moderate or severe disease course. Similarly, 53.5-67.1% of patients with a moderate or severe clinical disease course were also misclassified by the models as being in remission. Clearly, our models were quite deficient with regards to accurately classifying individuals into their appropriate clinical disease course categories within our cohort. This potentially reflects that our performance measures may have been predominantly derived by the accurate classification of individuals in remission who comprised the majority of the cohort. Therefore, our models might have a limited utility in predicting more severe clinical disease states if used in future studies. Furthermore, the noted degree of misclassification of patients into their true disease states reflects that our models should not be used to replace clinical information, if available, as clinical variables would probably allow for a better judgement of disease severity.

The distribution of disease course in our clinical cohort was quite different from that of the Manitoba clinical cohort (Table 4.2). In particular, our reference cohort from Ontario had an overall higher proportion of patients in remission, and lower proportion of patients with clinically severe, moderate, and mild IBD course compared to the Manitoba reference cohort. Furthermore, when analogous models were applied to predict disease course at the population level, the disease distribution in the Ontario population was noticeably different than that of the Manitoba population. In particular, the predicted disease distribution in Ontario tended considerably more towards individuals being in remission as compared to Manitoba. There are several potential reasons that might have contributed to these observed differences both at the clinical cohorts' level and at the population level. Firstly, there were slight

differences in the data collection methods between the two provinces. In Manitoba, IBD patients were prospectively recruited from the practice of a single experienced IBD specialist, whereas in Ontario, trained data abstractors characterized patients retrospectively from the practices of four gastroenterologists. Secondly, there were some coding differences between some of the predictors in between the two cohorts which might have resulted in some of the variables being more influential in identifying individuals with mild disease in the Manitoba cohort as compared to ours. Thirdly, this difference might have been related to differences in health care utilization and access to resources between the two provinces. Procedures and imaging studies in particular were considerably more frequent in the Manitoba cohort than in Ontario (85.5% vs 43.2% for endoscopic procedures, 66.3% vs 42.8% for general radiologic procedures, and 83.8% vs 39% for gastrointestinal related radiologic procedures in Manitoba vs Ontario, respectively) (Table 4.3). The higher utilization of these procedures in Manitoba might have resulted from an overall more sick panel of IBD patients within the Manitoba cohort which could have led to the observed differences in disease course. Lastly, this observed difference might have been due to actual differences in disease severity distribution between the two populations.

In this study, clinical disease severity was measured based on a composite definition that was developed by the authors of the Manitoba model through a search of the literature and expert consensus (Table 2.1). Individuals were classified into one of the four clinical disease course categories (remission, mild, moderate, or severe) retrospectively based on a chart review of the year preceding the index visit. On further examining the clinical definition used in this study, there was minimal clinical distinction between the categories which used symptoms and/or flares, use of various medication classes, as well as IBD related hospitalizations to separate patients into the separate categories (Table 2.1). For example, to

be classified into a mild disease course as compared to remission an individual needed to have experienced either a single symptom flare needing a change in medication without the introduction of corticosteroids or anti-tumour necrosis factor, or a single change in dosing of an immunosuppressive or a TNF therapy. Therefore, it is possible that we might have missed some of this information if changes were for example were done by a physician outside of TOH and were not captured in our records. Consequently, the assigned clinical disease course categories based on the chart review might not have accurately reflected the true disease severity.

Moreover, in the Manitoba study, a hospitalization with an IBD diagnosis within the first three diagnostic fields in the discharge summary was considered as an IBD related hospitalization which was one of the markers of severe disease course category in their clinical definition. However, while this information was readily obtainable in the administrative databases, the study authors opted not to include this variable within their model with their rationale being that they had already used this information as part of their clinical definition (1). In following their strategy, we excluded IBD hospitalizations in our adapted model and two of our derived models. However, we did take IBD hospitalizations into account in our two-step model to evaluate the difference in predicted IBD course when IBD related hospitalizations were considered in the model. As a result, when compared to the adapted PPO model, considering IBD hospitalizations for predicting IBD course in the OCCC resulted in overall slightly higher estimates for severe disease (5.9-8.4% vs 4.6-5.8% in the two-step model vs the adapted model, respectively) and moderate disease (2.4-3.2% vs 1.5-1.8% in the two-step model vs adapted model, respectively) and slightly lower estimates for remission (89.2-91.2% vs 92.6-93.7% in the two-step model vs adapted model, respectively).

## 5.3 Comparison to Literature

This is the second study in Canada and the first in Ontario to examine the use of healthcare utilization patterns to predict clinical disease course in IBD patients. Our results are consistent with prior studies in that the overall distribution of disease activity of IBD at a population level stays mostly constant throughout the years (110,111). However, if we assume that our remission rates also included patients with mild disease, our estimates of 92.6-93.7% for remission/mild disease are still higher, and our estimates of 1.5-1.8% for moderate disease, and 4.6-5.8% for severe disease are lower than what was previously reported in the literature.

In a systematic review of 15,316 patients with UC from 17 population-based inception cohorts, the majority of patients were reported to be in remission or mild disease after an initial active phase at diagnosis (7). Moreover, a study of 1,161 patients with UC with 25 years of follow-up from the time of diagnosis determined that approximately 50% of patients were in clinical remission every year throughout the study and approximately 10-15% of IBD patients are reported to have severe disease (110). Higher statistics were reported by a literature review where around 80% of patients who were in remission at one year after diagnosis stayed in remission in successive years (112). Furthermore, in an Asia-Pacific cohort of 413 patients with IBD 85.6% of CD patients and 63.5% of UC patients were in remission and approximately 1.8% of CD patients and 18.2% of UC patients had severe disease at one year of follow-up (113).

In reviewing the current literature, there were varying results among reported algorithms that have been developed to estimate disease severity for other conditions using claims data. Algorithms for predicting current and future disease severity for rheumatoid arthritis using prescription claims data through

machine learning demonstrated good discrimination results (area under the curve 0.77-0.79) across multiple independent databases (114). Similarly, three models developed and validated to estimate disease severity in stroke patients displayed correlation coefficients between 0.677 and 0.725 in comparison to clinical stroke severity measures (115). In contrast, a group of researchers attempted to develop and validate a PPO model to predict COPD severity using patient demographics and healthcare utilization data, however, they subsequently reported that their model failed to reliably predict disease severity (116). Furthermore, a systematic review of 54 publications that examined different algorithms for assessing asthma severity using health administrative data concluded that there was no best practice to identify disease severity using claims data, rather they suggested that a combination of different algorithms would offer a more pragmatic approach to categorizing asthma severity (109).

Prior to this study, there were no methods in Ontario to account for the disease course status of IBD patients in health administrative studies due to the lack of clinical information within claims data. However, our current study demonstrated that we could apply predictive models to estimate clinical disease states using healthcare utilization patterns. Although our models had clear deficiencies especially with regards to identifying individuals more severe disease course categories, this information, with caution can potentially be considered by some researcher to partially adjust for the confounding effects of disease course in future epidemiological studies using health care utilization data but should not be used to stratify individual groups of patients.

