Hospitalization Outcomes of Crohn's Disease Inpatients in the United States: A Retrospective Study

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ABSTRACT

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Background: Crohn's Disease is a chronic disease of the gastrointestinal tract. Crohn's disease most commonly, affects the small intestine and colon, but any portion of the bowel from the mouth to the anus may be involved. The disease is characterized by intermittent episodes of relapse, remission, and recurrence, often requiring surgical intervention and/or therapeutic agents such as steroids, and novel immunosuppressive drugs, as part of the medical management plan. This investigation offers an understanding on how age, race gender, medical insurance and medical comorbidities play a role in the hospitalization of patients with Crohn's disease across the four regions (Northeast, Midwest, South and West) within the United States. Descriptive statistical analysis was conducted to detect observations that were statistically significant to further conduction other statistical applications. Analysis of variance was performed using a statistical model ANOVA in an effort to expose and uncover differences that are statistically significant between patient length of stay and four numerical variables (LOS = Pay1, Race, Female and Agecat). Further, another ANOVA analysis was done to incorporate categorical variables (TOTCHG = Pay1, Race, Female, and Agecat). Logistic regression analysis was done to better understand the relation between patient demographic characteristics and outcomes of patients with Crohn's disease.

Methods: This is a retrospective, observational, cohort study of Crohn's disease patients in the existing HCUP database for the years beginning in 2008-2012. Patients being admitted to the hospital based on the following ICD-9-CM code for Crohn's disease (555.0, 555.1, 555.2, 555.9), inflammatory bowel disease (569.89) and ulcerative colitis (556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9).

Results: Crohn's disease, inflammatory bowel disease and ulcerative colitis are within the age group of 18-40. The disease is more prevalence in whites. Logistic regression suggests that there

are statistically significant predictive relations between patients demographics and outcomes of Crohn's disease in 65.5% of what is reported in the database.

Conclusion: Young patient's 18-40 exhibit higher hospitalization rates for Crohn's disease. Various medical comorbidities did not play a role in patient outcomes.

Keywords: Crohn's disease, inflammatory bowel disease, ulcerative colitis, hospitalization

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Table of Contents

List of Tables

LIST OF FIGURES

CHAPTER I

INTRODUCTION

1.1 Statement of the Problem

Crohn's Disease, a type of inflammatory bowel disease (IBD), affects as many as 1.4 million Americans, most of whom are diagnosed before the age of 30. Crohn's disease usually occurs in the lower part of the small intestine, called the ileum, but it can affect any part of the digestive tract, from the mouth to the anus. The inflammation can cause pain and can make the intestine empty frequently, resulting in diarrhea and rectal bleeding. The cause(s) of this disease is unknown; however, genetics/family history, and environmental factors appear to influence disease risk.

In the beginning of the 20th century inflammatory bowel disease (IBD) was a rarity, and at the end of the same century these disease entities were something gastroenterologists in the westernized world encounter not once, but repeatedly, on a daily basis. During the period of the past 50 years, clinicians and epidemiologists have been fascinated by these disease entities (i.e., ulcerative colitis and Crohn's disease) and there is an abundance of descriptive data both cross sectional and over time in different populations.

High socioeconomic status and Jewish ethnicity were two commonly accepted risk factors that were either questioned or have been refuted in observational studies. These strong correlations in the rate of occurrence of ulcerative colitis and Crohn's disease have been shown to exist. It's been reported that parts of the western hemisphere that have seen high rates of ulcerative colitis also showed high incidence of Crohn's disease.[1] In 1913 Dr. Kenneth Dalziel, a Scottish surgeon, came up with a hypothesis of the origin of the disease to be caused by *Mycobacterium paratuberculosis.* This hypothesis was refuted early on, then reintroduced, and later refuted again.

The cause of the disease as mentioned above has been refuted and reintroduced several times; therefore, the theories about what causes Crohn's disease abound, but none have been proven. Aside from mentioning *Mycobacterium paratuberculosis* as a potential agent for Crohn's

disease, another popular theory is that the body's immune system reacts to a virus or a bacterium by causing ongoing inflammation in the intestine. People with Crohn's disease tend to have abnormalities of the immune system.

Recorded figures of ulcerative colitis and Crohn's disease were rare until the 20th century. However, at the end of the 19th century several cases of ulcerative colitis and Crohn's disease were documented and reported in Great Britain and the United States. In 1913 when Dr. Kenneth Dalziel reported his nine cases of what appeared to constitute chronic intestinal enteritis which was later called Crohn's disease. It wasn't until 1932 when Dr. Burrill B. Crohn, introduced the term 'regional ileitis' for the disease that it was later named after him, and Crohn's disease became a distinct entity.

In the 1930s incidence figures for ulcerative colitis and Crohn's were kept in two retrospective studies in two defined populations. The first study was done retrospectively in Rochester, Minnesota, where an annual incidence of ulcerative colitis of 6.0 per 100,00 for the period 1934-1944[8] and an annual incidence of Crohn's disease of 1.9 per 100,000 for the period 1935-1954.[8-9]

In North America, the prevalence of Crohn's disease cases have produced a widely disparate estimates, which may represent the effect of environmental factors or genetic factors in the development of Crohn's disease. The prevalence rate of Crohn's disease, which is reported in literature, is in the range of 26.0 to 198.5 cases per 100,000 persons. This is based on an estimate of 300 million people in North America.[2-5] Studies on the incidence of Crohn's disease in North America have also produced widely disparate estimates. Incidence ranged from 3.1 to 14.6 cases per 100,000 persons. Based on an estimate of 300 million people, approximately 9000-44,000 people are diagnosed with Crohn's disease each year. Crohn's disease is increasing in North America at a high rate based on studies that were published between 1935-1993. One of the highest rates that was noted is among African-American children.[9] A series of hospital-based studies in Baltimore noted a different incidence rate between Caucasians and non-Caucasians: 3.4-3.5 cases per 100,000 person-year by 1977-79 in Caucasian vs. 1.3 cases per 100,000 person-year by 1977-79 in non-Caucasians means.[8]

The age specific incidence for ulcerative colitis and Crohn's disease vary in populations over time. It's been reported that low annual incidence rate have an almost flat age specific curve. Another area of recent interest is pediatric rate of ulcerative colitis and Crohn's disease. The rate is reported to be stable in both diseases. However, during the 1980s there were reports of increase in Crohn's disease.[7-9] The sex distribution of ulcerative colitis and Crohn's disease changed over time. In the case of ulcerative colitis there is a male predominance with an increasing rate whereas in Crohn's disease there is an opposite effect.

Previous studies have been done in the United States and internationally regarding ulcerative colitis and Crohn's disease. However, no specific studies have been conducted on data analysis related to Crohn's disease across multiple years done using the Nationwide Inpatient Sample (NIS) data.

1.2 Background of the Problem

Crohn's disease presents at any age, most cases are found to link the age group between 16-40 years, and it has a disproportionate effect on economically active individuals. The common presenting symptoms of the disease include diarrhea, abdominal pain, weight loss, and fatigue. The disease is characterized with intestinal inflammation, with occasional extraintestinal features such as arthropathy or dermopathy. Patients that are diagnosed with this disease require extensive medical management, which involve a variety of comorbidities. Comorbidities are factors that are used to determine the process of treatment, which is involved in managing the state of disease in an individual.

Patients that are facing a severe case of Crohn's disease require extensive hospitalization and diagnostic monitoring of disease progression. On the other hand, eliminating or reducing comorbidities associated with Crohn's disease could reduce the overall healthcare cost of medically managing the disease. Our medical society needs to scientifically understand what the external and internal factors are that lead individuals to contract or develop Crohn's disease in a western society. Researching factors associated with Crohn's disease will help assess medically and financially the causes of the disease and how much we need to invest in order to treat and prevent it from passing from generation to generation, which will help reduce

our overall medical cost. These factors will provide insight into how we can predict disease rate in the United States.

Since medical care is very expensive in treating Crohn's disease, factors such as gender, race, age, hospital geographic location, lifestyle and social economic status will help better understand how medical cost is associated amongst individuals and their related comorbidities. Therefore, this information can be used to develop future models within individuals with Crohn's disease to predict their overall medical cost while under medical supervision. Previous studies have focused on individual treatment plans such as surgeries, antibiotic treatment, biologic treatment and diet. Other studies focused on risks that might be associated with Crohn's disease, which down the line can increase the chance of developing cancer. Objective of treatment has also been an extensive topic of study. Medical professionals have worked to develop guidelines for treating Crohn's disease. Both American and European guidelines are based on systematic reviews and expert consensus. [6-9] They recommend that treatment be conceptualized in terms of induction and maintenance of remission. The patterns of disease vary, so therapeutic strategy should be tailored to the individual, rather than dictated by crises.

Data analysis and predictive models will establish a baseline that will take various factors, which are present in individuals with Crohn's disease to be addressed. This could allow for very specific treatment, not just in the conventional medical way, but with other possible treatments that are more homeopathic. Models can also help in taking preventive measures if a factor is present or if an individual is considered high risk due to genetic makeup.

1.3 Goals, Objectives, and Research Questions

The aim of this research is to study the effects of Crohn's disease on hospital resources for American individuals between the ages of 18-65. The research questions will help to establish an understanding of how Crohn's disease varies across demographics, regions and comorbidities in the United States. The purpose of this retrospective correlational study is to examine Crohn's disease with United States hospital data and examine other alternative methods that can potentially reduce resource use in treating Crohn's disease. The study will explore other related

diseases within the inflammatory bowel family of disease. It will explore relationships between length of stay, gender, and race resource utilization.

1.4 Significance of the Problem

1.4.1 Crohn's Disease Burden on Healthcare System

The increase in Crohn's disease in the United States will continue to strain the healthcare system with its increase in number of reported cases. Healthcare expenditures for Crohn's disease was significantly greater in children compared to adults. Based on data, it has been reported that total IBD-associated treatment costs in the United States are $6.3 billion ($3.6 billion for Crohn's, $2.7 billion for ulcerative colitis).[10] No recent study reported direct costs of Crohn's disease in the United States. In literature it has been reported that in past analysis of 1988-1989 data, estimates for annual medical costs of Crohn's disease in the United States are $6,561.[11] When this price is inflated per medical cost index for 2004 amounts, this would equal $13,844 for Crohn's. Earlier studies suggested that the majority of the cost contributed to hospitalization.[12]

1.4.2 Crohn's disease Burden on Hospital

Crohn's disease has been shown to be associated with high cost. Various studies have reported that patients suffering from Crohn's disease tend to have other underlying problems which contribute to the higher cost. Feagan et al. conducted a study using a claims data base obtained from Hewitt Associates, a benefits consulting firm that processes prescription drug and medical claims from employees of approximately 50 of the largest employers in the United States.

The data shows that Crohn's disease is associated with high cost. The data confirms that one of the major contributing factors for this increase in cost is hospitalization. This claim supports other studies which support earlier findings that Crohn's disease hospitalization increase medical expenditure. The study reported that 57% of the total costs were associated with hospitalization.

1.4.3 Application to Biomedical Informatics

The data obtained in this study demonstrates an application to the field of biomedical informatics, specifically studying patient outcomes and healthcare outcomes. The study will examine relationships between patient outcome variables and its impact on the hospital resource use. On a broader scale, the study will assist policy-makers in making calculated and informed decisions about hospital resource utilization for patients that are diagnosed with Crohn's disease.

1.5 Hypotheses and Research Questions

The aim of the study is to produce a predictive model demonstrating the impact of Crohn's disease across the United States over the time period of 2008-2010. There is no study that focuses on trying to understand the impact of Crohn's disease and hospitalization resource use. With new medications and dietary techniques and potentially other alternative treatments, this can significantly reduce the impact of the disease on the healthcare system. This study will set to answer the following questions and associated statistical hypotheses:

Research Question 1: What is the annual number of hospitalization associated with Crohn's diagnosis?

Research Question 2: What percentage of hospitalization associated with Crohn's disease has an ICD-9-CM code for Crohn's as a primary diagnosis?

Research Question 3: What is the most common diagnosis associated with hospitalization with Crohn's disease?

Research Question 4: Is there a relationship of Crohn's disease hospitalization between the years 2008-2012?

Research Question 5: What trends emerge for individuals with Crohn's disease among race, age, and gender for different comorbidities?

Research Question 6: Can an alternative medical management help to treat Crohn's disease that in turn can potentially reduce hospitalization resource use over the lifetime of the disease?

1.6 Overview of Crohn's Disease

Crohn's disease is a chronic, relapsing inflammatory disorder of the gastrointestinal tract that affects approximately 500,000 people in the United States.[1] Crohn's disease etiology, however, still remains unclear. This disease typically affects young adults throughout their working lives. Typically patients experience loss of productivity in their work life. They also experience a decrease in quality of life and at times have long hospitalizations. Once diagnosed, a patient's course of illness often fluctuates, varying among mild, moderate, and severe disease or remission.[13] Due to the nature of the disease, patients may require extensive medical care as well as hospitalizations. Therefore, medical expenditure for these services can accumulate to high levels over the course of a lifetime.

Patients suffering from Crohn's disease have near normal life expectancy, and the focus of the treatment is to control symptoms and maintain a normal quality of life.[14] The current standard care of treatment for Crohn's includes aminosalicylates, corticosteroids, immunomodulators, and antibiotics. Severely ill patients may require further hospitalization and surgery to help with their symptoms. The biggest issue that is facing the healthcare system with patient's suffering from Crohn's is the unknown data for hospital cost utilization. Also, understanding the prevalence in the United States is essential to understand and quantify the public health burden of disease to inform policy regarding the allocation of resources and health services for patients affected by this condition. Moreover, understanding epidemiological studies may offer clues to the root of the disease and its causes.

In the United States Crohn's disease and ulcerative colitis belong to the category of Inflammatory Bowel Disease, which is not a reportable condition and therefore, there are not national registries which can track the diagnosis, for population based studies. In literature it can be understood that treating a patient with Crohn's disease is very involved and had a great economic burden. Looking at alternative methods for treatment to change the quality of life is essential to changing the outcome of this disease. The study that is presented in this work will try to bring an unconventional method to treat Crohn's which in turn will help alleviate the burden of hospitalization and decrease medical expenditure in treating patients with the disease.

CHAPTER II

LITERATURE REVIEW

2.1 General Overview of Previous Literature

In literature Crohn's disease (CD) is described as a chronic disease of the gastrointestinal tract that is also referred to as idiopathic inflammatory bowel disease (IIBD). Crohn's disease most commonly affects the small intestine and colon, but any portion of the bowel from the mouth to the anus may be involved. The disease is characterized by intermittent episodes of relapse, remission, and recurrence, often requiring surgical intervention and/or therapeutic agents such as aminosalicylates, steroids, and novel immunosuppressive drugs, as part of the medical management plan.[1] The prevalence of Crohn's disease in North America ranges from 26.0 to 198.5 cases per 100,000 persons. There are approximately 400,000 to 600,000 patients with Crohn's disease in North America. Generally, more recent studies demonstrate higher prevalence rates. This finding, in combination with a recently stable incidence rate, suggests that individuals may be living longer with Crohn's disease. CD can be very difficult to diagnosis because its symptoms are similar to other intestinal disorders such as irritable bowel syndrome.

Crohn's disease most commonly affects the small intestine and colon, but any portion of the bowel from the mouth to the anus may be involved. The small-bowel is affected alone in about one third of patients, the colon in 20%-30% of patients, and combined involvement of the colon and small-bowel is seen in 40%-50% of patients. The severity of symptoms, frequency of complications, and the likelihood of intestinal resection due to CD are typically greater in patients with ileocolic involvement than in those with disease limited to the small-bowel or colon alone.[2]

Evidence suggests that a genetic predisposition combined with an abnormal relationship between the gut and microorganisms may play a role in the pathogenesis. About 60% of patients with Crohn's disease present with the onset of abdominal pain and diarrhea, which contains mucous, pus, and blood. The disease commonly presents with loss of energy, loss of weight, night sweats, mouth ulcers and joint pains. It is a lifelong disease that has no cure. Patients living

with this disease need to learn how to deal with the threat of significant morbidity throughout their lives. The disease generally affects individuals during the prime of their life, with the highest incidence being in the age group 15-24, often from homes where overall hygiene has been good.

Crohn's disease is characterized by intermittent episodes of relapse, remission, and recurrence, often requiring surgical intervention or therapeutic agents such as aminosalicylates (5-ASA), budesonide, and immunosuppressive drugs, as part of the medical management plan.

Crohn's disease was initially described in 1932 when several physicians (Crohn, Ginsburg and Oppenheimer) at Mount Sinai Hospital in New York City identified eight cases of regional ileitis.[3] However, Dalziel made the first clear description of the disease in 1913 at the Western Infirmary in Glasgow. Other physicians described the disease not to be confined to the ileum but referred to the colon. This entity was subsequently termed granulomatous colitis by American clinicians. Crohn's disease belongs to a family of disease more generally designated as "Chronic inflammatory bowel disease". Ulcerative colitis and unclassified chronic colitis also belong to the same classification as Crohn's disease.