## 5.4 Study Limitations

This study has several limitations. We had originally planned on carrying out a validation study of the Manitoba model for predicting IBD course but were not able to conduct a formal validation due to differences in data structure and coding between Manitoba and Ontario. Instead we adapted the model to the Ontario data structure. Furthermore, we were not able to directly reconstruct some of Manitoba's variables in our reference cohort due to small cell sizes. As a result, we had to construct variables closely resembling those in the original Manitoba study such as using the mean neighbourhood income quintile instead of the SEFI for SES and collapsing visits to a gastroenterologist for non-IBD reasons from three to two categories due to small numbers. We also had slightly different administrative coding definitions for general radiological procedures, endoscopic procedures, and gastrointestinal related radiologic procedures as compared to Manitoba. We also had no performance measures from the original Manitoba model rendering us unable to compare our model performance to that of Manitoba. Additionally, the definition of clinical disease severity that was used in this study (and in the original Manitoba study) was developed based on a review of the literature and consensus and has not been previously validated.

Another limitation of this study was the inability of any of the models to predict mild disease state for any individual within our reference cohort although the models showed acceptable performance measures and 11.4% of the cohort had clinically mild disease based on the chart review. This may have been due to the fact that individuals meeting the clinical mild disease course definition utilized the healthcare system quite similarly to those in remission which may have resulted in our models not being able to differentiate between the two. To examine this further we would have needed to re-trace the records of individuals with mild and moderate disease to diagnose the issue which was not possible due

to privacy restrictions. In addition, another possibility is that some of the predictors used may have been more influential for predicting mild disease in the original Manitoba model as compared to in our models. An additional limitation of this study is that our IBD reference cohort was established from the practice of four hospital-based gastroenterologists from a single hospital which might not be representative of the entire IBD population in Ontario. In particular, our reference cohort might have been affected by referral bias as we might have potentially captured a greater number of patients with a more active disease course and fewer patients in remission especially if they did not need to see a gastroenterologist during our study period. Moreover, misclassification error that is inherent to claims-based data may have led to inconsistent results.

## 5.5 Conclusion

Our study demonstrated that an adapted PPO model for predicting IBD course from another health care jurisdiction to Ontario health administrative data performed similarly to newly derived models within Ontario. However, all four models that we tested greatly misclassified individuals with active clinical disease (mild, moderate, severe) within our cohort as remission, with slightly more accurate classification in the two-step model. Furthermore, when our models were applied to the Ontario IBD population, we noted a considerable difference in our estimated distribution of disease course compared to that of the Manitoba IBD population, with a substantially greater number of patients in remission in Ontario. In the absence of clinical information within health administrative data, researchers interested in methods to account for the confounding effects of disease course among IBD patients could potentially consider using the two-step model to partially adjust for disease severity in future population-based studies involving claims data. This can be done by creating a variable in the OCCC that generates a predicted disease course category for each individual per fiscal year. This variable can then be

included as an adjustment variable in future analysis among IBD patients in the OCCC. However, given that our models did not perform as originally expected, especially with regards to accurately identifying individuals with more active disease states, we advise researchers to use these models at their own discretion. Moreover, additional research is still needed to examine various aspects within claims data that can be used to more accurately account for clinical disease severity in future population-based health administrative research. Moving forward, we plan to explore other modeling strategies including the use of binary logistic regression and to re-run the models in a subgroup of patients with more equally distributed clinical disease course categories to examine if we can further improve the models. Nonetheless, this study opens the door for the possibility of carrying out similar models to estimate disease course in other conditions that are currently being researched using health administrative data.

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# APPENDIX

**Table S.1: Summary of variables used and their definitions**

| Variable | Variable name/ description | Containing database |
|---|---|---|
| Age at diagnosis (years) | AGE | OCCC |
| Sex | SEX | RPDB |
| Socio economic status | Mean neighbourhood household income quintile | RPDB |
| Residential area (urban vs rural) | Rurality | |
| Disease type: CD/UC (based on latest OHIP) | DX_LATEST | OCCC |
| Disease duration from diagnosis date to index event (in years) | | OCCC, ref cohort |
| Hospitalizations for non-IBD | A record for the number of hospitalizations per patient within the past year in which the discharge diagnosis DX10CODE M,1,2 X,Y,Z **does NOT equal K51.x (UC) or K50.X (crohn's disease** | DAD |
| Visits to a Gastroenterologist for IBD | The number of OHIP claims in the past year with a billing code (FEECODE) in OHIP **consisting of 555 or 556** in which the physician's main speciality (MAINSPECIALTY), obtained by linking OHIP to IPDB through the physician number (PHYSNUM), is either<br>- Gastroenterology OR<br>- Internal medicine AND the physician has performed ≥50 lower endoscopies (OHIP codes any of Z555A, Z580, Z496A, Z497A, Z498A, Z499A, Z494A, Z495A, Z491A, Z492A, Z493A) in the year prior to the index event | OHIP, IPDB |
| A visit to a Gastroenterologist for non-IBD | The number of visits with a billing code (FEECODE) in OHIP of **anything other than 555 and 556** in which the physician's main speciality (MAINSPECIALTY), obtained by linking OHIP to IPDB through the physician number (PHYSNUM), is either<br>- Gastroenterology OR<br>- Internal medicine AND the physician has performed ≥50 lower endoscopies (OHIP codes any of Z555A, Z580, Z496A, Z497A, Z498A, Z499A, Z494A, Z495A, Z491A, Z492A, Z493A) in in the year prior to the index event | OHIP, IPDB |
| Visits to a FP/GP for IBD | The number of visits with a billing code (FEECODE) in OHIP **consisting of 555 or 556** in which the physician's main speciality | OHIP, IPDB |

| | | |
|---|---|---|
| | (MAINSPECIALTY), obtained by linking OHIP to IPDB through the physician number (PHYSNUM), is FP/GP | |
| Visits to a FP/GP for non-IBD | The number of visits with a billing code (FEECODE) in OHIP of **anything other than 555 and 556** in which the physician's main speciality (MAINSPECIALTY) obtained by linking OHIP to IPDB through the physician number (PHYSNUM) is FP/GP | OHIP, IPDB |
| General radiologic procedures | The number of OHIP billing code (FEECODE) corresponding to any of: A335, A330, A332, X090, X091, X092, X039, X040, X096, X195, X196, X025, X202, X203, X027, X204, X028, X205, X206, X032, X033, X031, X034, X207, X035, X208, X036, X037, X038, X045, X209, X046, X210, X047, X211, X048, X212, X049, X213, X050, X214, X051, X215, X216, X052, X217, X053, X218, X054, X219, X055, X220, X056, X221, X060, X063, X223, X065, X224, X225, X066, X226, X067, X227, X068, X228, X069, X229, X072, X230, X064, X100, X101, X197, X189, X105, X106, X17, X108, X104, X103, X110, X109, X111, X112, X113, X114, X120, X116, X117, X123, X129, X130, X137, X135, X131, X191, X138, X139, X134, X136, X141, X400, X403, X406, X235, X209, X231, X168, X417, J021, J022, J026, J802, J013, J028, X163, X164, X167, X145, X146, X152, X153, X142, X148, X149, X155, X147, J061, J055, X156, X122, J036, J068, J064 , S233, S234, X137 | OHIP |
| Endoscopic procedures | The number of OHIP billing code (FEECODE) corresponding to any of E698, Z400, E702, E629, Z515, Z399, Z400, E696, E702, E690, E795, E770, E692, E698, E703, E799, E695, E797, E798, E629, Z527, E674, E675, Z560, Z584, G332, Z497, Z499, Z492, Z493, Z496, Z494, Z498, Z495, Z491, Z555, Z570, E719, Z571, E720, Z580, Z535, Z536, E797, Z543, Z544, S236, S237, E802, E803, E804, E805, E800, Z561, Z558, G350, G251, G351, Z752 | OHIP, IPDB |
| Gastrointestinal related radiologic procedures | A single variable with the number of billing codes (FEECODE) in OHIP of US, CT scan Barium studies, or MRI: X105, X106, X107, X110, X111, X109, X197, X112, X113, X104, X103, X409, X410, X126, X231, X232, X233, X234, X451, X455, X461, X465, J135, J128, J162, J138, J206, J205 | OHIP, IPDB |
| Hospitalizations for IBD | A record for the number of hospitalizations per patient within the past year in which the discharge diagnosis DX10CODE M,1,2 X,Y,Z **equals K51.x (UC) or K50.X (crohn's disease)**, | DAD |
| ED visits without hospitalization for IBD | ED Visits in NACRS with a diagnostic code for **any of ulcerative colitis (K51.x), Crohn's disease (K50.x)** and a ED visit indicator ("edvisit") of 1 that did not result in a hospital admission in DAD. | NACRS, DAD |
| ED visits without hospitalization for non-IBD | The total number of ED visits in NACRS that **didn't include a diagnostic code for any of ulcerative colitis (K51.x), Crohn's disease (K50.x)** and had a ED visit indicator ("edvisit") of 1 that did not result in a hospital admission in DAD. | NACRS, DAD |