More importantly, CD may be caused by a combination of environmental and genetic factors. However, an alternative theory of CD causation is infection with the facultative intracellular bacterium, *Mycobacterium avium,* subspecies *paratuberculosis* (MAP).[4-5]

MAP causes a chronic disease of the intestine in a variety of animals, including nonhuman primates that share some histologic similarities to the changes found in Crohn's disease [6]. Other possible theories that are under consideration for causation of CD: 1) reaction to a persistent intestinal infection; 2) existence of a defective mucosal barrier to luminal antigens; and 3) a dysregulated host immune response to ubiquitous antigens. Cigarette smoking has also been linked to the long-term course of CD as well as to the recurrence of the disease after surgery.[4-6]

CD is a disease of developed societies in temperate regions of the globe, with efficient intensive farming. In North America, CD has also emerged as affecting children.[7] It is reported in literature that more than 80% of patients will require some kind of surgery during their life to help

manage CD. However, surgery is not usually a curative option for CD, as the disease often recurs in the remaining part of the bowel.

How is Crohn's disease diagnosed? As mentioned earlier, the symptoms of CD are abdominal pain (often in the lower right area), diarrhea, rectal bleeding, weight loss, and fever. Children with CD may suffer delayed development and stunted growth. Bleeding may be serious and persistent, leading to anemia. There are many underlying conditions that can lead to anemia, but the most common is iron deficiency anemia (IDA). The most appropriate definition of iron deficiency is the proliferative response of the bone marrow to intravenous iron depletion. Intestinal blood loss through the ulcerated mucosal surface is regarded as the predominant cause of iron deficiency. Iron is essential for all cells of the body. Symptoms of iron deficiency include fatigue, shortness of breath, nail growth problems, skin defects, mucosal regeneration, headaches, sleep disorders, libido and erectile dysfunction, and many more. Some of the drugs that are used to treat Crohn's disease, such as sulfasalazine, mesalazine, and purine analogues, may interfere with erythropoiesis. Therefore, they may contribute to the occurrence of anemia in a large number of patients suffering from Crohn's disease. All of this adds to an impairment of quality of life, which makes the diagnosis and treatment of iron deficiency so important in Crohn's disease.

The initial diagnosis of CD is based on a combination of clinical, laboratory, histological, and imaging findings. No single diagnostic test allows an unequivocal diagnosis. If a patient presents with the above symptoms, a thorough physical exam and a series of tests may be required to diagnose CD. Blood tests may be done to check for anemia, which would indicate bleeding in the intestines. Blood tests may also uncover a high white blood count and a high ESR (erythrocyte sedimentation rate), which are markers of inflammation somewhere in the body. A stool sample may be examined for bleeding or for infection in the intestine. A colonoscopy also may be conducted to take a closer look at the inflammation of the intestine and to check for further bleeding. Finally, a small tissue sample from the intestine called a biopsy may be taken to confirm that CD is present. If these tests come back positive, the physician would conduct an imaging test of the intestine to examine the status of CD.

For many years scientists have had various theories concerning the pathogenesis surrounding CD; however, there has been a paradigm shift over the past half-decade. The focus has moved from a primary defect in adaptive immunity to deficient acute inflammation. Marks et al. have developed a three phase model for the generation of Crohn's lesions[8], based on the penetration of gut luminal contents into the bowel wall, impaired clearance of this material by the innate immune response and propagation of a secondary inflammatory reaction by the adaptive immune system.[9]

CD is established as an immunodeficiency disease and central to this hypothesis were the observations of diminished neutrophil accumulation in patients with CD[10] and an impaired clearance of bacteria from the tissue.[11] The underlying problem appears to be a primary immunodeficiency of the macrophages, [12] which secrete an insufficient concentration of proinflammatory cytokines on bacterial challenge. The molecular mechanisms involved are likely to be heterogeneous and therefore difficult to delineate, given the number of genetic and environmental factors known to modulate susceptibility to CD. Furthermore, the degree both of exposure to bowel luminal contents as influenced by mucosal barrier function (common to both CD and ulcerative colitis) as well as that of the secondary deleterious adaptive immune response, will determine the clinical significance of the innate immunodeficiency.

Radiology has played an important role in diagnosing patients with inflammatory bowel disease. In the last decade many new therapeutic strategies have been developed that have allowed the gastroenterologist and surgeon to treat virtually all forms of CD effectively.[13] The success of the treatment depends on accurate diagnosis of the nature and extent of disease. Therefore, it is no longer sufficient for the radiologist to only detect the presence of CD; he or she must also accurately assess its subtype, location, and severity. New imaging techniques, such as Endoscopy, Magnetic Resonance Imaging (MRI), Computed Tomography and Ultrasound, all have contributed to the diagnosing and surveillance of patients with CD.

To better understand CD, it is important to understand the epidemiology of CD (e.g. prevalence of CD based on gender or geographical region), as this may open new areas for further research. Several studies have been carried out that report the incidence, prevalence,

gender distribution, and age of the onset of CD in a well-defined manner of population-based cohorts of patients in North America and Europe. These studies reported a wide variation in the prevalence and incidence of CD. Some of these differences are difficult to explain, but one theory is how the studies were carried out. However, possible difference in experimental methodologies, while some differences in trial results may be due to the true differences in the genetic and environmental factors present in certain populations.

Management of CD is based on two aspects: 1) treat acute disease flare-ups and 2) maintain remission. The choice of treatment that is available depends on the severity of the disease. Though several different medications are available, no “gold standard” exists to define how the disease will be treated. Working definitions of disease activity have been established to help guide therapy. These definitions are listed and defined as follows: 1) Mild to moderate disease, 2) Moderate to severe disease, 3) Severe fulminant disease and 4) Remission. Medication options that are available to treat CD include: 1) Salicylates, 2) Corticosteroids, 3) Antibiotics, 4) Immunosuppressant and 5) Antibody to human tumor necrosis factor alpha [14].

Looking into the Nationwide Inpatient Sample Data (NIS) as a research tool to help us model various aspects of Crohn’s disease, including medical management of disease, cost of treatment, and prognosis, are all comorbidities that will help establish a trend of disease in the United States and will help predict the future impact of Crohn’s on the overall population in the United States. Thus far no comprehensive study was done using multiple years of NIS data to help predict the future impact of Crohn’s on the population.

2.2 Prevalence of Crohn's Disease in North America:

Studies on the prevalence of Crohn's disease in North America ranged from 26.0 to 198.5 cases per 100,000 persons. There are approximately 400,000-600,000 patients with Crohn's disease in North America. The table below shows information regarding prevalence. Over a period of 8 years the number of Crohn's disease cases in North America has increased by 58% [56].

Study (reference)	Setting	Case ascertainment	Source population size	Prevalence date	Prevalence*
Pinchbeck *et al.*[21]	Northern Alberta	Population-based	1295000	12/31/81	44.4
Kurata *et al.*[20]	Southern California	HMO, out-patient	627000	1988	26.0
Loftus *et al.*[14]	Olmsted County, MN	Population-based	106000	1/1/91	144.1†
Bernstein *et al.*[19]	Manitoba	Population-based	1140000	12/31/94	198.5†

HMO, health maintenance organization.
*Cases per 100 000 persons (most recent prevalence data for source population shown).
†Rates known to be age- and sex-adjusted.

Table 1 Prevalence of Crohn's disease in North America.

Recurring flares altered by periods of inactive disease and remission characterizes Crohn's disease. In most cases patients need to take medication for large periods of their life, mostly to help maintain remission. Data from Denmark showed that the first years of diagnosis, 55% of Chron's patients are in remission and 15% only have mild disease after being placed on some type of medication.[45-48]

Between 40-50% of patients present with ileocolonic disease at the time of diagnosis already, about 30% will have isolated small bowel disease, and another 30% pure colonic disease.[49] Disease localization changes minimally over time and approximately 10-15% of patients will have a change in their disease localization 10 years after diagnosis.[51-53] The disease behavior is more susceptible to changes with increasing duration.

2.3 Diagnosis of Disease using Imaging Methods

Imaging plays an important role in diagnosing inflammatory bowel disease (IBD). Imaging provides initial diagnosis of disease providing evidence of the presence, as well as distribution, of abnormal bowel in patients with suspected IBD. Imaging is very important in assessing and evaluating CD to assess the small-bowel between the ligament of Treitz and ileocecal valve. Cross-sectional imaging modalities (CT, MRI) can provide information regarding extra luminal disease complications. The standard imaging reference for IBD evaluation was barium

fluoroscopy. Barium studies of small-bowel have traditionally been the primary imaging methods of choice to diagnosis of CD. New developments in image acquisition have been shown to offer improved sensitivity and are replacing barium studies as preferred diagnostic tests.[22] Recently a wireless capsule endoscopy has been introduced in the diagnosis of CD. There is a 5% incidence of capsule retention proximal to unsuspected strictures, imaging studies, such as small-bowel follow-through (SBFT), are likely to remain important screening tool prior to capsule endoscopy examinations.

Small-bowel can be evaluated by either SBFT or enteroclysis, and each has its benefits.[23] Both techniques have a high rate of success diagnosing small-bowel disease 89%-97% SBFT and 83%-100% for enteroclysis respectively.[23] Enteroclysis has a shorter overall examination time, the peroral SBFT requires less total room time and radiologist time and substantially less radiation exposure. Also it has fewer side effects and is tolerated and accepted among patients. Therefore, for the above reasons, detailed SBFT, with frequent fluoroscopy using graded compression, is the best means of evaluating small-bowel, particularly in younger patients. Enteroclysis is usually reserved for problematic cases.

Endoscopy is the preferred initial examination of the colon in patients suspected of having IBD. Barium enema is reserved for patients that have unsuccessful colonoscopy or with contraindications such as patients on anticoagulation therapy.

There is a need for new and more advanced endoscopic imaging techniques for surveillance in IBD. In recent years, new emerging technologies of endoscopic imaging have been introduced, allowing a detailed analysis of more mucosal and submucosal details. There are two endoscopic techniques that are in use today. However, one technique is considered more advanced, it is called chemoendoscopy. Chemoendoscopy is divided into two types: 1) dye-based chemoendoscopy (DBC) and 2) dye-less chemoendoscopy (DLC). The DLC principle behind chemoendoscopy is to enhance the mucosal details and /or submucosal vascular network with the use of various dyes or endoscopic/optical and computer based programs. Having the ability to use dyes provides a contrast enhancement of the mucosal surface, which results in an improved detection of subtle lesions. On the other hand, DBC uses different dye agents that are divided

into absorptive agents, contrast agents, and reactive staining agents. The dye agents are applied via plain biliary ERCP catheters.[26] Studies have shown the potential of chromoendoscopy to enhance detection of preneoplastic and neoplastic lesions in IBD. Chromoendoscopy permitted more accurate diagnosis of extent and severity of inflammatory activity in CD as compared with conventional colonoscopy.

In 2002 capsule endoscopy (CE) was introduced. On the market today there are several types of capsules available from various companies.[27] The capsule works by moving through the intestine by peristalsis while transmitting color images of the intestine [28]. CE offers the advantage of visualizing the whole small bowel. Nevertheless, the caecum cannot be reached in about 8%-40% of cases.[28] A study led by Dubceno et al. CE showed a sensitivity and specificity of 89.6% and 100% respectively. However, it's important to keep in mind that these studies used unequivocal gold standards and the diagnosis of Crohn's was always supported by the clinical presentations. At present diagnosis of CD cannot be solely based on CE examination.

In 2004 Confocal laser endomicroscopy (CLE) was introduced and rapidly emerged as a promising approach to obtain real time *in vivo* histology during ongoing endoscopy. The principle of this technique is based on tissue illumination with a blue laser light after topical or systemic application of fluorescence agents. Fluorescein sodium is the most commonly used fluorescence agent. It is administered intravenously thereby providing systemic tissue staining. Currently on the market there are two devices available that the FDA approved. One device is integrated into the distal tip of a high-resolution endoscope and one represents a stand-alone confocal probe that is capable of passing through the working channel of most standard endoscopes.[29]

Combination of using chromoendoscopy and endomicroscopy could detect 4.75-fold more neoplasias in surveillance colonoscopy of patients with CD compared to conventional endoscopy.[30] Results showed that 50% less biopsy specimens were required and CLE could predict neoplastic changes with sensitivity of 95%, and specificity of 98% respectively [31]. CLE was also feasible to differentiate dysplasia-associated lesion or mass (DALM) and sporadic adenoma with high accuracy of 97% and an excellent agreement between CLE and histological diagnosis (k=0.91).[32]

Another imaging technique that is used to assess mucosal structures is endocytoscopy (EC). Endocytoscopy enables *in vivo* microscopic imaging at a magnification up to 1390-fold magnification, thereby allowing the analysis of mucosal structures at cellular level. EC is based on contact light microscopy and it allows visualization of the very superficial mucosal layer.[33] The technique has shown to be reliable for the examination of mucosal surfaces.[34-35] Based on studies EC enabled clear visualization of different cellular structures within the intestinal mucosa, including size, arrangement, and density of cells.

Advance endoscopic imaging in IBD has seen a major innovation revolution during the last 15 years. These various techniques are used to evaluate the entire small-bowel and perform endoscopic therapies at a place where no one has gone before. With these advance-imaging techniques it allows physicians to obtain real time *in vivo* histology during ongoing endoscopy by using endomicroscopy or endocytoscopy. These imaging modalities enable physicians to detect and characterize more lesions and to predict mucosal inflation more precisely as compared to conventional white light endoscopy. These techniques are heading in the direction of becoming the standard for IBD. In the future these techniques will allow for better and more precise therapeutic strategies.

The next imaging technique that is used in the diagnosis process of CD is ultrasound (US). Several US studies have been carried out to document its ability of transabdominal finding and presences of CD. In the case of US it requires a high-frequency approximately 5-17 MHz linear array probe. By using the high array linear probe, it enables and provides increased spatial resolution of the intestinal wall, which is essential for the assessment of wall diameter and wall layer discrimination. It is recommended for conventional transabdominal US with a conventional 3.5-5 MHz convex probe to use prior to high frequency US of the intestinal tract so that the underlying extraintestinal causes of abdominal discomfort are not overlooked. In the case of CD, it can be localized in any part of the gastrointestinal tract, although the main location is the terminal ileum. Small intestinal localization of the disease is found in 30%-40% of patients with CD, and 40%-50% of patients show an ileum and colonic localization.[24]

In bowel studies it is considered to be thickened when the wall diameter exceeds 3 mm. Fraquelli *et al.* compared different cut-off values in CD and they were subjected to meta-analysis. The results yielded sensitivity and specificity of 88% and 93% respectively, when a bowel wall thickness threshold greater than 3 mm was used. At 4 mm 75% and 97% a sensitivity and specificity was achieved.[25] US use in the process of diagnosing CD does have the capability to do so as well as a fair to good reproducibility. It is important to note that patients with CD have significantly higher portal vein and mesenteric flow. US is a valuable tool in helping physicians to detect complications of CD, such as stenosis, fistulas, and abscesses. Sensitivity and specificity for detecting fistulae in transabdominal UC have been reported as 50%-89% and 90%-95%, respectively.[25] Sensitivity and specificity for detecting abscesses in transabdominal US is even higher with sensitivities of 71%-100% and specificities of 77%-94%.[25] Based on these results transabdominal US is accepted as clinically important first-line imaging technique in CD in initial diagnosis and throughout the course of disease monitoring. US has the advantage of being noninvasive, less costly, and easily repeatable, and thus can be very useful in following up patients with IBD. In addition, rising concern about radiation exposure in young adults indicates the demand for radiation-sparing techniques like US.

As mentioned above imaging techniques plays an important role in the evaluation of IBD patients. Various imaging techniques provide information in order to help physicians to better diagnose and treat the disease. In this review I have mentioned several imaging modalities that are used to examine the mucosal lining of the intestine in patients with IBD, more specifically CD. The use to cross-sectional imaging modalities such as CT and MRI can also provide information regarding extraluminal disease complications likely to require more acute intervention, as well as exrraintestinal manifestations of IBD. For years the standard imaging reference for IBD was barium fluoroscopy. However, physicians needed more sensitive technique to assist with their evaluation of the disease. Companies began to develop the MRI for IBD diagnosis and categorization. MRI has several advantages over other imaging modalities that make it more desirable for evaluating CD. One important aspect that makes MRI a desirable modality is lack of ionizing radiation exposure to patients, which is important to the IBD population, which requires

having several images taken over the course of their lifetime. In addition, MRI provides superior soft tissue contrast to other imaging techniques. Historically, MRI of the abdomen has been limited by long acquisition times and extensive motion artifact from respiration. As a result, the initial application of MRI in IBD was pelvic MRI for evaluation of perianal disease in CD. In the last 5-10 years MRI imaging has seen great development of MRI pulse sequences that provide motion-free, high-resolution images of the body, which has made MRI of the bowel possible.[36]

Today pelvic MRI has become part of the standard imaging workup of patients with CD and suspected perianal involvement. The superior soft tissue contrast of MRI provides detailed anatomic delineation of the anal sphincter complex. Typically, MRI evaluation of the bowel combines large volume enteric contrast distention of the bowel with dynamic imaging following intravenous contrast administration to increase sensitivity for detecting bowel wall abnormalities.[37] MR enteroclysis was the first dedicated MRI method for evaluation of small-bowel in CD and was based on fluoroscopic enteroclysis technique. Enteroclysis involves placement of a nasojejunal balloon-tipped catheter under flurorscopic guidance followed by instillation of a large volume of enteral contrast through the catheter, using a motorized pump to ensure uniform distention. With the development of newer MRI procedures, contrast is now routinely instilled under real-time MR guidance until adequate small-bowel distention is achieved.