**Table S.2: Comparison of billing codes used in between Manitoba and Ontario for general radiological procedures, endoscopic procedures, and gastrointestinal related radiologic procedures**

| RADIOLOGY MANITOBA | | RADIOLOGY ONTARIO | |
|---|---|---|---|
| 8550 | Radiology Consultation | A335 | Radiology Consultation |
| 7600 | Review of Submitted Imaging Study | A330 | Radiology second opinion of CT study, per study |
| 7024 | Chest, single P.A. | A332 | Radiology second opinion of MRI study, per study |
| 7025 | P.A. and lateral | X090 | Chest-single view |
| 7027 | Chest fluoroscopy | X091 | Chest -two views |
| 7032 | fluoroscopy and radiography | X092 | Chest -three or more views |
| 7033 | Pacemaker (fluoro and films) | X039 | Ribs -two or more views |
| 7026 | Portable chest | X040 | Sternum -two or more views |
| 7331 | Ribs, both sides | X096 | Thoracic inlet -two or more views |
| 7031 | Ribs one (1) side | X195 | Fluoroscopy- Chest |
| 7332 | Thoracic Inlet [two (2) views] | X196 | Fluoroscopy- Skeleton |
| 7401 | Added views of any of the above (not films) additional | X025 | Cervical spine -two or three views |
| 7039 | Pelvis, A.P. view | X202 | Cervical spine -four or five views |
| 7339 | Pelvis with lateral hip joint | X203 | Cervical spine -six or more views |
| 7041 | Sacroiliac joints | X027 | Thoracic spine -two views |
| 7341 | Skeletal survey [thorax, skull, thoracic and lumbar spine, pelvis, two (2) long bones] | X204 | Thoracic spine -three or more |
| 7035 | Spine, complete | X028 | Lumbar or lumbosacral spine -two or three views |
| 7037 | Spine-two (2) full areas | X205 | Lumbar or lumbosacral spine -four or five views |
| 7277 | Skeletal survey—suspect child abuse | X206 | Lumbar or lumbosacral spine -six or more views |
| 7036 | Cervical spine, routine views | X032 | Entire spine (scoliosis series) -four views |
| 7038 | Cervical spine with special added views (obliques, and/or flexion and extension) | X033 | Orthoroentgenogram (3 foot film) -single view |
| 7193 | Lumbo-sacral, routine views | X031 | Orthoroentgenogram (3 foot film) -two or more views |

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| 7054 | Lumbo-sacroal with special added views (obliques, and/or flexion and extension) | X034 | Sacrum and/or coccyx -two views |
| 7194 | Thoracic spine | X207 | Sacrum and/or coccyx -three or more views |
| 7061 | Single combining region (thoraco-lumbar) | X035 | Sacro-iliac joints -two or three views |
| 7034 | Sacrum and/or coccyx | X208 | Sacro-iliac joints -four or more views |
| 7057 | Scoliosis series | X036 | Pelvis and/or hip(s) -one view |
| 7402 | Special views [minimum two (2) views] e.g., obliques done as a special request (at a separate visit) | X037 | Pelvis and/or hip(s) -two views (e.g. AP and frog view, both hips, or AP both hips plus lateral one hip) |
| 7065 | Bone age studies | X038 | Pelvis and/or hip(s) -three or more views (e.g. pelvis and sacro-iliac joints, or AP both hips plus lateral each hip) |
| 7046 | Clavicle | X045 | Clavicle -two views |
| 7048 | Elbow | X209 | Clavicle -three or more views |
| 7052 | Fingers | X046 | Acromioclavicular joints (bilateral) with or without weighted distraction -two views |
| 7049 | Forearm | X210 | Acromioclavicular joints (bilateral) with or without weighted distraction -three or more views |
| 7051 | Hand | X047 | Sternoclavicular joints (bilateral) -two or three views |
| 7047 | Humerus | X211 | Sternoclavicular joints (bilateral) -four or more views |
| 7093 | Joints—acromio-clavicular with weights | X048 | Shoulder -two views |
| 7045 | sterno clavicular | X212 | Shoulder -three or more views |
| 7046 | Scapula | X049 | Scapula -two views |
| 7044 | Shoulder, A.P. and lateral routine | X213 | Scapula -three or more views |
| 7069 | Sternum.35 | X050 | Humerus including one joint -two views |
| 7050 | Wrist | X214 | Humerus including one joint -three or more views |
| 7403 | Added views of any of the above (not films) additional | X051 | Elbow -two views |
| 7059 | Ankle | X215 | Elbow -three or four views |
| 7066 | Bone length study with precise measurement | X216 | Elbow -five or more views |
| 7366 | Calcaneus | X052 | Forearm including one joint -two views |

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| 7055 | Femur | X217 | Forearm including one joint -three or more views |
| 7060 | Foot | X053 | Wrist -two or three views |
| 7053 | Hip | X218 | Wrist -four or more views |
| 7056 | Knee or patella | X054 | Hand -two or three views |
| 7058 | Tibia and fibula | X219 | Hand -four or more views |
| 7062 | Toes | X055 | Wrist and hand -two or three views |
| 7404 | Added views of any of the above (not films) additional | X220 | Wrist and hand -four or more views |
| 7067 | Abdomen, single view | X056 | Finger or thumb -two views |
| 7068 | Abdomen two (2) views | X221 | Finger or thumb -three or more views |
| 7072 | Management of long intestinal tube manipulation fluoroscopy | X060 | Hip (unilateral) -two or more views |
| 7073 | Esophagus, fluoroscopy and radiography | X063 | Femur including one joint -two views |
| 7116 | Swallowing function, pharynx and/or esophagus with fluoroscopy and/or video. | X223 | Femur including one joint -three or more views |
| 7117 | Video palate study fluoroscopy and/or video | X065 | Knee -two views |
| 7074 | Stomach and duodenum, fluoroscopy and radiography (including esophagus) | X224 | Knee -three or four views |
| 7190 | hypotonic duodenography | X225 | Knee -five or more views |
| 7376 | Esophagus, stomach, duodenum (including survey films, if taken) double contrast with or without glucagon or other relaxant | X066 | Tibia and fibula including one joint -two views |
| 7077 | Colon—Single contrast barium enema | X226 | Tibia and fibula including one joint -three or more views |
| 7078 | Colon—Double contrast barium enema | X067 | Ankle -two or three views |
| 7079 | Cholecystogram, oral | X227 | Ankle -four or more views |
| 7081 | retrograde/tube cholangiogram | X068 | Calcaneus -two views |
| 7082 | in operating room | X228 | Calcaneus -three or more views |
| 7192 | Ileal Conduit Loopogram | X069 | Foot -two or three views |
| 7083 | K.U.B. | X229 | Foot -four or more views |
| 7084 | Pyelogram, intravenous, routine including preliminary film | X072 | Toe -two views |

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| 7385 | Retrograde pyelogram | X230 | Toe -three or more views |
| 7387 | Retrograde urethrography | X064 | Toe Leg length studies (orthoroentgenogram) |
| 7405 | Added views of any of the above (not films) additional | X100 | Abdomen -single view |
| 7118 | Nephrostogram | X101 | Abdomen -two or more views |
| 7089 | Abdomen and pelvis for fetus | X197 | Fluoroscopy- Abdomen |
| 7090 | Pelvimetry | X189 | Fluoroscopic control of clinical procedures done by another physician per ¼ hour |
| 7221 | CT-Skull base (internal auditory canals, sella turcica) examination | X105 | Palatopharyngeal analysis -cine or videotape |
| 7222 | CT-Facial bone (orbits) examination | X106 | Pharynx and oesophagus -cine or videotape |
| 7223 | CT-Neck examination | X107 | Pharynx and oesophagus -Oesophagus when X103, X104, X108 or X109 not claimed |
| 7224 | CT- Thorax examination | X108 | Oesophagus, stomach and duodenum - including survey film, if taken |
| 7225 | CT-Abdomen and/or pelvis examination | X104 | Double contrast, including survey film, if taken |
| 7226 | CT-Musculoskeletal examination | X103 | Double contrast, including survey film, if taken, and small bowel |
| 7227 | CT- Spine—cervical examination | X110 | Oesophagus, stomach and duodenum - Hypotonic duodenogram |
| 7228 | CT- thoracic examination | X109 | Oesophagus, stomach and duodenum - Oesophagus, stomach and small bowel |
| 7229 | CT- lumbar examination | X111 | Small bowel only -when only examination performed during patient's visit |
| 7201 | CT- Cardiac CT/CT Coronary Angiography | X112 | colon -barium enema including survey film, if taken |
| 7230 | Biopsy and/or drainage | X113 | colon -air contrast, primary or secondary, including survey films, if taken |
| 7231 | 3-D Workstation Review (applies to CT schedule and tariffs listed in Note 4) | X114 | Gallbladder -one or multiple day examinations |
| 7136 | Selective angiogram- Celiac | X120 | Gallbladder -one or multiple day examinations with preliminary plain film |
| 7139 | Selective angiogram- Hepatic | X116 | T-tube cholangiogram |
| 7140 | Selective angiogram- Inferior mesenteric | X117 | Operative cholangiogram |

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| 7144 | Selective angiogram- Superior mesenteric | X123 | Operative pancreatogram or ERCP. |
| 7145 | Selective angiogram- Subclavian | X129 | Retrograde pyelogram, unilateral or bilateral |
| 7146 | Selective angiogram- Splenic | X130 | Intravenous pyelogram including preliminary film |
| 7128 | Selective angiogram- Left gastric | X137 | Cystogram (catheter |
| 7180 | Selective angiogram- Gastroduodenal | X135 | Cystourethrogram, stress or voiding (catheter) |
| 7153 | Azygogram | X131 | Cystourethrogram (non-catheter) |
| 7154 | Venogram- Femoral | X191 | Intestinal conduit examination or nephrostogram |
| 7155 | Venogram- Iliac | X138 | Percutaneous antegrade pyelogram |
| 7156 | Venogram- Inferior vena cavogram | X139 | Percutaneous nephrostogram |
| 7157 | Venogram- Intraosseous | X134 | Retrograde urethrogram |
| 7158 | Venogram- Jugular | X136 | Vasogram |
| 7159 | Venogram- Lower limb | X141 | Cavernosography |
| 7179 | Venogram- Orbital venogram | X400 | Head -without IV contrast |
| 7160 | Venogram- Subclavian | X403 | Neck -without IV contrast |
| 7161 | Venogram- Superior vena cavogram | X406 | Thorax -without IV contrast |
| 7162 | Venogram- Umbilical vein catheterization | X235 | X235 -Cardiothoracic |
| 7163 | Venogram- Upper limb | X209 | Abdomen -without IV contrast |
| 7164 | Venogram- For two (2) examinations done on same patient, on same day | X231 | Pelvis -without Iv contrast |
| 7166 | Selective venogram- Hepatic | X168 | CT guidance of biopsy |
| 7382 | Cholangiography, percutaneous | X417 | Three dimensional CT acquisition sequencing, including post-processing (minimum of 60 slices; maximum 1 scan per patient per day) |
| 7086 | Cystogram | J021 | Insertion of catheter (including cut down, if necessary) and injection, if given... |
| 7087 | Stress cysto urethrogram | J022 | Selective catheterization |
| 7088 | Voiding Cysto-urethrogram | J026 | Peripheral venogram -Direct puncture |
| 7389 | Vaginogram | J802 | Venography –peripheral and superior vena cava |
| 7386 | Dacrocystography | J013 | Percutaneous trans-hepatic cholangiogram |
| 7394 | Fistula, injection with fluoroscopy | J028 | Urethrogram and/or urethrocystogram and/or or intestinal conduit examination, cystogram |

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| 7071 | Fluoroscopy (isolated) | X163 | Dacrocystogram |
| 7371 | Fluoroscopic control of clinical procedures done by another physician, per ¼ hour | X164 | Discogram(s) -one or more levels |
| 7092 | Hysterosalpingography | X167 | Discogram(s) - Fistula or sinus |
| 7301 | with contrast procedure, add | X145 | BMD -one site |
| 7100 | Bone Mineral Densitometry with DEXA (Dual—Energy X-ray Absorptiometry), one or more sites | X146 | BMD -two or more sites |
| 7108 | Vertebral Fracture Assessment (VFA) (Review of low radiation dose imaging acquired with Bone Mineral Densitometry), add | X152 | BMD Second test - low risk patient -one site |
| 7378 | Percutaneous cecostomy | X153 | BMD Second test - low risk patient -two or more sites |
| 7379 | Percutaneous gastrostomy | X142 | BMD Subsequent test - low risk patient -one site |
| 6110 | Arthrography | X148 | BMD Subsequent test - low risk patient -two or more sites |
| 6109 | Biliary tract stones—non-operative extraction | X149 | BMD Subsequent test - high risk patient -one site |
| 6107 | Percutaneous transhepatic catheter drainage of obstructed bile ducts, including daily supervision and including percutaneous Cholangiogram and catheterization to duodenum, if achieved | X155 | BMD Subsequent test - high risk patient -two or more sites |
| 6108 | Replacement of catheter in above | X147 | Hysterosalpingogram |
| 6191 | Percutaneous diagnostic biopsies/aspirations | J061 | Percutaneous cecostomy |
| 6198 | Therapeutic procedure of large needle and tube insertion for drainage of abnormal fluid collections, including subsequent catheter care, and adjustment as required | J055 | Percutaneous gastrostomy |
| 6106 | Biliary stent placement | X156 | Arthrogram, tenogram or bursogram |
| 6120 | Cystogram | X122 | Cholangiogram, percutaneous trans-hepatic |
| 6126 | Vaginogram | J036 | Fistula or sinus injection |