MR enterography technique was developed as a noninvasive alternative to enteroclysis for small-bowel evaluation, analogous to the development of CT enterography due to the fact that a significant proportion of patients refuse nasojejunal catheter placement.

MRI is most frequently compared with other modalities for CD diagnosis. More specifically MRI has been compared with MR enterography. A number of studies have been conducted to evaluate MRI and MR enterography results show that MR enterography are comparable to other imaging modalities for detection of small-bowel disease in patients with CD. In one study where MRI was compared with CT, the images showed that the MRI was superior for detecting subtle inflammatory changes.[38]

MRI imaging has been shown to be sensitive for detecting certain aspects of CD such as small-bowel inflammation, perianal fistulae, and abscesses. With the advancement in MRI,

including higher magnet field strength, parallel imaging processing, and motion artifact reduction techniques, should lead to shorter scan times and increased spatial resolution for detecting subtle inflammatory changes.[39] This advancement should make it possible for MRI to replace CT as the primary imaging modality for CD patients in the near future. This would extend MRI surveillance beyond its current indications to include detection of chronic inflammatory changes, as well as extraluminal imaging features of disease such as mesenteric lymphadenopathy, ascites, and fibrofatty proliferative changes. Another role of MRI in CD is the detection of mural fibrosis. MRI protocols have been developed for evaluation of the small-bowel (MR enterography) or the colon (MR colonography). In the case of CD, a combined protocol of small and large bowel would be useful in evaluating CD patients.

The role of MRI in the assessment of IBD continues to expand due to its lack of ionizing radiation exposure and superior soft tissue contrast. As the spatial resolution and scanning time of MRI continues to improve as a result of technical innovation, MRI will likely also prove to be suitable as the primary modality for IBD imaging surveillance.

2.4 Crohn's Comorbidity Impact

Other unrelated diseases can affect patients with inflammatory bowel disease (IBD). These conditions are called comorbid, and can include any secondary health problems that affect a person suffering from a primary or main disease, and which is neither linked physiopathologically to the primary condition. It is important to note that comorbid conditions cannot be overlooked in a patient with IBD. The presence of comorbidity can significantly change the medical approach.[39] The scenarios are as follows: 1) Clinical manifestations of IBD and its activity; 2) Prognosis of IBD; 3) Use of drugs for treatment of IBD; 4) Set-up of multidisciplinary teams to empower patient care.

Different sets of clinical indices have been developed and proposed for the specific study of comorbidity. In the case of IBD the comorbidity is associated with the quality of life. However, in IBD this specific has not been addressed yet, but it is known that in other chronic conditions there is an increased cost of care and higher complexity of medical activity.[40]

The importance of comorbidity in IBD patients is important, although data is scarce. Its prevalence has been poorly studied, and refers to other related diseases such as pulmonary thromboembolism, arthritis or immune-based conditions. When examining quality of life in patients with IBD, activity of the disease and other comorbidities not directly related, also have an impact on the physical scores, especially cardiovascular disease. [41-42]

2.4.1 Hepatic Comorbidity

Patients with IBD after a long-term follow-up do show a transient elevation in liver function tests. Prevalence is high in aminotransferase levels showing 5% and 50%, but more adjusted figures show that around 20%-40% of patients. The elevations in liver function tests are usually discrete, in a range below twice the upper normal level.[43-44]

The causes of altered hepatic biochemistry are many fold, but the most frequent causes are steatosis and drug toxicity.[43] In order to categorize the different degree of altered hepatic biochemistry, four different situations need to be defined: 1) Slight and transient elevation of aminotransferease, γ-glutamyl transferase, alkaline phosphatase or bilirubin; 2) Sustained elevation has to be approached as it would be in general population; 3) Some alterations in liver function tests tend to be more specific, and deserve a different approach, such as predominant cholestasis; 4) Liver tests in patients with normal values , after starting a new therapy has to be approached and managed as possible liver toxicity.

A range of lesions known as steatosis are more frequent in general population, but also in IBD patients, in which it accounts for the majority diagnosis when investigating altered liver tests.[43]

2.4.2 Celiac Disease

Chron's disease and celiac disease share some physiopathological, epidemiological and clinical features.[45] In the past it was difficult to rule celiac disease in populations with IBD, mainly due to the clinical superposition. It is shown that the higher specificity of both antiendomysium and antitransglutaminase antibodies in the diagnosis of celiac disease, has finally allowed the performance of studies on the prevalence of this condition in patients with an unequivocal diagnosis of IBD. Data suggests that it's very difficult to conclude or confirm results that celiac

disease is present in patients with Crohn's disease. On the other hand, although data is limited, it seems that Crohn's is more frequent in patients with celiac disease than in the general population.

2.4.3 Skin Disorders

Skin disorders represent the most common extraintestinal complication of inflammatory bowel disease (IBD). These affect up to 20% of patients with IBD. The most commonly seen skin disorders in IBD patients are as follows: Erhthema Nodosum which are red nodules, tend to appear over the shins or ankles and sometimes on the arms, can affect 2-10% of the IBD population. Women are more commonly affected than men. Erythema nodosum generally appears during a flare-up of IBD, but can also occur just before a flare-up. The next skin disorder also seen in IBD patients is Pyoderma Gangrenosum, in which the skin is associated with deep ulcerations. It is also mostly found in shins and ankles but sometimes can occur on the arms. They begin as small blisters, which eventually form into deep, chronic ulcers. This skin disorder affects 0.5-2% of patients with IBD.[42] Enterocutaneous Fistulas is another type of skin disorder that is present with patients with IBD. An enterocutaneous fistula is an abnormal channel from the intestine to the skin often from the rectum to the vagina, bladder, or buttocks. This can also be a complication from surgery. This type of fistula may leak pus or fecal matter. This affects approximately 30% of people with Crohn's.[42] Skin tags are common among people with Crohn's disease and they tend to develop around the anus. Anal fissures are small tears in the lining of the anal canal and they may crack and bleed, therefore causing pain and itchiness.

2.4.4 Cardiovascular Disease

Cardio vascular disease (CVD) is a leading cause of death in developed countries and its prevalence increase with age. IBD patients therefore, are likely to experience these entities throughout their life or, at least, be affected by some risk factor associated with this disease. The health impact of CVD on IBD is the same as in the general population, increasing complications and remaining a common cause of mortality.[44]

Venous thromboembolism (VTE) has been considered a manifestation which is directly related to intestinal inflammatory activity, but in other chronic inflammatory disease the incidence of VTE remain the same as in the general population.[44] Furthermore, it has been shown in clinical studies that IBD patients in remissions have an increased risk of VTE.[44] In recent epidemiological studies, the incidence of VTE in IBD was 26 cases/1000 person-years with a hazard ratio 3.4 (95% CI: 2.7-4.3).[45] The risk is three times higher in patients with IBD. Also IBD activity tends to increase the likelihood of VTE up to 8 times higher.[45] it is worth mentioning that these VTE events occur in patients that are over 60 years of age.[45] IBD itself acts as a predisposing factor for thrombosis.

The appearance of VTE in a patient with IBD carries a poor prognosis reaching a mortality of 22-25%[46-47], while hospital stay also increased by 48% and associated health costs doubled.[46] The treatment of thromboembolic episodes of IBD is the same as in the general population with the use of anticoagulation, first with low molecular weight heprins, (LMWH) and then oral anticoagulants which should be sufficient for most patients.[46] The duration use of anticoagulants therapy is unknown, but generally will vary depending on the severity of the thrombosis and bleeding risk. It has to be noted that some drugs that are used in the management of cardiovascular risk factors may be beneficial for IBD such as atorvastatin.[46]

2.4.5 Psychiatric Comorbidity

Mood disorders and anxiety have been extensively studied in IBD patients. There may be some connections, because of the use of drugs used in the management of IBD such as steroids[46] can precipitate psychotic manifestations. In IBD the prevalence of anxiety is higher as compared to normal population. Psychiatric comorbidity in IBD has been considered a risk factor for the onset of IBD itself. Moreover, the frequency of anxiety and depression increases after diagnosis of IBD, suggesting that is it a consequence rather than a cause of the disease.[47]

Stress plays a major contributor in the precipitation of flares and therefore has a greater chance of disease reactivation.[48-49]

Psychiatric Comorbidity has an impact on the management of IBD because it is, together with disease activity, the main determinant of quality of life in patients. Additionally, it is one of the

factors associated with poorer adherence to treatment. It is very important to be able to identify these issues and treat them appropriately with the correct medical management in order to avoid other complications that will affect the patients further. It is a good idea to use screen tests to identify the severity of the psychiatric condition. The treatment should not be any different from standard regiment of anxiety and mood disorders.

2.5 Pathogenesis

The mechanism responsible for initiating chronic intestinal inflammation remains unclear in patients with CD. Scientists speculate that there is an interaction of genetic and environmental factors. The intracellular bacterium, *Mycobacterium avium* subspecies *paratuberculosis* (MAP) has been linked to be present in patients with CD. MAP is an organism that is found in animal feces. It infects and causes a clinical disease, called Johne's (Yo-Knees) disease, in a wide variety of animal species. Several studies have identified the MAP organism in CD using various techniques but often used ulcerative colitis as the "negative" control, under the assumption that it is present in CD and not in ulcerative colitis.[15-16] However, since in some cases MAP is identified in both CD and ulcerative colitis, scientists concluded that MAP causes neither disease. In certain populations around the world serum antibodies to various MAP antigens are found in a third of the population in countries with a high incidence of ulcerative colitis and CD[17] and in patients with both diseases.[17-19] MAP is identified by using PCR (polymerase chain reaction) in the tissues and cultured from the bloodstreams of patients with ulcerative colitis as well as patients with CD.

It has been reported in the literature, as well as mentioned above, that not all patients develop CD from MAP. A review of the literature suggests that five factors influence whether an individual develops ulcerative colitis or CD when infected with MAP:

1) The dose of the MAP organism. Small doses of MAP cause ulcerative colitis, while a larger dose causes CD.
2) The route of infection. The routes of infection are aerosolized water from rivers contaminated with MAP, and MAP present in hyperosmolar milk.
3) The age at which the individual is infected.

4) Genes that control how an individual processes intracellular bacteria, and specifically mycobacteria.
5) Gender male or female. Infant males and adult females are at higher risk of developing CD.

There are two routes of MAP infection: manure and milk. As mentioned earlier MAP is excreted in infected animal feces and secreted in its milk. Therefore, there are two different ways in which humans can be infected with MAP: fecal-oral transmission via contaminated water, and consumption of contaminated milk or products made from contaminated milk. Fecal-oral transmission is an important means of transmission of a variety of bacterial, viral, and parasitic diseases. It may involve finger to mouth spread.[20] In the case of CD it is reported that contamination of water source is one of the prime transmission of MAP.

In animals, MAP causes chronic intestinal disease whether it is ingested, injected subcutaneously, or inhaled via aerosolization from possibly MAP-contaminated bodies of water, particularly rivers.[17-18] Pierce et al, believes that the largest concentration of MAP bacteria that causes CD is present in aerosolized water bubbles.

The second route of transmission into humans is through contaminated milk. Reports suggest that unpasteurized raw milk or milk products carry a greater risk of infection. Literature suggests that MAP in milk is more invasive than MAP in water, due to the passage through mammary gland epithelial cells and because of the hyperosmolar nature of milk.[21]

Paratuberculosis is diagnosed with a variety of tests; the type of test varies with the stage of disease. Delayed-type hypersensitivity (DTH) reaction, PCR assays, or fecal culture, can help with the identification of the infection. A Ziehl-Neelsen stain can be used to detect MAP in the feces; organism may also be found in smears from the intestinal mucosa or the cut surfaces of lymph nodes.

To check for cell-mediated, immunity several tests have been developed. Usually, humoral immunity develops 10 to 17 months after infection. Serology can be used for the presumptive identification of infected animals, as well as to estimate the prevalence of infection in a herd. The serologic tests currently available include complement fixation, enzyme-linked immunosorbent

assays (ELISAs), and agar gel immunodiffusion. Recently a milk ELISA has been licensed in the United States.

2.5.1 Interleukin responses in Inflammatory Bowel Disease

Immune response is believed to present and play a key role in the pathogenesis of tissue damage in Crohn's disease and ulcerative colitis.[39-40] In Crohn's disease and ulcerative colitis, the inflamed tissue is heavily infiltrated with leukocytes, mostly T lymphocytes. When these cells are activated by some type of a trigger mechanism (i.e., stress, environmental, infection) they increase the production of cytokines, which are thought to have a primary role in promoting the disease cascade. Sensitivity assays have shown that there is a predominant synthesis of type 1 helper T-cell (Th1) cytokines, including IFN-γ and TNF-α. Other type of cytokines are more relevant to ulcerative colitis such as Th2 cytokines, IL-5 and IL-13.[40]

Some of the immunological precursors seem to be shared by Crohn's disease and ulcerative colitis, there are however, important distinguishing features, possibly reflecting different pathways of immune mediated intestinal inflammation. Research indicates that there is evidence that macrophages and T cell derived cytokines play a key role in the amplification and perpetuation of the inflammatory response in both disorders. No cytokine secretion has been documented in inflammatory bowel disease and no convincing evidence has as yet been provided that cytokines changes occur as a result of disease specific immune activation.

Examining morphological and immunohistochemical observations suggest that during chronic intestinal inflammation, recently recruited lymphocytes undergo functional differentiation within the gut.[41] Interleukin 12 is a naturally produced by dendritic cells, macrophages, neutrophils, and human B-lymphoblatoid cells in response to antigenic stimulation. IL-12 mediates its biological activities through a receptor composed of two subunits, β1 and β2.[41] While it appears the IL-12 is responsible for triggering the Th1 cell response in the gut additional signal factors are required to maintain the process. It is important to note that IL-12 proved to play an important role in the generation of Th1 type cell clones.[42] As expected bioactive IL-12 was found in the intestinal mucosal samples of patients with Crohn's disease. The structure of IL-12 is composed of a heterodimer consisting of two covalently linked polypeptides subunits (p35 and

p40) and produced mainly by monocytes/macrophages in response to bacteria, bacterial products or their components.[42] Transcripts for both IL-12 subunits (p35 and p40) were detected in Crohn's disease lamina propria mononuclear cells. Moreover, IL-12 synthesis seems to be compartmentalized in Crohn's disease.[43]

It's been shown that lamina propria T lymphocytes (T-LPL) isolated from normal mucosal samples synthesize IFN-γ after exposure to recombinant human IL-12. In addition, antibodies to IL-12 inhibited the development of IFN-γ producing T cells in Crohn's disease gut specimen cultures.[44] Therefore, IL-12 may account for the predominance of the Th1 response in Crohn's disease. Ultimately it's important to understand what induces IL-12 production in Crohn's disease. It has been noted that IL-12 has been detected in Crohn's disease indicating that IL-12 production may not be an epiphenomenon of active inflammation.[43]

2.5.2 Johne's Disease

Johne's disease is chronic, granulomatous enteritis caused by *Mycobacterium avium subspecies paratuberculosis* (MAP). The disease predominantly affects ruminants, but infection with MAP has been demonstrated in wild rabbits, and a number of non-ruminant wildlife has been shown to be susceptible to infection.[40] In cattle, the disease is characterized by chronic diarrhea and progressive weight loss. The disease has pathologic similarities to the human enteric condition Crohn's disease, and MAP has been described to be present in tissue of Crohn's sufferers.

Johne and Frothingham described the disease in 1895 and demonstrated the presence of acid-fast staining bacilli in sections of the diseased bovine intestine. At the turn of the century the disease became recognized throughout Northern Europe and the United States. In 1912, Frederick Twort isolated the causative organism and named it *Mycobacterium enteriditis chronicae pseudotuberculosae bovis* Johne, which later was referred to as *Mycobacterium paratuberculosis.*[50] This strain of bacteria does not cause tuberculosis. Linnabary et al. designates *Mycobacterium paratuberculosis* as the causative organism of Johne's disease.

Mycobacterium paratuberculosis survives outside the host animal for significant period. The bacillus can remain viable for 163 days in river water, 270 days in pond water, and 11

months in bovine feces and black soil; but it survives only 7 days in urine. The bacteria can survive in low temperatures, i.e., 14° C, for at least a year. [51-52]

Understanding the transmission of Johne's disease is essential in controlling its spread. Most of the diseased cattle are infected before or soon after birth. The calf can be infected across the uterine and placental barriers before birth and after birth from the ingestion of infected milk or feces. The primary mode of infection in post-weaned animals is by ingestion of feed or water contaminated with feces from infected animals shedding. The *Mycobacterium paratuberculosis* organism can be excreted in milk, including from cows, with no clinical evidence of disease. In the later stages of infection, organisms are disseminated throughout body tissues and can penetrate the placenta tissues, thereby infecting a fetus. Several studies on fetuses obtained from cows showing clinical signs of Johne's disease revealed that 20 to 40% of fetuses were infected in the uterus before birth.[52] Embryo transfer is another possible means of transmission among animals. An infected embryo-recipient cow is more likely to cause fetal infection.[52]

The incubation period of Johne's disease is long. Typically, cattle would demonstrate illness by the age of two. Once the *Mycobacterium paratuberculosis* organism is ingested orally, it is taken up by the mucosal cells of the small intestine and lymphoid tissue.[53] The major site for bacterial replication is the terminal portion of the small intestine and the large intestine. Bacterial replication proceeds at a variable rate. Some animals can become resistant, never develop lesions or shed the organism, and have so signs of disease.

Lesions develop in the intestinal wall, which gradually result in malaborption syndrome. Animals begin to demonstrate diarrhea and, occasionally later, edema in the submandibular jaw area. Lesions of Johne's disease are characterized by intestinal thickening with corrugation. Lymph nodes and lymphoid tissue are enlarged several times.

Diagnosing Johne's disease it presents a challenge because of unlikely detection until the animal has progressed to Stages III or IV of the disease. In the early stages of disease, the diagnostic tools that are available are not apt to detect an immune response or the intermittent shedding of the organism.

There are two means to detect Johne's disease: culturing the organism and determining antibody response to the organism. Culture and microscopic examination of tissue are two methods of detecting the organism. Fecal cultures are advantageous for detecting cattle that are excreting the organism and thus disseminating the infection to others in the herd. The disadvantage of Mycobacterium *paratuberculosis* is that it grows very slowly in laboratory cultures; conventional techniques require at least 12 to 16 weeks.[54] A genetic probe is also used to detect Johne's disease. A probe, referred to as a deoxyribonucleic acid (DNA), employs a polymerase chain reaction (PCR) technique to determine the presence of Johne's disease organism within three days. PCR testing offers the most sensitive methods for detection of the *Mycobacterium paratuberculosis* infection because the presence of only one organism should provide a positive signal.

Antibodies to *Mycobacterium paratuberculosis* can be detected in the serum of infected animals by a means of variety techniques: agar gel immunodiffusion, and enzyme-linked immunosorbent assay (ELISA). The slow development of Johne's disease restricts detection by serum antibody tests until Stages III and IV of the disease. ELISA sensitivity was only reported to be 15% in low-level fecal shedders. In animals with clinical signs of the disease with heavy fecal shedding of bacteria, the sensitivity of the ELISA was 87%. Overall ELISA sensitivity is 45%.[45] It is reported that antibody detection using the ELISA method will detect less than half of the infected animals.[55] In late stages of the disease, antibody detection is limited by the inherent biological fact that the host until late in the disease process does not produce detectable antibodies.

Another method of measuring disease is by skin test. Cell-mediated immunity to the injected antigen has been used to determine exposure to tuberculosis in humans and cattle. However, skin testing for Johne's disease using extract of *Mycobacterium paratuberculosis* has not been as successful as humoral immunologic techniques.

Treatment of Johne's disease is available but might not be valuable. It is a large expense that will have an impact on the product produced from the cow. Since residues of the treatment remains in the animal, the owner cannot sell the meat or milk from that animal. Also, the

therapeutics that are available do not cure the disease; rather, they may ameliorate the clinical condition, and the animal will likely have to receive medication for the rest of its life.

It is suggested that *Mycobacterium paratuberculosis* is the cause for human Crohn's disease. Crohn's disease and Johne's disease share similarities. Both are diseases of the small and large intestines and have a long incubation period and prolonged courses. Crohn's disease is a segmental disease of the intestine, whereas Johne's disease is a diffuse disease usually of the distal small intestine with extension into the cecum and colon. In CD, the disease extends through the intestinal wall, but the disease is confined to the internal layers in Johne's. There are several features that are found in Crohn's but not in Johne's; a few include fibrosis, fissures, fistulas, abscesses, bowel loop adhesions, blood in stools, and fibrous thickening of the mesentery.[52,56]

2.6 Management of Crohn's Disease

There is now a general consensus that IBD is the result of the combined effects of 4 factors: environmental influences, genetic variations, intestinal microbiota alterations, and disturbances in the innate and adaptive immune responses. Therefore, all of these factors is probably necessary for the disease to be clinically expressed. Unfortunately, every patient seems to have different factors leading to the disease, explaining why each patient displays their own clinical picture and response to therapy.[58]

Management of Cohn's disease is based on the location and severity of disease and extra-intestinal complications. The medical approach to treat Crohn's disease has two goals: 1) to treat acute disease flare-ups and 2) to maintain remission. There is no standard that exists which defines severity; working definitions of disease activity have been established to help guide the therapy. The following are definitions that can be used to evaluate and manage Crohn's disease flare-ups.

1. **Mild to moderate disease:**

   The patient is able to move and able to take oral alimentation. There is no dehydration, high fever, abdominal tenderness, painful mass, obstruction, or weight loss of more than 10 percent.

2. **Moderate to severe disease:**

   Patient has more pronounced symptoms including fever, significant weight loss, abdominal pain or tenderness, intermittent nausea and vomiting, or

significant anemia.

3. Severe Fulminant disease:

Patient has persistent symptoms despite outpatient steroid therapy or has high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

4. Remission:

The patient is asymptomatic or without inflammatory sequelae, including the patient responding to acute medical intervention.

Crohn's disease is characterized by a variable course with spontaneous flare-ups and remissions. It is difficult to prove therapeutic benefit from intervention. Therapeutic guidelines have been developed to better manage Crohn's disease. An algorithm for the medical management of Crohn's disease provides a systematic treatment plan. Figure 1. depicts the algorithm process of various treatments to Crohn's disease at different levels of disease activity.

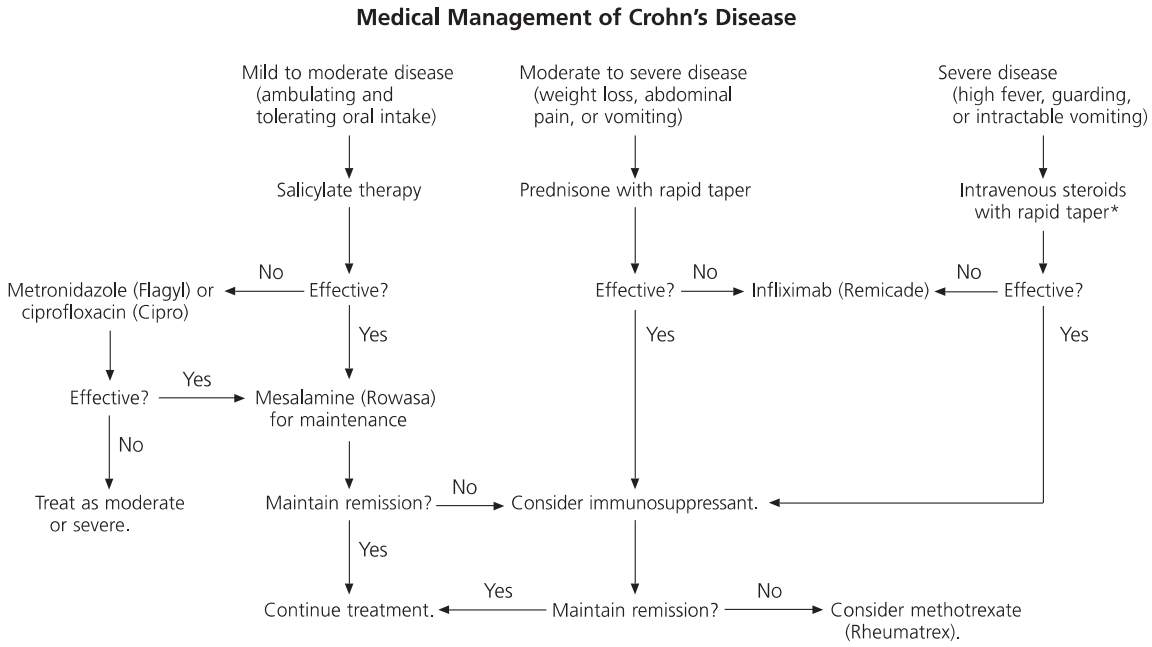


Figure 1. Algorithm for the medical management of Crohn's disease. Adopted from Knutson *et al.* 2003.

2.7 Treatments for Crohn's Disease:

Conventional therapies remain the cornerstone of treatment for the majority of patients with Crohn's disease, as only a small proportion require biologic therapies. Over the last several years, a great deal of attention has been given to the development of new therapies for Crohn's Disease. Significant progress has been made in identifying new therapies. Pharmaceutical treatment of Crohn's disease includes five major categories, namely anti-inflammatory drugs, immunosuppressants, biologic agents, antibiotics, and drugs for symptomatic relief. Figure 2 lists some of the available treatments for Crohn's disease.

Mild to moderate disease:

A patient who presents with mild to moderate symptoms of Crohn's disease can be treated with a salicylate preparation, and in patients who are unresponsive, an antibiotic.[47] Evaluation takes place after several weeks; patients who do not respond will be treated for moderate to severe disease or with alterative therapy. The class of salicylates drugs includes mesalamine and sulfasalazine. Mesalamine can be released in the stomach, duodenum, ileum, and colon.[48] The dosage of oral mesalamine is 3.2 to 4 g per day. In a study conducted in 1979, sulfasalazine demonstrated great benefits with approximately 50 percent of patients enrolled achieving remission.[49] The suggested dose of sulfasalazine is 3 to 6 g per day.

In cases of mild to moderate active Crohn's disease, therapy with the antibiotic metronidazole is acceptable as an alternative. Ciprofloxacin (Cipro) can be used as a treatment. A study comparing the efficacy of patients treated with Cipro and metronidazole to those treated with prednisone showed no differences after twelve weeks of treatment.[50]

Moderate to severe disease:

Patients that present with Crohn's disease that are classified as moderate to severe should be treated with steroids until symptoms resolve and weight loss is reversed.[57] There are two types of drugs that can be used at this level of severity; azathioprine and mercaptopurine, but full response may not be achieved for several months. Another treatment that can be used is Infliximab, which is a good alternative if corticosteroids are ineffective or contraindicated. Corticosteroids have been used as the standard for treating moderate to severe active Crohn's

disease. Their effectiveness in inducing remission has long been known, and their onset of action is more rapid than that of salicylates. After clinical response, dosage is tapered according to rapidity and completeness of response, often requiring months to discontinue.[51] Steroids do not play a role in remission. There is a concern regarding the long-term use of steroids, which can have significant side effects such as diabetes mellitus, osteoporosis, and adrenal suppression. Budesonide is a type of corticosteroid with poor systemic absorption. It is superior to mesalamine in patients with active Crohn's disease.[52]

Severe disease:

Patients with severe Crohn's disease frequently require hospitalization. Indications for hospitalization include persistent symptoms despite the use of steroids or other medications, fever, vomiting, intestinal obstruction, and acute abdomen. In such cases a CT or ultrasound may be required to examine the abdomen. Surgical cure of Crohn's is not possible; however surgery can cure some complications of CD, such as intestinal obstruction, formation of an abscess, or fistula. Some of these manifestations may subside after resection. Management of severe Crohn's disease also includes nutritional support.[55]

Crohn's disease may create a negative impact on self-image, employability, and psychologic functioning. Stress appears to play a role in the exacerbation of Crohn's disease.[53] No study has shown that relaxation techniques for Crohn's disease have improved patient emotional status; however, one study showed improvement in patients that were active in low-impact exercise programs. Exercise also helps improve quality of life and bone density, an important consideration for those patients requiring chronic steroid use.[54]

Generally, patients suffering from Crohn's disease need vitamin and mineral supplementation. Vitamin B_{12}, folic acid, fat soluble vitamins, and calcium should be considered, and periodic checks may be necessary. Osteoporosis is a potential complication of Crohn's disease, often aggravated by chronic steroid use. Patients should be monitored appropriately. Regular colonoscopy monitoring is recommended for Crohn's patients, depending on disease activity.

Treatment Options in Crohn's Disease

Treatment	*Examples*	*Results*	*Problems with use*
Salicylates	Mesalamine (Rowasa), sulfasalazine (Azulfidine)	Beneficial for mild to moderate active disease, proctosigmoiditis	Inconclusive maintenance of remission, risk of GI bleed or upset
Corticosteroids	Oral prednisone, budesonide (Entocort), IV preparations	Beneficial for moderate to severe active disease, generally accepted therapy	Side effects from long-term use, budesonide not approved for use in the United States
Antibiotics	Metronidazole (Flagyl), ciprofloxacin (Cipro)	Beneficial in treatment of mild to moderate disease, maintenance of remission	Specific antibiotic side effects include metallic taste in mouth, disulfiram effects, GI upset, peripheral neuropathy
Immunosuppressants	Azathioprine (Imuran), 6-mercaptopurine (Purinethol), methotrexate (Rheumatrex), cyclosporine (Sandimmune), others	Beneficial in treatment and in maintenance of remission, beneficial to decrease steroid use	Questionable risks for neoplasia, leukopenia (requires blood monitoring)
Antibody to human tumor necrosis factor alpha	Infliximab (Remicade)	Significant improvement when compared with placebo	Costly, IV administration, mild infusion reactions might be seen

GI = gastrointestinal; IV = intravenous.

Table 2. A table of available treatments for Crohn's disease. Adopted from Knutson *et al.* 2003.

2.7.1 Anti-inflammatory drugs

Mesalazine has two other names and is also known as Mesalamine or 5-aminosalicylic acid (5-ASA), used to treat inflammation of the digestive tract and mild-to-moderate Crohn's disease. The drug is available in specially formulated oral and rectal forms for treatment. It is also used for maintenance therapy for disease remission. The drug has characteristics that act as a chemopreventive agent of colorectal cancer. In a recent study of the meta-analysis evaluated the efficacy of aminosalicylates compared to placebo and other aminosalicylates in active Crohn's disease.[59] Results showed that sulfasalazine was superior to placebo in inducing remission, with benefit confined mainly to patients with colitis. However, the data do not support a role of Meclizine in the treatment of active Crohn's disease.

Corticosteroids suppress inflammation by blocking early manifestations of inflammation, including enhanced vascular permeability, vasodilation, and infiltration by neutrophils. Corticosteroids can also influence immunological responses such as T-responses to antigens, down regulate production of inflammatory cytokines, and interfere with nuclear factor-kB production, thereby reducing inflammatory response.[60] In patients with active Crohn's disease, corticosteroids are highly effective for induction of remission. There are several formulations of corticosteroids that can act fast on active Crohn's disease and induce remission and improve

symptoms in a few days, but they cannot achieve mucosal healing and they have a number of side effects. Corticosteroids still remain the treatment of choice in the initial therapy in active Crohn's disease. There are still a third of patients that will fail to respond. Further studies require studying the effects of the treatment in long-term use.

2.7.2 Immunosuppressives Drugs

This group of drugs acts by inhibiting proliferation and activation of lymphocytes. In recent years several drugs in this category have seen an increase use. The drugs that are in this category are: 6-mercaptopurine (6-MP), methotrexate, cyclosporine, and tacrolimus. 6-MP is considered to be effective in approximately 40% of IBD patients after 5 years of treatment. Some patients had to stop treatment due to adverse events. If result of treatment is favorable in the first month then the treatment can be extended over many years.[61] 6-MP is effective drug for helping to induce remission in patients with active Crohn's disease as well as continued maintenance of remission. The rate of response increases after 17 weeks of therapy. 6-MP is in the front line of Crohn's disease combating. Recent data supports that it is a safe drug to use in pregnant and lactating women.

2.7.3 Antibiotics

As mentioned earlier Crohn's disease is caused by a series of events. In literature it has been reported that there is a strong correlation between MAP and Crohn's disease. MAP is a bacterium that is found in animal feces and is transmitted via water supply or simply by drinking milk that came from an infected animal (Cow). In any event the first line of defense to treat bacterial infection is with an antibiotic. Since Crohn's disease is an infection caused by a bacterium it makes sense to treat it with some kind of antibiotic with the hope that it will kill the bacterial infection. Patients suffering from Crohn's disease contain large amounts of bacteria concentration in their ileum. The beneficial effect of antibiotics in Crohn's disease patients supports the assumption of the existence of an impaired mucosal antibacterial activity.[62] The last several years saw an increase in research on the use of broad-spectrum antibiotic in Crohn's disease patients. The types of antibiotic used to treat Crohn's patients include metronidazole, ornidazole, ciprofloxacin, tobramycin, clarithromycin, cotrimoxazole, and anti-TB treatment.

Metronidazole is a type of antibiotic that has been investigated from the early 1970s. Studies showed that metronidazole had positive effects on patients with Crohn's disease. In a study conducted in Sweden between metronidazole and sulfasalazine as primary treatment for Crohn's disease no significant difference was observed but patients that failed to respond to sulfasalazine did respond to metronidazole.[63] In another study, metronidazole was used as a single therapy or in combination with cortimoxazole and compared with cortimoxazole alone. After 4 weeks of treatment there was no difference in response among the groups.[64] In a subsequent study treatment with metronidazole for 16 weeks significantly decreased the Crohn's disease activity index (CDAI), no difference of remission were reported compared with the placebo.[65] Metronidazole does present side effects that have been recorded during the clinical study. They include nausea, anorexia, dysgeusia, dyspepsia, and peripheral neuropathy, which limit its use in approximately 20% of patients.