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| 6146 | Retrograde urethrography | J068 | Hydrostatic/pneumatic reduction of intussusception |
| 6147 | Hydrostatic reduction of intussusception by barium enema | J064 | Exchange of drainage tubes, including supervision, imaging and hard copy film interpretation if any |
| 6100 | Percutaneous cecostomy | S233 | Percutaneous trans-hepatic catheter drainage of obstructed bile ducts including daily supervision and including percutaneous cholangiogram and catheterization to duodenum if achieved. |
| 6101 | Retrograde cholangiogram | S234 | Replacement of catheter in above |
| 6102 | Abscessogram | X137 | Cystogram (catheter) |
| 6104 | Percutaneous Gastrostomy | | |
| 6105 | Jejunal Biopsy | | |
| 6119 | Cecostomy/Gastrostomy Tube Catheter Exchange | | |
| 6166 | Gastrointestinal stent placement | | |
| **ENDOSCOPY MANITOBA** | | **ENDOSCOPY ONTARIO** | |
| 3000 | Balloon dilatation of colonic, pyloric, esophageal or small bowel strictures, add | E698 | Oesophagoscopy-gastroscopy, with or without duodenoscopy with pneumatic or balloon dilation |
| 3002 | Botox injection, add | Z400 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding |
| 3004 | Hemostasis G. I. Tract by any endoscopic method or technique (e.g., cautery, injection, banding), add | E702 | Endoscopic retrograde cholangiopancreatography (ERCP) through gastrojejunostomy following previous Billroth II with multiple (3 or more) biopsies of specific lesion |
| 3006 | Hemodynamic instability, add | E629 | endoscopic placement of stent in duodenum |
| 3008 | Placement of jejunal or small bowel feeding tube beyond pyloris, add | Z515 | Oesophagoscopy, with or without biopsy(ies) |
| 3010 | Insertion of small bowel or colonic stent (s) (includes dilatation if necessary), add | Z399 | elective Oesophagoscopy-gastroscopy, with or without duodenoscopy |
| 3012 | Multiple, ten (10) or more, endoscopic biopsies, add | Z400 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding |
| 3013 | Multiple, ten (10) or more, endoscopic biopsies of the upper GI tract add on to procedural fee | E696 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding-with dilatation of oesophagus |

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| 3055 | Esophagoscopy, diagnostic, with or without biopsy | E702 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding with multiple (3 or more) biopsies of specific lesion |
| 3063 | Subsequent, same hospital admission | E690 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding with removal of foreign body(ies |
| 3057 | Esophagoscopywith foreign body removal | E795 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - with brushing of oesophagus, stomach, and/or duodenum |
| 3065 | Esophagoscopy with injection of varices or band ligation | E770 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - with duodenoscopy and drainage of bile after I.V. CCK stimulation |
| 3121 | Gastroscopy, diagnostic with or without biopsy | E692 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - with laser debulking |
| 3122 | Gastroscopy with polypectomy | E698 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - with pneumatic or balloon dilation |
| 3123 | Esophagogastroduodenoscopy (EGD) with or without biopsy | E703 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - with snare polypectomy first polyp (> 1 cm) |
| 3190 | Small bowel enteroscopy by mouth using designated enteroscope or colonoscope | E799 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - each additional polyp, by snare polypectomy (> 1 cm) (to a maximum of 2) |
| 3192 | Capsule Endoscopy–Includes the review of imaging of the small bowel and report to the referring physician | E695 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - laser palliation of oesophageal tumour, extensive, complete obstruction (see General Preamble GP8) |
| 3185 | Colonoscopy | E797 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - management of uncomplicated upper or lower gastrointestinal bleeding, by any technique (e.g. laser, injection, diathermy, banding etc.) |
| 3186 | Colonoscopy with biopsy | E798 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding - |

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| | | | management of complicated upper gastrointestinal bleeding by any technique in haemodynamically unstable patients with active bleeding during endoscopy |
| 3187 | Colonoscopy with polypectomy using snare | E629 | Oesophagoscopy-gastroscopy, with or without duodenoscopy for active bleeding-endoscopic placement of stent in duodenum |
| 3189 | Colonoscopy with polypectomy using electro-cautery device | Z527 | Gastroscopy -may include biopsies, photography and removal of polyps less than or equal to 1 cm |
| 3188 | Colonoscopy with more than one (1) polyp removed at the same sitting, add to 3187 or 3189 for each to a maximum of four (4) additional polyps, (using snare or electro-cautery device) | E674 | Gastroscopy -with snare polypectomy - 1st polyp > 1 cm (maximum 1 |
| 3196 | Ileal intubation, in conjunction with colonoscopy, with or without biopsies, add | E675 | Gastroscopy -with snare polypectomy each - additional polyp > 1 cm (maximum 2) |
| 3311 | Proctosigmoidoscopy, rigid or flexible up to 25 cm., alone | Z560 | Z560 Duodenoscopy (not to be claimed if Z399 and/or Z400 performed on same patient within 3 months |
| 3313 | Proctosigmoidoscopy with biopsy | Z584 | Small bowel push enteroscopy |
| 3315 | Proctosigmoidoscopy, with removal of single lesion | G332 | Capsule endoscopy |
| 3317 | Proctosigmoidoscopy multiple lesions | Z497 | Confirmatory colonoscopy - sigmoid to descending colon |
| 3319 | Proctosigmoidoscopy complicated for hemorrhage control or removal of foreign body | Z499 | Colonoscopy- Absence of signs or symptoms, family history associated with an increased risk of malignancy (e.g. a first degree relative or at least two second degree relatives with colorectal cancer or a premalignant lesion) – sigmoid to descending colon |
| 3320 | flexible sigmoidoscopy between 25 cm. and 65 cm., with or without biopsy | Z492 | Five year follow up of normal colonoscopy (Z499), absence of intervening signs or symptoms - sigmoid to descending |
| 3323 | Flexible sigmoidoscopy without biopsy, with removal of a single polyp | Z493 | Ten year follow up of normal colonoscopy (Z497, Z555), absence of intervening signs or symptoms - sigmoid to descending |