Ornidazole is a derivate with similar chemical structure and properties to that of metronidazole. Patients with active Crohn's disease received a 500 mg/day of ornidazole for 4 weeks; the results showed that the CDAI decreased significantly from week 0 to week 4 while patients going into remission increased gradually. All other symptoms of abdominal pain and bowel movement decreased as well.[66] Other observations noted patient overall well-being improved significantly. Increase in body weight was also noted.

Ciprofloxacin has been used in patients with active Crohn's disease with or without perennial involvement. A study conducted comparing ciprofloxacin with placebo twice daily for 6 months, showed a reduce CDAI score compared to placebo. In another study, patients suffering from mild-to-moderate flare-ups of Crohn's disease received 1000 mg/day. A complete remission was observed in 56% of patients treated with ciprofloxacin.

The drug also found applications in patients with fistulizing disease. Again results showed that patients receiving ciprofloxacin responded better and enter remission faster. With ciprofloxacin clinical remission was observed in 68% of patients, and 76% showed clinical response.[67] Ciprofloxacin is an effective treatment in a portion of patients with Crohn's disease mainly located in the colon.

Clarithromycin is another type of antibiotic that has been used in treating Crohn's disease. It is a broad spectrum antibiotic that has a good penetration into macrophages. It was found that within the first three months the benefits of clarithromycin were ineffective. This suggests that the bacteria built resistance against the antibiotic. However, in the first month of treatment it showed promising results.[68]

Antibiotics have also been examined for preventive of postoperative disease recurrence of Crohn's disease. Results suggest that antibiotics are useful in the treatment of Crohn's disease. Many exports believe that incorporating antibiotics with other therapeutics such as immunosuppressive drugs might be a rational strategy.[69] With that said, there are still unanswered questions as to why antibiotics work on only a certain population of patients and not on others. More research needs to be conducted on the mechanism on how the antibiotic works on patients with advanced Crohn's disease. Once these questions are answered it will open more doors on how to better treat all types of Crohn's disease cases from mild to severe.

2.7.4 Probiotics

Probiotics are non-pathogenic microorganisms administered to improve microbial balance in gastrointestinal tract. Probiotics exert their beneficial effects through various mechanisms, including reduced intestinal pH, decreased colonization and invasion by pathogenic organisms, and modification of immune response. It needs to be understood that not all strains of probiotics exert the same mechanism of biochemical process. Also there is no consensus about the number of microorganisms that must be ingested to obtain a beneficial effect; however, a probiotic should typically contain several billion microorganisms to increase chances of adequate gut colonization.[70] The characterization of Crohn's disease is increased intestinal permeability that permits antigen penetration into the intestinal tissue. For patients with Crohn's disease in remission, S*. boulardii* added to the therapy may improve intestinal permeability.[71] Thus far, none of the probiotics tested showed any effect in induction of remission or in maintenance of remission with patients suffering from Crohn's disease.

2.8 Health-related quality of life (HRQoL)

The world health organization (WHO) defines Health-related quality of life (HRQoL) as a broad multidimensional concept that includes a subject evaluation of both positive and negative aspects of life. For example, physical, mental, and social well-being is considered to be part of the definition of HRQoL. The other part of HRQoL describes the general well-being of an individual in society which measures the following parameters: an individual wealth and employment, environment, education, re-creation, leisure time, and social inclusion exclusion.[71] Aspects of culture, values, and spirituality are also key aspects of overall quality of life that add to the complexity of its measurement. Nevertheless, researchers have developed useful techniques that have helped to conceptualize and measure these multiple domains and how they to each other.

HRQoL indicates the overall effect of a disease on person's ability to enjoy life. It is a measure of the functional impact of a chronic illness and a given therapy on a daily life of an individual, as seen from that individual's view point.

It's worth noting that most conceptualistic models of HRQoL includes the dimensions of physical, social and role functioning, in addition to mental health and general perceptions of health. These dimensions impinge on each other, and they are affected by the patient's personality characteristics, social support, economical support, and non-medical factors such as political and cultural factors.[72-73]

2.8.1 Applications of quality of life measurement

HRQoL evaluation has become an important factor in meeting the objective of medical therapy to improve patients' well-being. HRQoL assist the medical professional in better designing and treating patients with different therapies. HRQoL can be broken down into several levels. For example, on the population level, HRQoL measurement can be used to monitoring population health changes in it, for evaluating the effects of health and social policies, and for allocating health care resources in relation to need. On the individual level, HRQoL measurement serves to evaluate the effects of treatment, to describe the nature and severity of a disease, and to assess prognosis.

In outcomes research HRQoL measurement has become an essential tool for analyzing cost-effectiveness and cost utility analysis. The purpose of the HRQoL instruments is to calculate a score based on a person's perception of his/her quality of life. HRQoL essentially is a valuation of life lived in a particular state of health. The primary sources of information for HRQoL measurement should be the patient him or herself.

2.8.2 Categories and structures of HRQoL instruments

HRQoL comprises of two main types of HRQoL instruments, generic and disease-specific. These two groups can be broken down further into two groups: health profiles containing instruments that attempt to measure separately all important aspects of HRQoL, and utility measures comprising instruments that reflect preferences of patients for treatment process and outcome, and yield a single score. Some of the generic instruments have features of both groups. Global HRQoL assessment refers to a summary of overall HRQoL by using a visual analogue scale, which is usually a horizontal line with one indicating the worst health and the other end the best health. These assessments are easy to perform, but do not identify specific areas of dysfunction. One important note to mention is that these measurements must have the prerequisite characteristics that make them useful for the purpose intended. It is a key that the instrument must be reliable. The concept of reliability consists of three aspects: test-retest repeatability, inter-observer repeatability, and internal consistency. Another important characteristic of an instrument is validity. Validity refers to the ability of an instrument to correspond to the results of the criterion standard. Responsiveness, or sensitivity to change, is the instrument's ability to detect change in HRQoL.

2.9 Camel Milk

Milk is the sole fluid that provides complete nutritional requirements for mammals. The milk contains components that provide critical nutritive elements, immunological protection, and biologically active substances to both neonates and adults. The taste of camel milk is usually, sweet, when the camels are fed on green fodder, but sometimes salty, due to the feeding on certain shrubs and herbs. Camel seems to be similar to cow milk but not to human milk. Casein content of camel and cow milk are similar; however, the whey protein fraction is higher in camel milk. The ratio of whey protein to casein in camel milk is higher than in cow but lower than in human milk. This may potentially explain why the coagulum of camel milk is softer than of cow milk. Based on chemical composition, camel milk can meet at least as well or better, significant portions of the daily nutrient requirements of humans.

Milk contains elements that have anticariogenic properties such as calcium, phosphate, casein, and lipids.[81] Milk contains minor protective proteins; these are antibodies and non-antibody components, i.e., complements, lysozyme, lactoferrin, lactoperoxidase, xanthine oxidase, and leukocytes. Camel milk is characterized by higher contents of immunoglobulins, lysozyme, and lactoferrin. In addition to these protective proteins, milk contains caseins, α-lactalbumin, β-lactoglobulin, proteose-peptone fractions, serum albumin, and other minor peptides. Understanding the primary structure of α-lactalbumin in camel milk could potentially explain the therapeutic power of the milk in treating patients with Crohn's disease. α-lactalbumin is a protein present in milk of mammals and is a component of lactose synthase. It facilitates lactose synthesis of the galactosyltransferase component of the enzyme. The camel α-lactalbumin contains 123 residues, like bovine α-lactalbumin. The structure of the α-lactalbumin has a molecular mass of 14.6 kDa. It has been shown that the camel α-lactalbumin exhibits comparatively large differences from proteins of the other species.[72] What is reported is that the residues of camel milk 1-123 and 4-123, differ in size respectively, and occur with the longer form in a larger amount.

Camel milk has shown that it may have properties towards medicinal use. Camel milk in its raw state and its fermented products are used as therapeutic agents to treat stomach ulcers, liver disorders, diarrhea, constipation, and wounds, as well as to enhance female ovaries for ovulations.

CHAPTER III

METHODOLOGY

3.1 Research Summary

Crohn's disease (CD) and ulcerative colitis (UC) are known as inflammatory bowel disease (IBD) that causes chronic disorders of the gastrointestinal tract. The precise causes of these disorders are unknown; however, many scientists and physicians have speculated that patients are susceptible to a host of triggers. The burden of the illness for an individual case is high because the condition is associated with a substantial morbidity and decreased quality of life.[72-75] The main goal of this study is to better understand hospitalization for patients dealing with chronic inflammatory bowel disease. Using the HCUP data set for the years 2008-2012 will help better understand how the disease is reported across various regions in the United States dealing with this disease.

This is a retrospective, observational, cohort study of Crohn's disease patients in an existing HCUP database. Limited by the available data, the study period for this comparison will be from 2008-2012. The goals and objectives of this dissertation are related to the study of Crohn's disease as a major health issue that people face. The key goal and objective is to be able to produce a predictive model demonstrating the impact of Crohn's disease across the United States over the next several years. The model will present several comorbidities of Crohn's disease and how they impact medical management, prognosis and overall medical expenditure.

This dissertation will seek to answer the following questions relating to Crohn's disease after extensive data analysis of past and present conditions of the disease.

1) What is the medical expenditure of Crohn's disease to health care providers?
2) What factors influence the cost of Crohn's disease?
3) What are the cost differences of Crohn's disease by state or other social economic factors?
4) Who is most likely to be diagnosed with Crohn's disease?

5) What trends emerge for individuals with Crohn's disease amongst race, age, and gender for different comorbidities?
6) How does lifestyle impact the cost of Crohn's disease?
7) What is the alternative medical management that can help with treatment of Crohn's that will reduce medical cost over the lifetime of the treatment?

Chapter 3 will present a road map of the statistical and bioinformatics techniques used in this study. This overview will include the following: study design, population, sampling method, sample size, and data analysis methods.

3.2 Nationwide Inpatient Sample Introduction

In the United States, hospitals participate in a program which collect data on patient treatment during their hospital stay. The hospitals, which are included in this database, are part of either an urban network of healthcare systems or they are located in rural areas across the country. For this research dissertation, data will be extracted from the Nationwide Inpatient Sample (NIS) for years 2008-2012. The NIS is part of The Health Cost and Utilization Project (HCUP). HCUP is a collective software and database that was developed through a Federal-State-Industry partnership and is sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP brings together in an organized manner data that is collected by state data organizations, hospital associations, private data organizations, and the Federal government. These databases enable researchers to study healthcare issues relating to health care policies, which include cost and quality of health care services at the national, state and local levels. Broader information about this HCUP project can be found online at www.hcup-us.arq.gov.

3.2.1 Data Instrumentation

For this study, no measurement instruments or scientific tools will be used to collect the data. The data will be taken from NIS dataset which will be provided through HCUP. The data is collected across hospitals using discharge records from participating hospitals across the United States. The NIS depends on the hospital to provide accurate and complete information. The validity and reliability and the quality of the data submitted to HCUP is out of the researcher's control.

3.3 Study Variables and Data Element Collection

There are four ICD-9-CM codes for Crohn's disease which are defined as follows: 555.0, 555.1, 555.2 and 555.9. For Inflammatory bowel disease the following ICD-9-CM code was defined: 569.89; and ulcerative colitis was defined as follows: 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.7 556.8, 556.9. Each of these codes will be used to examine Crohn's disease, inflammatory bowel disease and ulcerative colitis events for the following years: 2008-2010. There are over 100 data elements for each NIS data year. The following data elements were selected for all three years.

Data Element	Type	Description
AGE	Numeric	Age in years at admission
RACE	Categorical	Race, uniform coding (1) White, (2) black, (3) Hispanic, (4) Asian or pacific islander, (5) Native American, (6) other
DX1-DX25	Numeric	Principal and secondary diagnosis codes (ICD-9-CM)
FEMALE	Categorical	Gender of patient: (0) male, (1) female
HOSPST	Categorical	State postal code for hospital (e.g., AZ for Arizona)
HOSP_LOCATION	Categorical	Location: (0) rural, (1) urban
HOSP_REGION	Categorical	Region of Hospital: (1) Northeast, (2)Midwest, (3) South, (4) West
LOS	Numeric	Length of stay, edited
PAY1	Categorical	Expected primary payer, uniform: (1) Medicare, (2) Medicaid, (3) private including HMO, (4) self-pay, (5) no charge, (6) other
RACE	Categorical	Race includes (1) white, (2) black, (3) Hispanic, (4) Asian or Pacific Islander, (5) Native American, (6) other
TOTCHG	Numeric	Total charges, edited
YEAR	Numeric	Calendar year: 2008, 2009, 2010, 2011, 2012
CM_ARTH	Severity	Rheumatoid arthritis/collagen vascular disease
CM_BLDLOSS	Severity	Blood loss
CM_DM	Severity	Diabetes
CM_Liver	Severity	Liver Disease
CM_WGHTLOSS	Severity	Weight Loss
CM_ANEMDEF	Severity	Deficiency anemias

Table 3: Nationwide Inpatient Sample Data Elements

3.4 Analytical Techniques

In this section, statistical analysis of the 2008-2010 core data sets will be analyzed. Statistical modeling analysis will be performed using SAS software version 9.4 within a Windows 10 environment. Descriptive statistics of mean and standard deviation for continuous variables with approximately normal distribution, and percentages for categorical and binary variables will be calculated for all baseline measures including demographics and clinical characteristics, commodities, indices, events, and other healthcare utilization costs.

Univariate comparisons of Crohn's diagnosis and treatment related healthcare utilization and costs and treatment patterns indices by treatment will be conducted. For treatment comparisons of continuous variables with an approximately normal distribution student t-test will be used. For comparison of categorical variables or binary variables, chi-square test will be used.

3.4.1 Descriptive Statistical Analysis

The descriptive statistical analysis is to produce a detailed summary of the data set which includes percentage counts and uncovers general trends and variations among different groups of patients who are being treated for Crohn's disease with standard care of treatment. The descriptive statistics are a combination of methods, processes, and decisions used in making statistical observation of sample size. In this dissertation, descriptive analysis will examine whether there are stastically significant numerical observations within the 2008-2010 dataset from HCUP.

Data elements will be analyzed to determine the frequency and percentages of Crohn's disease diagnoses on the national and state level. Using SAS functions such as PROC SORT, PROC MEANS, PROC TABULATE, PROC UNIVARIATE, PROC FREQ, would allow obtaining a preliminary analysis of the patient population for Crohn's diagnosis and initial treatment.

3.5 Regression Methods

A regression method will be used to determine the variables for use in the model being studied and to understand if the model fits the data. A stepwise method will be used and compared to the results for a multiple regression and /or logistic regression. A regression method is represented mathematically as follows: The parameters α, β_1, ..., β_k are usually estimated by maximum likelihood.

Figure 2: Logistic Regression Model Equation

$$\operatorname{logit}(p_i) = \ln\left(\frac{p_i}{1-p_i}\right) = \alpha + \beta_1 x_{1,i} + \cdots + \beta_k x_{k,i},$$

$$i = 1, \ldots, n, \qquad p_i = \Pr(Y_i = 1).$$

$$p_i = \Pr(Y_i = 1|X) = \frac{e^{\alpha+\beta_1 x_{1,i}+\cdots+\beta_k x_{k,i}}}{1+e^{\alpha+\beta_1 x_{1,i}+\cdots+\beta_k x_{k,i}}}.$$

A general linear model (GLM), which was previously described as represented as $\mathbf{Y} = \mathbf{XB} + \mathbf{U}$, is a type of multiple regression and will be compared to the other models for fit.

3.6 Analysis of Variance (ANOVA)

Analysis of variance was developed to analyze difference among group means and their associated procedures. This method was developed by Ronald Fisher. In ANOVA setting, the observed variance in a particular variable is partitioned into components attributed to different sources of variation. ANOVA provides a statistical test of whether or not the means of several groups are equal, and therefore generalizes the t-*test* to more than two groups. ANOVA is useful in comparing three or more means for statistical significance. In this section of the thesis, ANOVA is used to study and assess the difference among means of the data set for 2008-2012 by comparing the value of *F ratio* to the *F crit.* The *F ratio* represents the ratio of the variance between groups to the variance within groups. The *F crit* represents the threshold value when the test is to be rejected. ANOVA will be necessary to evaluate the difference among race, age and gender within the years 2008-2012. The results obtained from ANOVA analysis will give a better

understanding to the underlying probability that Crohn's disease is more prevalent among certain ethnic groups and age categories.

3.7 Summary

Chapter 3 summarizes the methodology process that is going to be carried out for this retrospective study examining hospitalization data related to Crohn's disease. Both male and females between ages 18 and 65 and the various ethnic groups (White, Black, Hispanic, Asian, Native American, Others) make up the population of this study. Insurance information data is captured and added to this analysis. The data was taken directly from the NIS HCUP database, namely core and severity datasheets, for the years 2008, 2009, 2010, 2011 and 2012.

Bio statistical analysis techniques will be applied to understand the relationship between independent variables and dependent variables. Hypothesis testing will be done using logistic regressions to better understand the relationships. Preliminary descriptive results are discussed in chapter 4.

CHAPTER IV

RESULTS

This chapter discusses preliminary results obtained by examining the HCUP data set for the years 2008-2012. The analysis preformed is described in chapter 3 methodology. The results measure frequencies and percentages for descriptive statistical analysis variables. Each variable was examined separately.

4.1 Research Summary

Healthcare costs in the US are higher than any other country. Recent studies have shown that the cost of Crohn's Disease (CD) is more expensive in the US than in other Western countries. Patients living with CD in the US, depending on location, have shown differences in the cost of treatment and diagnosis. The cost of treatment is driven by the type of treatment that a patient is being put on. Treatment type is dependent on the severity of the disease. It is an individualized treatment process. For example, 5-ASA compounds, used primarily for mild to moderate active disease, is generally more affordable than immunomodulator or biologic therapies.

Results for Crohn's disease discharge patients between the time periods of 2008-2012 across hospitals in five states (NJ, FL, CA, WA and NE):

Years	New Jersey	Florida	California	Washington	Nebraska
2008	1,628	4,379	3,750	1,089	276
2009	1,623	4,415	3,904	1,113	250
2010	1,640	4,701	3,835	1,204	257
2011	1,700	5,041	3,886	1,110	274
2012	1,702	5,021	3,939	1,137	295

Table 4. Total Number of Crohn's Disease Discharge per State for 2008-2012.

4.2 Descriptive Statistical Analysis

The source population for this study included ~ 60,000 individuals. Overall, ~6,200 (67.5%) were adults between the ages of 18-40. Approximately ~ 60% of the population was males, ~70% were insured by Medicaid programs, and the regional distribution was as follows: 27% Northeast, 23% Midwest, 36% South, and 14% West. Overall, 35,987 Crohn's disease (CD) patients were identified. Over the 3-year period, patients had at least 1 CD-related hospitalization. For Ulcerative Colitis (UC), 20,725 patients were identified; For Inflammatory Bowel Disease, (IBD), 2,245 patients were identified. Overall, prevalence of CD, UC and IBD is estimated by age group, sex, race, region and healthcare plan type, which are presented in Table 5, 7, and 9 respectively. Tables 6, 8 and 10 present comorbidities associated with CD, UC and IBD according to gender.

The results from the descriptive statistical analysis will provide an insight with a clear understanding to the data set that was used to analyze hospital data for patients with CD for the years 2008-2010. As a comparison factor, IBD and UC were used to show differences and trends in patients that are diagnosed with these diseases. These diseases are very similar in nature and therefore are important to the analysis of this work. The tables below will show the descriptive analysis of the data for years 2008-2012.

Table 5. Baseline Patient Demographics for 2008

	(N)	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Characteristics	20,347	12,393	791	7,163
Length of Stay mean	5.7 ± 6.04			
Age Group, N (%)				
18-40	9,550 (46.9%)	6,506 (68.1%)	130 (1.3%)	2,914 (30.5%)
41-64	7,277 (35.8%)	4,478 (61.5%)	307 (4.2 %)	2,492 (34.2%)
65+	3,520 (17.3%)	1,409 (40.0%)	354 (10.1%)	1,757 (49.9%)
Sex N (%)				
Male	8,918 (43.9%)	5,276 (59.2%)	348 (3.9%)	3,294 (36.9%)
Female	11,390 (56.1%)	7,098 (62.3%)	442 (3.9%)	3,850 (33.8%)
Race N (%)				
White	12,589 (77.1%)	7,736 (61.4%)	483 (3.8%)	4,370 (34.7%)
Black	1,820 (7.2%)	1,173 (64.4%)	61 (3.3%)	586 (32.2%)
Hispanic	1,188 (7.2%)	584 (49.1%)	53 (4.4%)	551 (46.3%)
Asian	188 (1.2%)	80 (42.6%)	7 (3.7%)	101 (53.7%)
Native American	49 (0.3%)	28 (57.1%)	0 (0%)	21 (42.9%)
Other	498 (3.1%)	253 (50.8%)	13 (2.6%)	232 (46.6%)
Health Plan Type, N (%)				
Medicare	4,794 (23.6%)	2,551 (53.2%)	40 (8.4%)	1,842 (38.4%)
Medicaid	2,420 (11.9%)	1,718 (71.0%)	59 (2.4%)	643 (26.6%)
Private Including HMO	10,684 (52.6%)	6,561 (61.4%)	275 (2.5%)	3,848 (36.0%)
Self Pay	1,372 (6.8%)	897 (65.3%)	30 (2.2%)	445 (32.4%)
Nocharge	216 (1.1%)	145 (67.1%)	4 (1.9%)	67 (31.4%)
Other	834 (4.1%)	500 (59.9%)	22 (2.6%)	312 (37.4%)
Region N (%) Discharge				
Northeast	33,730	17,071 (27.0%)	7,385 (18.9%)	9,274 (25.6%)
Midwest	31,219	14,120 (22.6%)	9,778 (25.1%)	7,321 (20.1%)
South	50,402	22,932 (36.3%)	14,715 (37.8%)	12,755 (35.2%)
West	22,907	9,018 (14.3%)	7,015 (18.0%)	6,874 (18.9%)

Table 6. Baseline Clinical Comorbidities 2008

	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Deficiency Anemia			
Male	9,728 (61.1%)	663 (4.2%)	5,526 (34.7%)
Female	2,665 (60.2%)	128 (2.9%)	1,637 (36.9%)
Blood Loss Anemia			
Male	11,982 (62.1%)	768 (3.9%)	6,539 (33.9%)
Female	411 (38.8%)	23 (2.2%)	624 (58.9%)
Rheumatoid Arthritis			
Male	12,056 (60.8%)	768 (3.9%)	7001 (35.3%)
Female	337 (64.5%)	23 (4.4%)	162 (31.0%
Diabetes			
Male	11,600 (62.1%)	668 (3.5%)	6,408 (34.3%)
Female	793 (47.5%)	123 (7.3%)	755 (45.1%)
Liver Disease			
Male	12,173 (61.2%)	750 (3.7%)	6,968 (35.0%)
Female	220 (48.2%)	41 (8.9%)	195 (42.8%)
Obesity			
Male	11,872 (61.0%)	729 (3.9%)	6,420 (34.6%)
Female	521 (58.5%)	56 (6.3%)	313 (35.1%)
Weight Loss			
Male	11,386 (61.4%)	729 (3.9%)	6,420 (34.6%))
Female	1,007 (55.5%)	62 (3.4%)	743 (41.0%

Table 7. Baseline Patient Demographics for 2009

	(N)	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Characteristics	19,327	11,762	742	6,823
Length of stay mean	5.6 ± 5.9			
Age Group, N (%)				
18-40	8,972 (46.4%)	6,097 (67.9%)	109 (1.2%)	2,766 (30.8%)
41-64	7,134 (36.9%)	4,301 (60.2%)	296 (4.1%)	2,537 (35.5%)
65+	3,221 (16.6%)	1,364 (42.3%)	337 (10.5%)	1,520 (47.2%)
Sex N (%)				
Male	8,607 (44.6%)	5,078 (59.0%)	320 (3.7%)	3,209 (37.3%)
Female	10,693 (55.4%)	6,676 (62.4%)	420 (3.9%)	3,597 (33.6%)
Race N (%)				
White	12,310 (77.3%)	7,489 (60.8%)	475 (3.8%)	4,346 (35.3%)
Black	1,803 (11.3%)	1,165 (64.6%)	78 (4.3%)	560 (31.1%)
Hispanic	1,058 (6.6%)	500 (47.2%)	47 (4.4%)	511 (48.3%)
Asian	196 (1.2%)	95 (48.4%)	7 (3.5%)	94 (47.9%)
Native American	65 (0.41%)	39 (60.0%)	3 (4.6%)	23 (35.4%)
Other	487 (3.1%)	245 (50.3%)	23 (4.7%)	219 (44.9%)
Health Plan Type, N (%)				
Medicare	4,558 (23.6%)	2,504 (54.9%)	373 (8.2%)	1,681 (36.9%)
Medicaid	2,384 (12.3%)	1,681 (70.5%)	56 (2.3%)	647 (27.1%)
Private Including HMO	9,717 (50.4%)	5,883 (60.5%)	251 (2.6%)	3,583 (36.8%)
Self Pay	1,638 (8.5%)	1,057 (64.5%)	35 (2.1%)	546 (33.3%)
Nocharge	192 (1.0%)	135 (70.3%)	4 (2.1%)	53 (27.6%)
Other	784 (4.1%)	465 (59.3%)	21 (2.6%)	298 (38.0%)
Region N (%) Discharge				
Northeast	21,412	13,001 (21.4%)	727 (18.8%)	7,684 (21.6%)
Midwest	27,625	17,608 (28.9%)	874 (22.6%)	9,143 (25.7%)
South	34,032	20,949 (34.4%)	1,405 (36.3%)	11,678 (32.9%)
West	17,092	9,260 (15.2%)	861 (22.2%)	6,971 (19.6%)

Table 8. Baseline Clinical Comorbidities 2009

	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Deficiency Anemia			
Male	9,019 (61.01%)	601 (4.1%)	5,146 (34.8%)
Female	2,743 (60.1%)	141 (3.1%)	1,677 (36.7)
Blood Loss Anemia			
Male	11,418 (62.1%)	725 (3.9%)	6,250 (33.9%)
Female	344 (36.4%)	17 (1.8%)	583 (61.7%)
Rheumatoid Arthritis			
Male	11,418 (60.8%)	719 (3.8%)	6,636 (35.3%)
Female	344 (62.1%)	23 (4.1%)	187 (33.7%)
Diabetes			
Male	10,961 (62.2%)	619 (3.5%)	6,057 (34.3%)
Female	801 (47.4%)	123 (7.28%)	766 (45.3%)
Liver Disease			
Male	11,524 (61.1%)	723 (3.8%)	6,626 (35.1%)
Female	238 (52.4%)	19 (4.2%)	197 (43.4%)
Obesity			
Male	11,179 (61.0%)	691 (3.7%)	6,449 (35.2%)
Female	583 (57.8%)	51 (5.1%)	374 (37.1%)
Weight Loss			
Male	10,586 (61.1%)	665 (3.8%)	6,085 (35.1%)
Female	1,176 (59.1%)	77 (3.8%)	738 (37.1%)

Table 9. Baseline Patient Demographics for 2010

	(N)	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Characteristics	19,283	11,832	712	6,739
Length of stay mean	5.4 ± 5.9			
Age Group, N (%)				
18-40	9,087 (47.1%)	6,201 (68.2%)	107 (1.1%)	2,779 (30.6%)
41-64	7,021 (36.4%)	4,306 (61.3%)	286 (4.1%)	2,429 (34.6%)
65+	3,175 (16.5%)	1,325 (41.7%)	319 (10.1%)	1,531 (48.2%)
Sex N (%)				
Male	8,576 (44.5%)	5,043 (58.8%)	317 (3.7%)	3,216 (37.5%)
Female	10,694 (55.5%)	6,782 (63.4%)	395 (3.6%)	3,517 (32.9%)
Race N (%)				
White	12,850 (66.6%)	8,035 (64.3%)	458 (3.6%)	4,357 (33.9%)
Black	2,382 (12.3%)	1,532 (64.3%)	77 (3.2%)	77 (32.5%)
Hispanic	1,218 (6.3%)	546 (44.8%)	55 (4.5%)	617 (50.7%)
Asian	232 (1.2%)	100 (43.1%)	17 (7.3%)	115 (49.5%)
Native American	83 (0.43%)	44 (53.0%)	6 (7.2%)	33 (39.7%)
Other	500 (2.6%)	282 (56.4%)	8 (1.6%)	210 (42.0%)
Health Plan Type, N (%)				
Medicare	4,710 (24.5%)	2,622 (55.7%)	360 (7.6%)	1,728 (36.7%)
Medicaid	2,806 (14.6%)	1,944 (69.2%)	60 (2.1%)	802 (28.6%)
Private Including HMO	9,029 (46.9%)	5,616 (62.2%)	224 (2.5%)	3,189 (35.3%)
Self-Pay	1,600 (8.7%)	1,049 (62.1%)	47 (2.8%)	594 (35.2%)
Nocharge	197 (1.0%)	128 (65.0%)	3 (1.5%)	66 (33.5%)
Other	809 (4.2%)	443 (54.8%)	17 (2.1%)	349 (43.1%)
Region N (%) Discharge				
Northeast	22,308	13,765 (22.4%)	680 (17.6%)	7,864 (22.1%)
Midwest	24,687	15,836 (25.8%)	949 (24.6%)	7,901 (22.2%)
South	36,346	22,781 (37.1%)	1,390 (36.0%)	12,175 (34.3%)
West	17,309	8,951 (14.5%)	838 (21.7%)	7,520 (21.2%)

Table 10. Baseline Clinical Comorbidities 2010

	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Deficiency Anemia			
Male	8,985 (61.4%)	579 (3.9%)	5,047 (34.5%)
Female	2,847 (60.9%)	133 (2.8%)	1,692 (36.2%)
Blood Loss Anemia			
Male	11,498 (62.6%)	699 (3.8%)	6,175 (33.6%)
Female	334 (36.7%)	13 (1.4%)	564 (61.9%)
Rheumatoid Arthritis			
Male	11,429 (61.1%)	693 (3.7%)	6,574 (35.2%)
Female	403 (68.7%)	19 (3.2%)	165 (28.1%)
Diabetes			
Male	10,982 (62.8%)	588 (3.4%)	5,930 (33.9%)
Female	850 (47.7%)	124 (6.9%)	809 (45.4%)
Liver Disease			
Male	11,562 (61.7%)	679 (3.6%)	6,494 (34.7%)
Female	270 (49.3%)	33 (6.0%)	245 (44.7%)
Obesity			
Male	11,244 (61.5%)	651 (3.6%)	6,389 (34.9%)
Female	588 (58.9%)	61 (6.1%)	350 (35.0%)
Weight Loss			
Male	10,716 (61.9%)	630 (3.6%)	5,946 (34.4%)
Female	1,116 (56.1%)	82 (4.1%)	793 (39.7%)

Table 11. Baseline Patient Demographics for 2011

	(N)	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Characteristics	21,262	12,996	810	7,456
Length of stay mean	5.2 ± 5.2			
Age Group, N (%)				
18-40	9,868 (46.1%)	6,703 (35.1%)	120 (0.5%)	3,045 (14.3%)
41-64	7,807 (36.7%)	4,727 (22.2%)	326 (1.53%)	2,754 (12.9
65+	3,587 (16.8%)	1,566 (7.3%)	364 (1.7%)	1,657 (7.7%)
Sex N (%)				
Male	9,419 (44.3%)	5,593 (26.3)	365 (1.7%)	3,461 (16.2%)
Female	11,824 (55.6%)	7,398 (34.8%)	445 (2.1%)	3,981 (18.7%)
Race N (%)				
White	14,175 (73.8%)	8,740 (45.5%)	531 (2.7%)	4,904 (25.5%)
Black	2,765 (14.4%)	1,831 (9.5%)	91 (0.4%)	843 (4.3%)
Hispanic	1,437 (7.4%)	634 (3.3%)	84 (0.4%)	719 (3.7%)
Asian	237 (1.2%)	106 (0.5%)	8 (0.4%)	123 (0.6%)
Native American	43 (0.2%	2 (0.01%)	21 (0.11%)	66 (0.34%)
Other	291 (1.5%)	23 (0.12%)	203 (1.0%)	517 (2.6%)
Health Plan Type, N (%)				
Medicare	5,249 (24.7%)	2,901 (13.6%)	405 (1.9%)	1,943 (9.1%)
Medicaid	3,017 (14.2%)	2,057(9.7%)	80 (0.38%)	880 (4.1%)
Private Including HMO	10,259 (48.4%)	6,305 (29.7%)	275 (1.3%)	3,679 (17.3%)
Self Pay	1,671 (7.8%)	1,122 (5.3%)	32 (0.15%)	517 (2.4%)
Nocharge	95 (0.45%)	1 (0.00%)	76 (0.36%)	172 (0.81%)
Other	818 (3.8%)	465 (2.1%)	16 (0.8%)	337 (1.59%)
Region N (%) Discharge				
Northeast	22,920	14,317 (22.7%)	744 (18.5%)	7,859 (22.4%)
Midwest	23,869	15,529 (24.6%)	997 (24.8%)	7,343 (20.9%)
South	39,671	24,853 (39.5%)	1,528 (30.1%)	13,290 (37.9%)
West	15,480	8, 210 (13.0%)	737 (18.4%)	6,533 (18.6%)