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| 3324 | Flexible sigmoidoscopy more than one (1) polyp removed at the same time, add $43.25 for each to a maximum of four (4) additional polyps | Z496 | Colonoscopy- Presence of signs or symptoms - sigmoid to descending colon |
| 3312 | Proctosigmoidoscopy with deep muscle biopsies (separate specimens) under regional or general anesthesia, e.g., for Hirschsprung's Disease. | Z494 | Colonoscopy- Hereditary (e.g. Familial adenomatous Polyposis or Hereditary Non-Polyposis Colorectal Cancer) or other bowel disorders (e.g. inflammatory bowel disease) associated with increased risk of malignancy |
| 3020 | Endoscopic ultrasound using linear or radial echo-endoscope excluding biliary or pancreatic examination | Z498 | Follow up of abnormal colonoscopy - sigmoid to descending colon |
| 3022 | Endoscopic ultrasound using linear or radial echo-endoscope including biliary and/or pancreatic examination | Z495 | Follow up of unsatisfactory colonoscopy |
| 3024 | Fine needle aspiration (FNA), each FNA to a maximum of five (5) per lesion, add | Z491 | Follow up of incomplete polyp resection |
| 3026 | Core needle biopsy, each biopsy to a maximum of two (2) biopsies per lesion, add | Z555 | Absence of signs or symptoms or risk factors, 50 years of age or older - sigmoid to descending colon |
| 3028 | Fine needle aspiration of pancreatic cyst with removal of cyst fluid, including fine needle aspiration of cyst wall, add | Z570 | Fulguration of first polyp through colonoscope |
| 3030 | Injection into one or more of the following–metastases, nodes, masses, or celiac plexus, add | E719 | Fulguration of each additional polyp (maximum of 4 |
| 3034 | Cap-assisted endoscopic mucosal or sub-mucosal resection, per resection, add | Z571 | Excision of first polyp greater than or equal to 3mm through colonoscope |
| 3036 | Endoscopic ultrasound assisted drainage of pancreatic pseudocyst including stent insertion, add | E720 | Excision of each additional polyp greater than or equal to 3mm (maximum of 2) |
| 3038 | Endoscopic ultrasound, radial or linear mini probe through endoscope to endoscopy fee, add | Z580 | Sigmoidoscopy (using 60 cm. flexible endoscope |
| 3039 | Where doppler is used as an additional diagnostic modality on | Z535 | Sigmoidoscopy with or without anoscopy with rigid scope |

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| | any endoscopic ultrasound procedure, add | | |
| 3505 | E.R.C.P. (endoscopic retrograde cholangio-pancreatography) | Z536 | Sigmoidoscopy with biopsy(ies) |
| 3506 | E.R.C.P., subsequent, when provided within sixty (60) days of tariff 3505 | E797 | Sigmoidoscopy-management of uncomplicated upper or lower gastrointestinal bleeding, by any technique (e.g. laser, injection, diathermy, banding etc.) |
| 3498 | Add-on to E.R.C.P. (any combination of spincterotomy, dilatation, stent, naso-biliary tubing) | Z543 | Anoscopy (proctoscopy) |
| 3064 | Esophageal manometry | Z544 | Anoscopy with Biopsy |
| 3071 | Oesophageal PH monitoring | S236 | Linear or radial echo-endoscope -excluding biliary or pancreatic examination (scope also used for therapeutic procedures). |
| 3320 | Flexible sigmoidoscopy between 25 cm. and 65 cm., with or without biopsy | S237 | Linear or radial echo-endoscope -including biliary and/or pancreatic examination (scope also used for therapeutic procedures). |
| 3323 | Flexible sigmoidoscopy without biopsy, with removal of a single polyp | E802 | Linear or radial echo-endoscope -including biliary and/or pancreatic examination (scope also used for therapeutic procedures). -biopsy or fine needle aspiration, to a maximum of 3, per lesion |
| 3324 | Flexible sigmoidoscopy more than one (1) polyp removed at the same time, add $43.25 for each to a maximum of four (4) additional polyps | E803 | Linear or radial echo-endoscope -including biliary and/or pancreatic examination (scope also used for therapeutic procedures). -dilation of stricture |
| 3311 | Proctosigmoidoscopy, rigid or flexible up to 25 cm., alone | E804 | Linear or radial echo-endoscope -including biliary and/or pancreatic examination (scope also used for therapeutic procedures). -injection of one or more of any of the following - metastases, nodes, masses, or celiac plexus |
| 3313 | Proctosigmoidoscopy with biopsy | E805 | Linear or radial echo-endoscope -including biliary and/or pancreatic examination (scope also used for therapeutic procedures). -drainage of pseudocyst (including stent insertion if performed) |

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| 3315 | Proctosigmoidoscopy, with removal of single lesion | E800 | Radial or linear probe through endoscope to endoscopy fee |
| 3317 | Proctosigmoidoscopy multiple lesions | Z561 | Endoscopic retrograde cholangiopancreatography (ERCP) with cannulation of common bile duct and/or pancreatic duct |
| 3319 | Proctosigmoidoscopy complicated for hemorrhage control or removal of foreign body | Z558 | Endoscopic retrograde cholangiopancreatography (ERCP) including sphincterotomy and may include removal of one or more bile duct stones |
| 3312 | Proctosigmoidoscopy with deep muscle biopsies (separate specimens) under regional or general anesthesia, e.g., for Hirschsprung's Disease. | G350 | Oesophageal motility study(ies) with manometry |
| | | G251 | Oesophageal pH study for reflux, with installation of acid |
| | | G351 | Oesophageal pH study for reflux, with installation of acid, with 24-hour monitoring |
| **CT/MRI/US/BARIUM MANITOBA** | | **CT/MRI/US/BARIUM ONTARIO** | |
| 7067 | Abdomen, single view | X105 | palatopharyngeal analysis -cine or videotape |
| 7068 | Abdomen two (2) views | X106 | Pharynx and oesophagus -cine or videotape |
| 7072 | Management of long intestinal tube manipulation fluoroscopy | X107 | Oesophagus when X103, X104, X108 or X109 not claimed |
| 7073 | Esophagus, fluoroscopy and radiography | X110 | Hypotonic duodenogram |
| 7116 | Swallowing function, pharynx and/or esophagus with fluoroscopy and/or video. | X111 | Small bowel only -when only examination performed during patient's visit |
| 7117 | Video palate study fluoroscopy and/or video | X109 | Oesophagus, stomach and small bowel |
| 7074 | Stomach and duodenum, fluoroscopy and radiography (including esophagus) | X197 | Fluoroscopy- abdomen |
| 7190 | hypotonic duodenography | X112 | colon -barium enema including survey film, if taken |
| 7075 | with small bowel series | X113 | colon -air contrast, primary or secondary, including survey films, if taken |
| 7376 | Esophagus, stomach, duodenum (including survey films, if taken) | X409 | CT Abdomen -without IV contrast |

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| 7377 | double contrast with or without glucagon or other relaxant with small bowel series | X410 | CT Abdomen -with IV contrast |
| 7076 | Small bowel series—radiography and fluoroscopy | X126 | CT Abdomen -with and without IV contrast |
| 7077 | Colon—Single contrast barium enema | X231 | CT Pelvis -without IV contrast |
| 7078 | Colon—Double contrast barium enema | X232 | CT Pelvis -with IV contrast |
| 7225 | CT- Abdomen and/or pelvis examination | X233 | CT Pelvis -with and without IV contrast |
| 7510 | MRI Abdomen Multislice T2 (1 or 2 echoes) | X234 | CT colonography |
| 7511 | MRI Abdomen Multislice I.R. or T1 | X451 | MRI Abdomen -multislice sequence.. |
| 7512 | MRI Abdomen Repeat (another plane, different pulse sequence to a maximum of 3 repeats) | X455 | MRI Abdomen-repeat (another plane, different pulse sequence - to a maximum of 3 repeats). |
| 7513 | MRI Pelvis Multislice T2 (1 or 2 echoes) | X461 | MRI pelvismultislice sequence |
| 7514 | MRI Pelvis Multislice I.R. or T1 | X465 | MRI pelvis- repeat (another plane, different pulse sequence - to a maximum of 3 repeats). |
| 7515 | MEI Pelvis Repeat (another plane, different pulse sequence to a maximum of 3 repeats) | J135 | US Abdomen -complete |
| 7309 | Sonography, abdominal complete real time | J128 | US Abdomen -limited study (e.g. gallbladder only, aorta only or follow-up study |
| 7310 | Sonography, abdominal limited (e.g. single organ, quadrant, follow up time) real time | J162 | Pelvis-complete* |
| 7311 | Sonography, renal (bilateral), or aorta or retroperitoneum real time | J138 | Pelvis- Intracavitary ultrasound* (e.g. transrectal, transvaginal) |
| 7312 | Sonography of organ transplant real time & doppler studies | J206 | Duplex evaluation of portal hypertension - must include doppler interrogation and documentation of superior mesenteric vein, splenic vein, portal veins, hepatic veins and hepatic arteries |
| 7313 | Complete doppler exam of portal venous system | J205 | Doppler evaluation of organ transplantation - arterial and/or venous |
| 7314 | Complete doppler exam of mesenteric veins | | |