Table 12. Baseline Clinical Comorbidities 2011

	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Deficiency Anemia			
Male	9,695 (45.6%)	665 (3.1%)	5,528 (26.0%)
Female	396 (1.8%)	20 (0.09%)	611 (2.8%)
Blood Loss Anemia			
Male	12,600 (59.2%)	790 (3.7%)	6,845 (32.1%)
Female	396 (1.8%)	30 (0.09%)	611 (2.8%)
Rheumatoid Arthritis			
Male	12,509 (58.8%)	772 (3.6%)	7,244 (34.0%)
Female	487 (2.2%)	38 (0.1`8%)	212 (1.00%)
Diabetes			
Male	12,044 (56.6%)	670 (3.1%)	6,629 (31.1%)
Female	952 (4.4%)	140 (0.66%)	827 (3.8%)
Liver Disease			
Male	12,633 (59.4%)	760 (3.5%)	7,187 (33.8%)
Female	363 (1.7%)	50 (0.24%)	269 (1.2%)
Obesity			
Male	12,253 (57.6%)	741 (3.4%)	6,976 (32.8%)
Female	743 (3.4%)	69 (0.32%)	480 (2.2%)
Weight Loss			
Male	11,573 (54.4%)	724 (3.4%)	6,404 (30.1%)
Female	1,423 (6.6%)	86 (0.40%)	1,052 (4.9%)

Table 13. Baseline Patient Demographics for 2012

	(N)	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Characteristics	18,593	12,593	757	7,138
Length of stay mean	5.1 ± 5.3			
Age Group, N (%)				
18-40	8,700 (45.9%)	5,923 (68.1%)	112 (1.2%)	2,665 (30.6%)
41-64	7,008 (36.9%)	4,348 (62.0%)	257 (3.6%)	2,403 (34.2%)
65+	3,244 (17.1%)	1,420 (43.7%)	323 (9.9%)	1,501 (46.2%)
Sex N (%)				
Male	8,577 (45.2%)	5,114 (26.9%)	319 (1.6%)	3,144 (16.5%)
Female	10,375 (54.7%)	6,577 (34.7%)	373 (1.9%)	3,425 (18.0%)
Race N (%)				
White	13,323 (74.3%)	8,412 (46.9%)	464 (2.5%)	4447 (24.8%)
Black	2,484 (13.8%)	1,642 (9.1%)	89 (3.5%)	753 (30.3%)
Hispanic	1,261 (7.0%)	556 (44.0%)	58 (4.6%)	647 (51.3%)
Asian	234 (1.3%)	112 (47.8%)	27 (11.5%)	95 (40.6%)
Native American	71 (0.40%)	38 (53.5%)	6 (8.4%)	27 (38.0%)
Other	551 (3.0%)	298 (54.0%)	14 (2.5%)	239 (43.3%)
Health Plan Type, N (%)				
Medicare	4,801 (25.3%)	2,718 (56.6%)	361 (7.5%)	1,722 (35.8%)
Medicaid	2,730 (14.4%)	1,871 (68.5%)	71 (2.6%)	788 (30.3%)
Private Including HMO	8,825 (46.6%)	5,497 (62.2%)	203 (2.3%)	3,125 (35.4%)
Self-Pay	1,602 (8.4%)	1,024 (63.9%)	31 (1.9%)	547 (34.1%)
No charge	148 (0.78%)	94 (63.5%)	2 (1.3%)	52 (35.1%)
Other	804 (4.2%)	458 (56.9%)	24 (2.9%)	322 (40.1%)
Region N (%) Discharge				
Northeast	22,795	13,910 (22.0%)	835 (22.0%)	8,050 (22.5%)
Midwest	25,140	16,070 (25.5%)	965 (25.5%)	8,105 (27.7%)
South	38,045	24,275 (38.5%)	1,225 (32.3%)	12,545 (35.1%)
West	16,460	8,710 (23.8%)	760 (20.1%)	6,990 (19.5%)

Table 14. Baseline Clinical Comorbidities 2012

	Crohn's Disease	Inflammatory Bowel Disease	Ulcerative Colitis
Deficiency Anemia			
Male	8,775 (46.3%)	580 (4.1%)	4,817 (33.9%)
Female	2,916 (61.0%)	112 (2.3%)	1,752 (36.6%)
Blood Loss Anemia			
Male	11,365 (62.8%)	681 (3.7%)	6,038 (33.3%)
Female	326 (37.5%)	11 (1.2%)	531 (61.1%)
Rheumatoid Arthritis			
Male	11,297 (61.5%)	660 (3.6%)	6,392 (34.8%)
Female	394 (65.3%)	32 (5.3%)	177 (29.3%)
Diabetes			
Male	10,849 (62.9%)	559 (3.2%)	5,821 (33.7%)
Female	842 (48.8%)	133 (7.7%)	748 (43.4%)
Liver Disease			
Male	11,376 (61.9%)	661 (3.6%)	6,335 (34.4%)
Female	315 (54.3%)	31 (5.3%)	234 (40.3%)
Obesity			
Male	10,962 (61.9%)	639 (3.6%)	6,099 (34.4%)
Female	729 (58.2%)	53 (4.2%)	470 (37.5%)
Weight Loss			
Male	10,498 (62.5%)	615 (3.6%)	5,676 (33.8%)
Female	1,193 (55.1%)	77 (3.5%)	893 (41.2%)

4.3 Logistic Regression Analysis Results

The results of the logistic regression analysis are presented in this section. The first parts of these results predict the relationship between patient's race and the outcome of Crohn's disease for the years 2008-2012. The second part of the results of the logistic regression tests the relation between age, gender, insurance type and medical comorbidities. Using results obtained from SAS 9.4 output will validate the results and determine if the models are suitable for the analysis made. The logistic model will use parameters to test the probability if outside factors contribute to Crohn's disease. The parameters of the models are validated by the AIC, SC and -2 Log L as they positively adjust the log-likelihood of the model depending on the number of predictors. The *c* (stands for c-statistic) shows the predicted probabilities of the model and validated for the particular model. For years 2008, 2009, 2010, 2011, and 2012 the *c*-statics values are as follows 0.6557, 0.6461, 0.6617, 0.6522, and 0.6530. This percentage refers to all the outcomes pairs that are correctly predicted by the model. Given a high value for *c*-statics suggests that the model does not predict the outcomes randomly but in a more positive outcome as seen with the following *c*-statics values of 65.5%, 64.5%, 66.1%, 65.2% and 65.3% respectively. Furthermore, the *c*-statics is used in a general term to reveal the predictive value of the logistic regression model. In this work, the outcome of the logistic model presented here is binary, which refers and is similar to the area under the ROC (receiver operating characteristic) curve. The ROC curves represents a plot of the true positive rate versus the false positive rate (1-Specificity).

The LOGISTIC Procedure

Model Information	
Data Set	WORK.MERGE2008ALL
Response Variable	Crohn’s
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	20347
Number of Observations Used	16313

Response Profile		
Ordered Value	**Crohn’s**	**Total Frequency**
1	1	9838
2	0	6475

Probability modeled is Crohn’s=1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	21918.326	21273.931
SC	21926.025	21297.030
-2 Log L	21916.326	21267.931

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	648.3952	2	<.0001
Score	658.3684	2	<.0001
Wald	629.7920	2	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.9957	0.0842	139.9684	<.0001
RACE	**(2)Black**		1	-0.0603	0.0555	1.1795	0.2775
RACE	**(3)Hispanic**		1	-0.6305	0.0640	96.9723	<.0001
RACE	**(4)Asian**		1	-0.7123	0.1547	21.2040	<.0001
RACE	**(5)Native American**		1	-0.1507	0.2960	0.2592	0.6106
RACE	**(6)Other**		1	-0.5215	0.0945	30.4264	<.0001
agecat	**(2)41-64**		1	-0.5306	0.1390	14.5634	0.0001
agecat	**(3) 65+**		1	-1.3984	0.7208	3.7641	0.0524
PAY1	**(1)medicare**		1	0.8833	0.1496	34.8771	<.0001
PAY1	**(2)medicaid**		1	0.2125	0.1036	4.2077	0.0402
PAY1	**(3) Private including HMO**		1	-0.2755	0.0885	9.6850	0.0019
PAY1	**(5)nocharge**		1	0.1830	0.2270	0.6501	0.4201
PAY1	**(6)other**		1	-0.1976	0.1334	2.1945	0.1385
agecat*PAY1	**(2)41-64**	**(1)medicare**	1	-0.1784	0.2018	0.7814	0.3767
agecat*PAY1	**(2)41-64**	**(2)medicaid**	1	0.1708	0.1745	0.9574	0.3279
agecat*PAY1	**(2)41-64**	**(3) Private including HMO**	1	0.3176	0.1464	4.7105	0.0300
agecat*PAY1	**(2)41-64**	**(5)nocharge**	1	0.1251	0.3513	0.1268	0.7218
agecat*PAY1	**(2)41-64**	**(6)other**	1	0.1898	0.2207	0.7400	0.3897
agecat*PAY1	**(3) 65+**	**(1)medicare**	1	-0.7129	0.7326	0.9471	0.3305
agecat*PAY1	**(3) 65+**	**(2)medicaid**	1	0.2653	0.8444	0.0987	0.7534
agecat*PAY1	**(3) 65+**	**(3) Private including HMO**	1	0.6498	0.7307	0.7908	0.3738
agecat*PAY1	**(3) 65+**	**(5)nocharge**	1	-0.1421	1.4666	0.0094	0.9228
agecat*PAY1	**(3) 65+**	**(6)other**	1	-0.3363	0.8695	0.1496	0.6989
CM_ARTH			1	0.3206	0.1089	8.6618	0.0032
CM_BLDLOSS			1	-0.8891	0.0740	144.5496	<.0001
CM_DM			1	-0.3758	0.0615	37.3540	<.0001
CM_LIVER			1	-0.6402	0.1111	33.2306	<.0001
CM_WGHTLOSS			1	-0.1663	0.0584	8.0988	0.0044

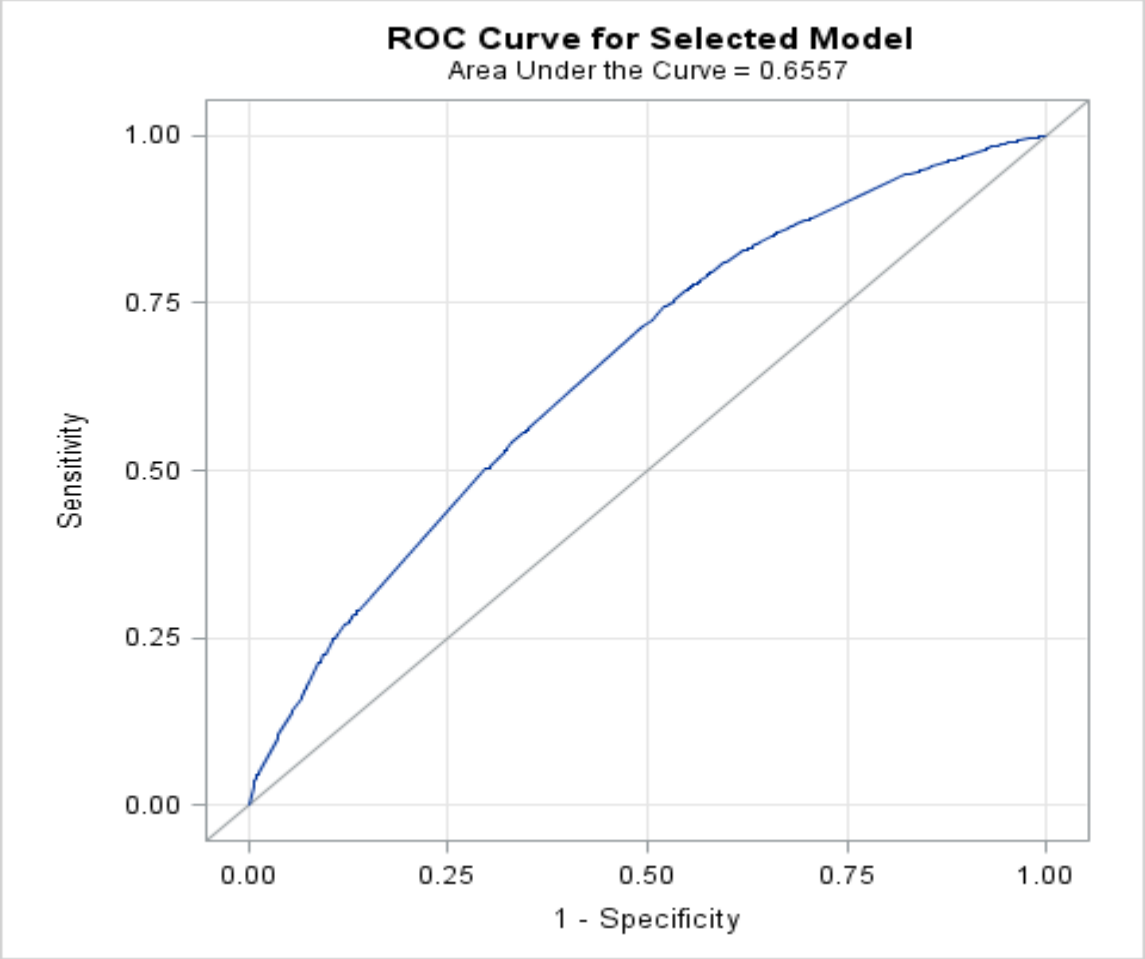


Figure 3: ROC Curve Logistic Regression Model with an area of 0.655 for 2008

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
RACE (2)Black vs (1)white	**1.0000**	0.942	0.844	1.050
RACE (3)Hispanic vs (1)white	**1.0000**	0.532	0.470	0.603
RACE (4)Asian vs (1)white	**1.0000**	0.491	0.362	0.664
RACE (5)Native American vs (1)white	**1.0000**	0.860	0.482	1.536
RACE (6)Other vs (1)white	**1.0000**	0.594	0.493	0.714
CM_ARTH	**1.0000**	1.378	1.113	1.706
CM_BLDLOSS	**1.0000**	0.411	0.356	0.475
CM_DM	**1.0000**	0.687	0.609	0.775
CM_LIVER	**1.0000**	0.527	0.424	0.655
CM_WGHTLOSS	**1.0000**	0.847	0.755	0.950

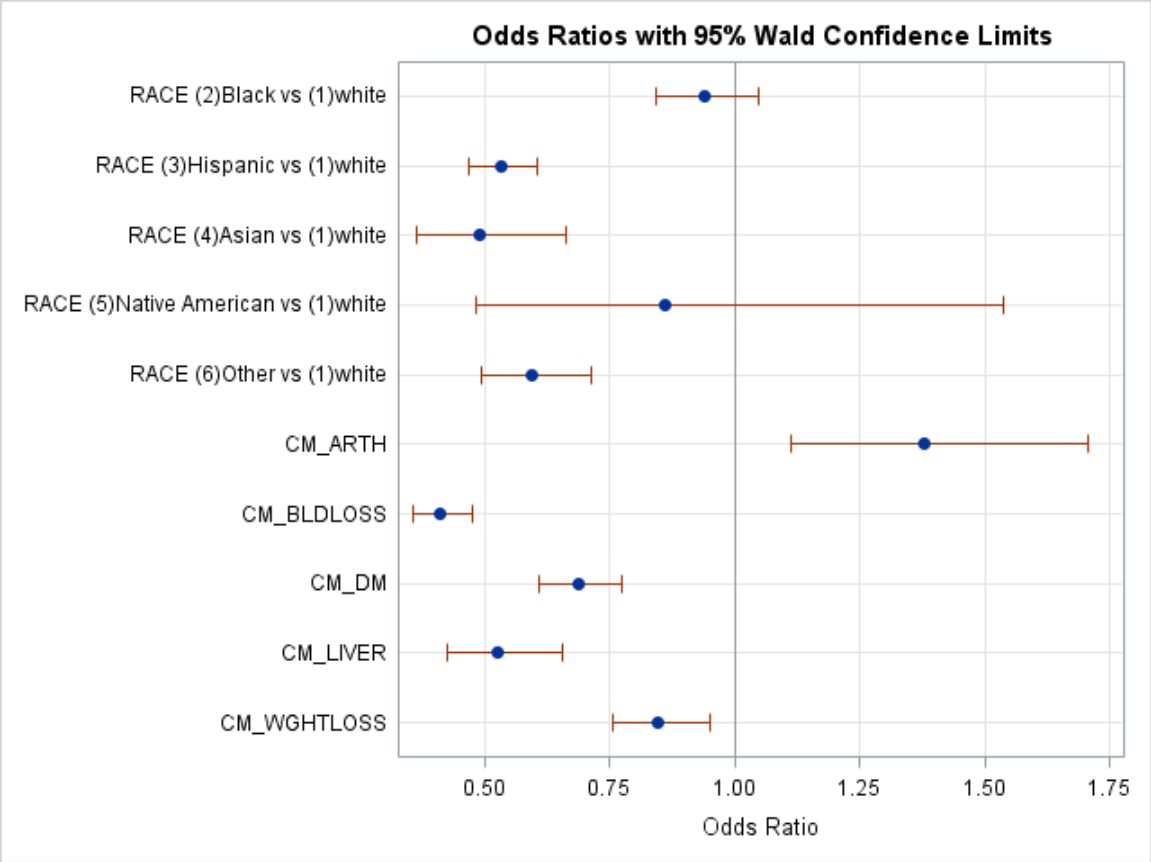


Figure 4: Odds Ratio Graph 2008

The LOGISTIC Procedure HCUP DATA 2009

Model Information	
Data Set	WORK.MERGE2009ALL
Response Variable	Crohn's
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	19327
Number of Observations Used	15882