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| 9907 | White blood cell labelling | | |
| 9980 | Gastrointestinal mucosa scan | | |
| 9940 | Gastrointestinal motility, including esophageal, gastric, and bowel studies | | |
| 9950 | Gastrointestinal bleeding | | |
| 9986 | Blood flow to an organ, or an add on to another procedure when not otherwise listed | | |

**Table S.3: Summary of proportional odds assumption testing after initial structuring of the variables to resemble those from the Manitoba study**

| | **Score test from individual models** ($p<0.1$) | **Non-proportional cumulative odds model** ($p<0.2$) | **Empirical plots** | **Mosaic plots** |
|---|---|---|---|---|
| **Visits to a gastroenterologist for IBD †** | yes | yes | possibly | possibly |
| **Visits to a gastroenterologist for non-IBD** | | | | |
| **Visits to a FP/GP for IBD †** | yes | yes | possibly | possibly |
| **Visits to a FP/GP for non-IBD** | | | possibly | |
| **Hospitalizations for non-IBD** | | | | possibly |
| **Endoscopic procedures** | | | | |
| **General radiologic procedures †** | yes | yes | possibly | possibly |
| **Gastrointestinal related radiologic procedures** | yes | | possibly | possibly |
| † Entered as non-proportional variables in the adapted PPO model | | | | |

**Table S.4: Summary of proportional odds assumption testing for all variables**

| | **Score test from individual models** ($p<0.1$) | **Non-proportional cumulative odds model** ($p<0.2$) | **Empirical plots** | **Mosaic plots** |
|---|---|---|---|---|
| **Visits to a gastroenterologist for IBD † ¶** | Yes | Yes | possibly | possibly |
| **Visits to a gastroenterologist for non-IBD** | | | | |
| **Visits to a FP/GP for IBD ¶** | Yes | | possibly | possibly |
| **Visits to a FP/GP for non-IBD** | | | possibly | |
| **Hospitalizations for non-IBD** | | | | possibly |
| **Endoscopic procedures** | | | | |
| **General radiologic procedures†** | Yes | Yes | possibly | possibly |
| **Gastrointestinal related radiologic procedures** | Yes | | possibly | possibly |
| **ED visits without hospitalization for IBD** | | | possibly | possibly |
| **ED visits without hospitalization for non-IBD** | | | | |
| **Age at diagnosis** | | | | |
| **Disease duration** | Yes | | probably | probably |
| **Disease type** | | | | |
| **Sex** | | Yes | | |
| **Location of residence** | | | | |
| **Socioeconomic status** | | Yes | possibly | |

† Entered as non-proportional variables
¶ Restructured variables

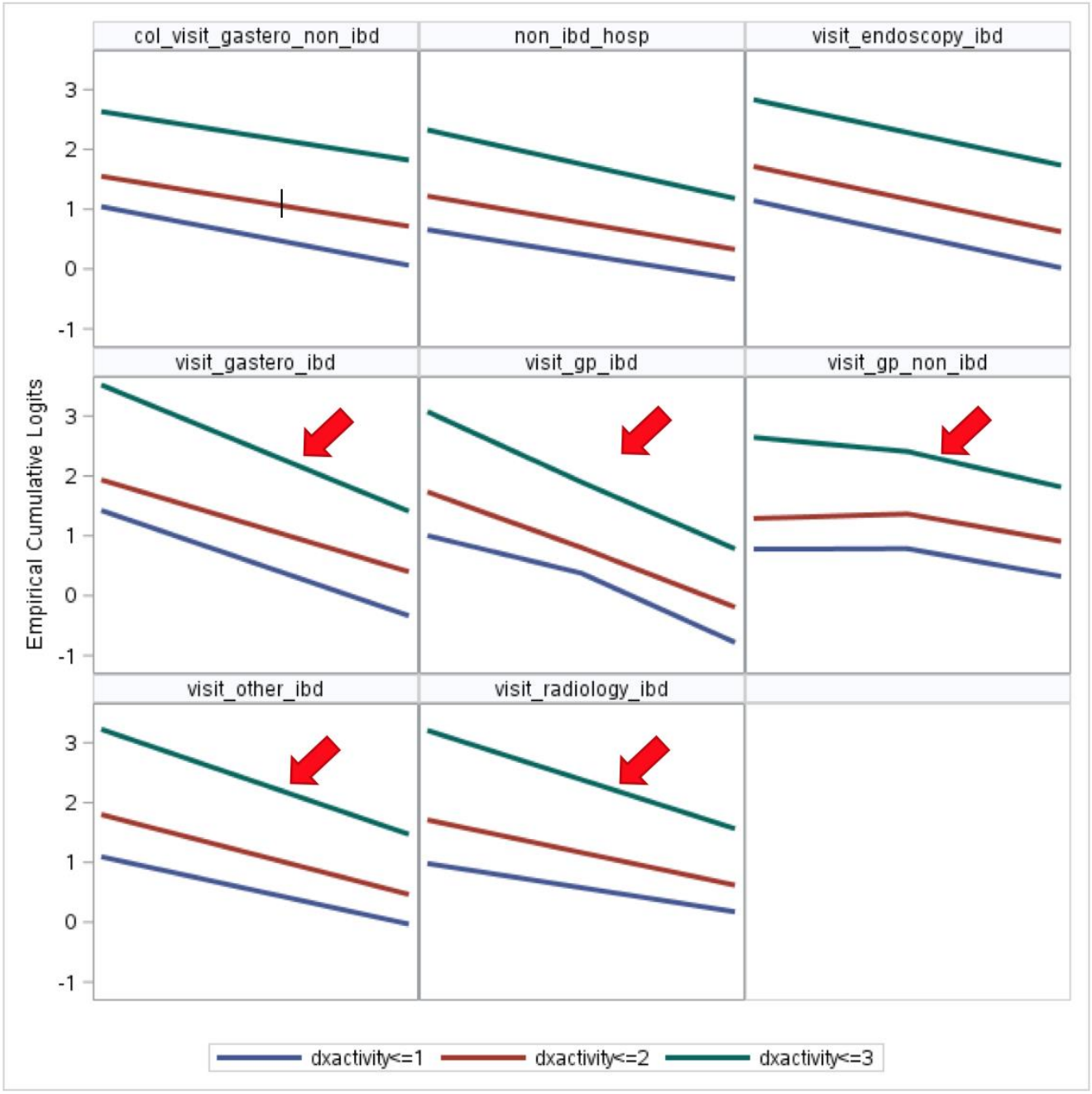



**Figure S.1: Empirical logit plots**

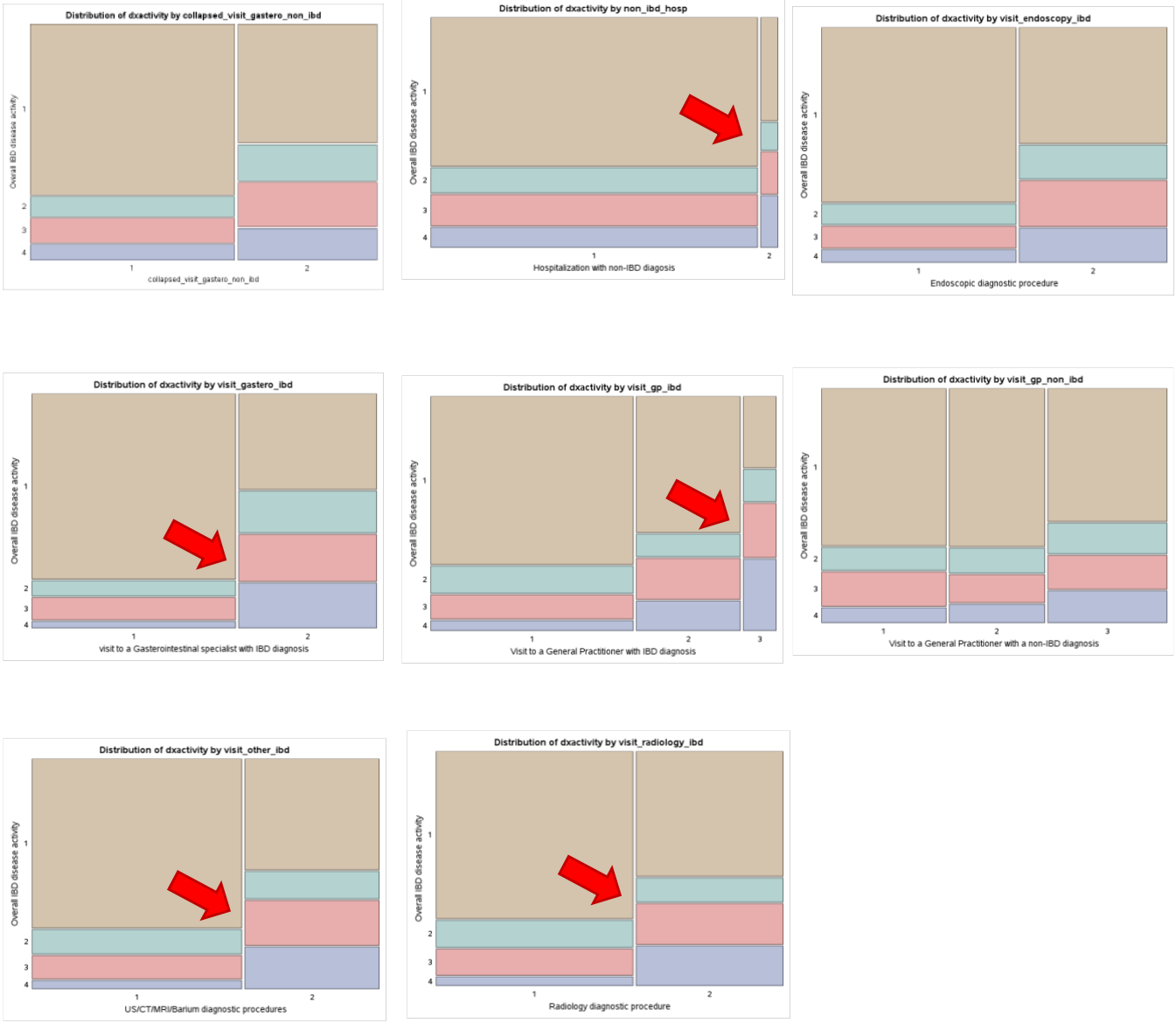
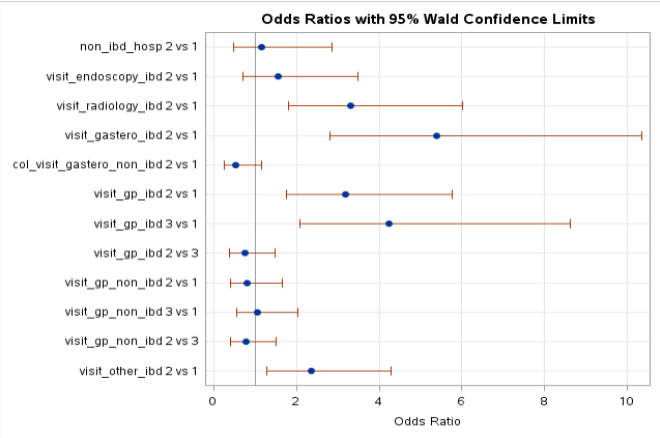
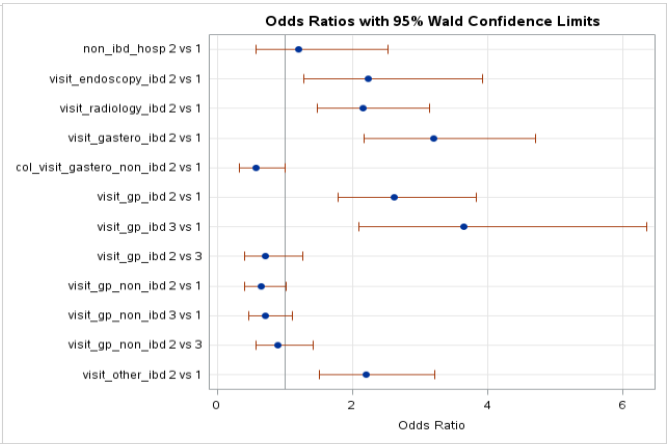



**Figure S.2: Mosaic logit plots**

a) Severe vs remission/ mild/moderate disease course categories




b) Severe/moderate vs remission/mild disease course categories




c) Severe/moderate/mild vs remission disease course categories

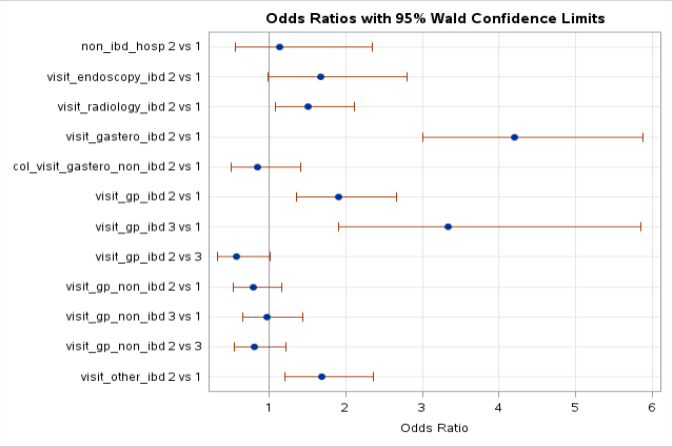



**Figure S.3: Binary logistic models for the adapted model**