Response Profile		
Ordered Value	**Crohn's**	**Total Frequency**
1	1	9509
2	0	6373

Probability modeled is Crohn's=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	21395.816	20877.035
SC	21403.489	20900.054
-2 Log L	21393.816	20871.035

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	522.7812	2	<.0001
Score	528.7491	2	<.0001
Wald	511.3035	2	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.8659	0.0738	137.5125	<.0001
RACE	**(2)Black**		1	-0.00141	0.0559	0.0006	0.9799
RACE	**(3)Hispanic**		1	-0.6629	0.0674	96.7636	<.0001
RACE	**(4)Asian**		1	-0.4852	0.1487	10.6531	0.0011
RACE	**(5)Native American**		1	-0.0588	0.2653	0.0491	0.8247
RACE	**(6)Other**		1	-0.4661	0.0958	23.6921	<.0001
agecat	**(2)41-64**		1	-0.3746	0.1246	9.0400	0.0026
agecat	**(3) 65+**		1	-2.0697	0.6514	10.0948	0.0015
PAY1	**(1)medicare**		1	1.0629	0.1514	49.3184	<.0001
PAY1	**(2)medicaid**		1	0.3380	0.0962	12.3428	0.0004
PAY1	**(3) Private including HMO**		1	-0.1698	0.0792	4.5889	0.0322
PAY1	**(5)nocharge**		1	0.3752	0.2323	2.6087	0.1063
PAY1	**(6)other**		1	-0.0770	0.1291	0.3556	0.5510
agecat*PAY1	**(2)41-64**	**(1)medicare**	1	-0.5732	0.1959	8.5635	0.0034
agecat*PAY1	**(2)41-64**	**(2)medicaid**	1	-0.1160	0.1626	0.5095	0.4754
agecat*PAY1	**(2)41-64**	**(3) Private including HMO**	1	0.1208	0.1332	0.8225	0.3645
agecat*PAY1	**(2)41-64**	**(5)nocharge**	1	0.2342	0.3667	0.4078	0.5231
agecat*PAY1	**(2)41-64**	**(6)other**	1	0.0764	0.2119	0.1299	0.7185
agecat*PAY1	**(3) 65+**	**(1)medicare**	1	0.0162	0.6661	0.0006	0.9805
agecat*PAY1	**(3) 65+**	**(2)medicaid**	1	0.6564	0.7960	0.6800	0.4096
agecat*PAY1	**(3) 65+**	**(3) Private including HMO**	1	1.3792	0.6637	4.3179	0.0377
agecat*PAY1	**(3) 65+**	**(5)nocharge**	1	-10.3005	161.8	0.0041	0.9492
agecat*PAY1	**(3) 65+**	**(6)other**	1	1.4607	0.7857	3.4561	0.0630
CM_BLDLOSS			1	-1.0027	0.0779	165.6020	<.0001
CM_DM			1	-0.3769	0.0604	38.9155	<.0001
CM_LIVER			1	-0.3075	0.1097	7.8598	0.0051

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
CM_ANEMDEF			1	-0.0864	0.0392	4.8516	0.0276

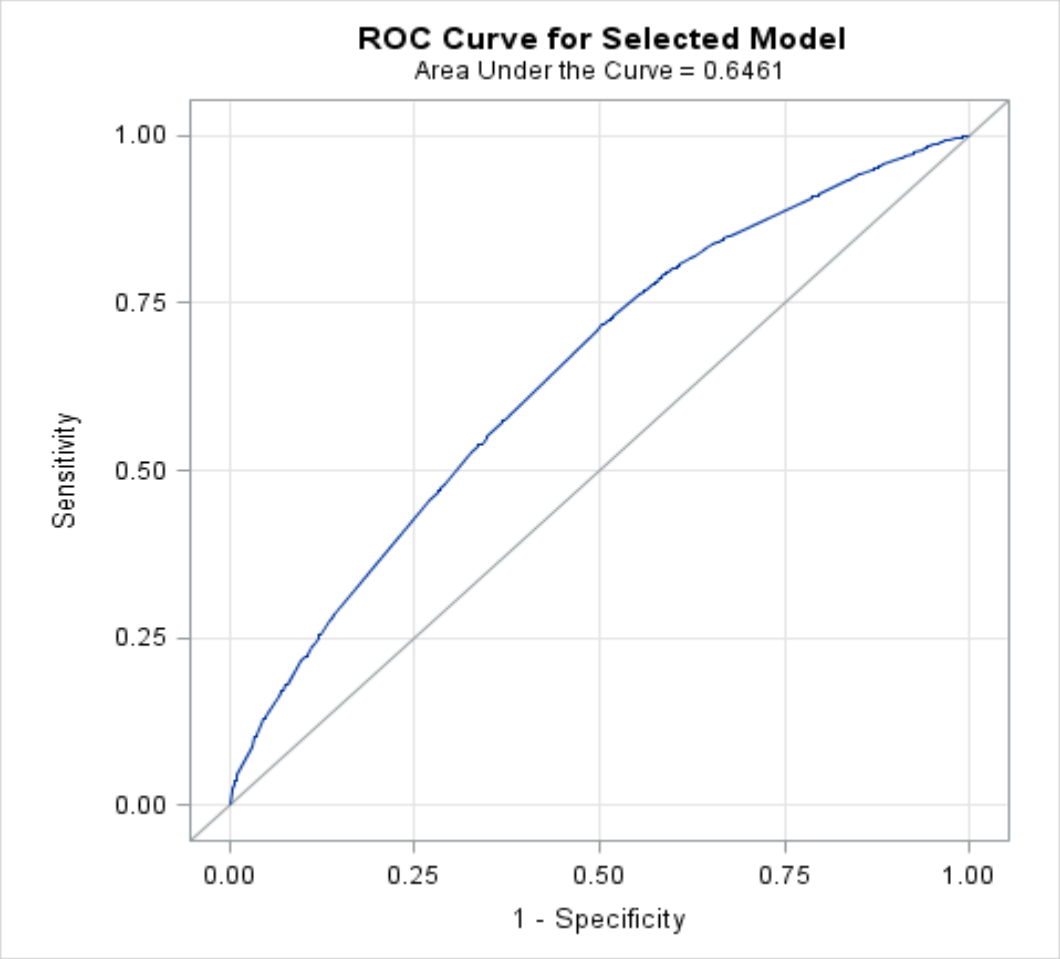


Figure 5: ROC Curve Logistic Regression Model with an area of 0.646 for 2009

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
RACE (2)Black vs (1)white	**1.0000**	0.999	0.895	1.114
RACE (3)Hispanic vs (1)white	**1.0000**	0.515	0.452	0.588
RACE (4)Asian vs (1)white	**1.0000**	0.616	0.460	0.824
RACE (5)Native American vs (1)white	**1.0000**	0.943	0.561	1.586
RACE (6)Other vs (1)white	**1.0000**	0.627	0.520	0.757
CM_BLDLOSS	**1.0000**	0.367	0.315	0.427
CM_DM	**1.0000**	0.686	0.609	0.772
CM_LIVER	**1.0000**	0.735	0.593	0.912
CM_ANEMDEF	**1.0000**	0.917	0.849	0.991

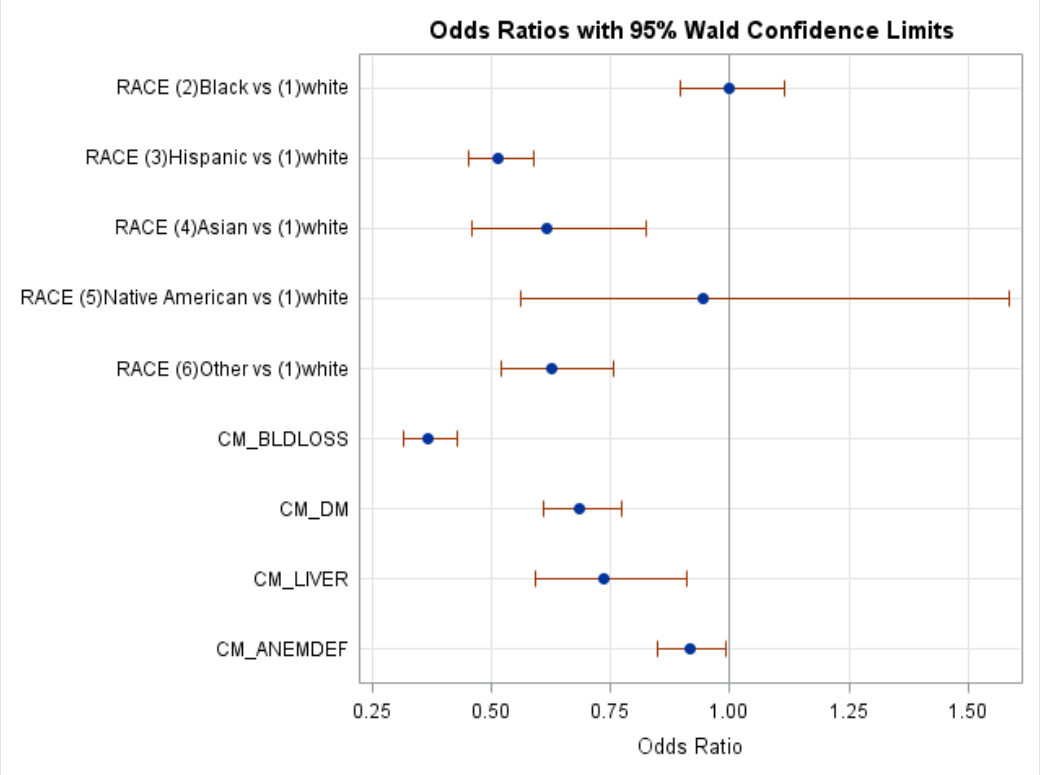


Figure 6: Odds Ratio Graph 2009

The LOGISTIC Procedure HCUP 2010

Model Information	
Data Set	WORK.MERGE2010ALL
Response Variable	Crohn’s
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	19283
Number of Observations Used	17230

Response Profile		
Ordered Value	**Crohn’s**	**Total Frequency**
1	1	10514
2	0	6716

Probability modeled is Crohn’s=1

Model Convergence Status		
Convergence criterion (GCONV=1E-8) satisfied.		
Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	23043.746	22427.012
SC	23051.500	22450.276
-2 Log L	23041.746	22421.012

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	620.7333	2	<.0001
Score	631.7118	2	<.0001
Wald	605.9236	2	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.8897	0.0679	171.8325	<.0001
RACE	**(2)Black**		1	-0.0659	0.0495	1.7705	0.1833
RACE	**(3)Hispanic**		1	-0.8062	0.0637	160.1839	<.0001
RACE	**(4)Asian**		1	-0.8024	0.1382	33.7142	<.0001
RACE	**(5)Native American**		1	-0.5431	0.2295	5.5993	0.0180
RACE	**(6)Other**		1	-0.3287	0.0952	11.9216	0.0006
agecat	**(2)41-64**		1	-0.5644	0.1193	22.3820	<.0001
agecat	**(3) 65+**		1	-0.6127	0.5539	1.2234	0.2687
PAY1	**(1)medicare**		1	1.0361	0.1314	62.2168	<.0001
PAY1	**(2)medicaid**		1	0.4323	0.0871	24.6062	<.0001
PAY1	**(3) Private including HMO**		1	-0.1291	0.0737	3.0686	0.0798
PAY1	**(5)nocharge**		1	0.1004	0.2133	0.2214	0.6380
PAY1	**(6)other**		1	-0.3994	0.1195	11.1691	0.0008
agecat*PAY1	**(2)41-64**	**(1)medicare**	1	-0.2726	0.1780	2.3434	0.1258
agecat*PAY1	**(2)41-64**	**(2)medicaid**	1	-0.1051	0.1509	0.4846	0.4863
agecat*PAY1	**(2)41-64**	**(3) Private including HMO**	1	0.3865	0.1283	9.0669	0.0026
agecat*PAY1	**(2)41-64**	**(5)nocharge**	1	0.4280	0.3547	1.4561	0.2276
agecat*PAY1	**(2)41-64**	**(6)other**	1	0.5617	0.1983	8.0188	0.0046
agecat*PAY1	**(3) 65+**	**(1)medicare**	1	-1.4448	0.5670	6.4929	0.0108
agecat*PAY1	**(3) 65+**	**(2)medicaid**	1	-1.0131	0.6726	2.2689	0.1320
agecat*PAY1	**(3) 65+**	**(3) Private including HMO**	1	-0.2363	0.5683	0.1729	0.6776
agecat*PAY1	**(3) 65+**	**(5)nocharge**	1	-9.1328	104.5	0.0076	0.9304
agecat*PAY1	**(3) 65+**	**(6)other**	1	-1.0700	0.7564	2.0013	0.1572
CM_ARTH			1	0.3865	0.0992	15.1662	<.0001
CM_BLDLOSS			1	-1.0455	0.0770	184.4334	<.0001
CM_DM			1	-0.4115	0.0570	52.0375	<.0001
CM_LIVER			1	-0.4675	0.0952	24.1045	<.0001
CM_WGHTLOSS			1	-0.1745	0.0530	10.8394	0.0010

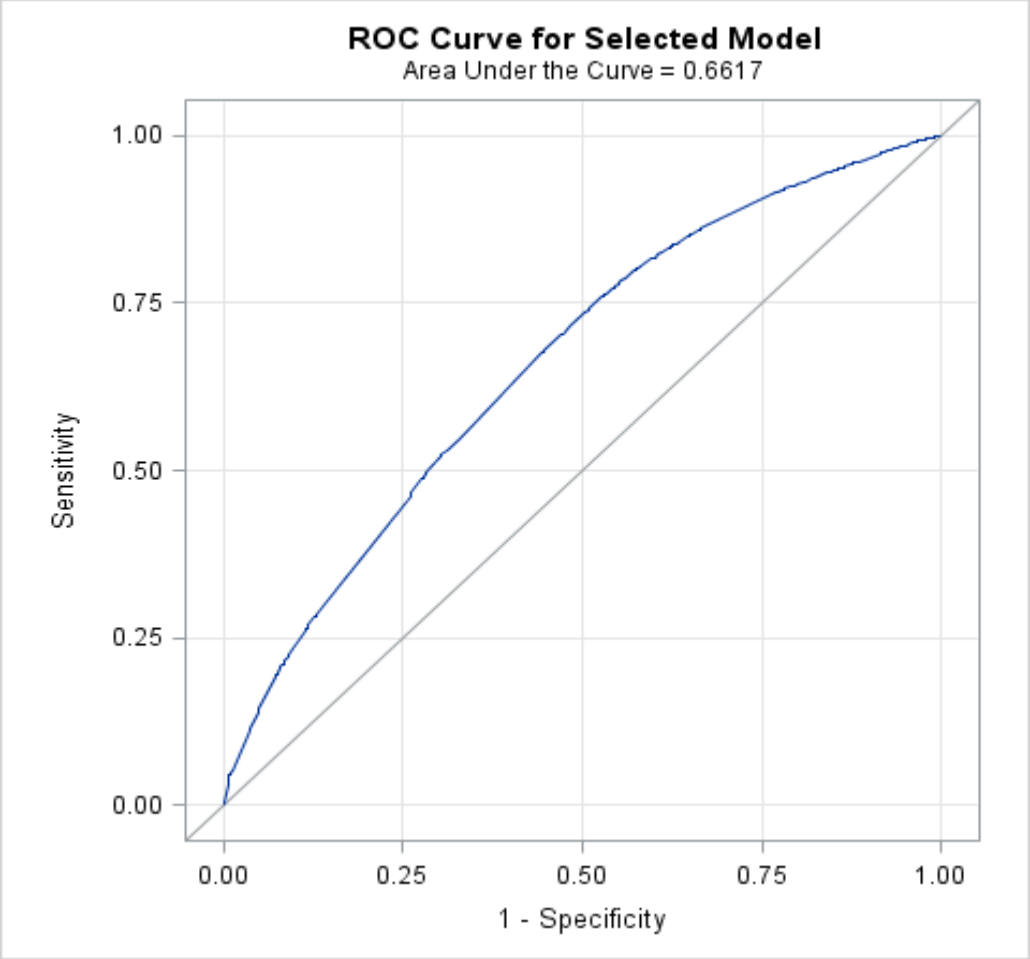


Figure 7: ROC Curve Logistic Regression Model with an area of 0.661 for 2010

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
RACE (2)Black vs (1)white	**1.0000**	0.936	0.850	1.032
RACE (3)Hispanic vs (1)white	**1.0000**	0.447	0.394	0.506
RACE (4)Asian vs (1)white	**1.0000**	0.448	0.342	0.588
RACE (5)Native American vs (1)white	**1.0000**	0.581	0.370	0.911
RACE (6)Other vs (1)white	**1.0000**	0.720	0.597	0.868
CM_ARTH	**1.0000**	1.472	1.212	1.788
CM_BLDLOSS	**1.0000**	0.352	0.302	0.409
CM_DM	**1.0000**	0.663	0.593	0.741
CM_LIVER	**1.0000**	0.627	0.520	0.755
CM_WGHTLOSS	**1.0000**	0.840	0.757	0.932

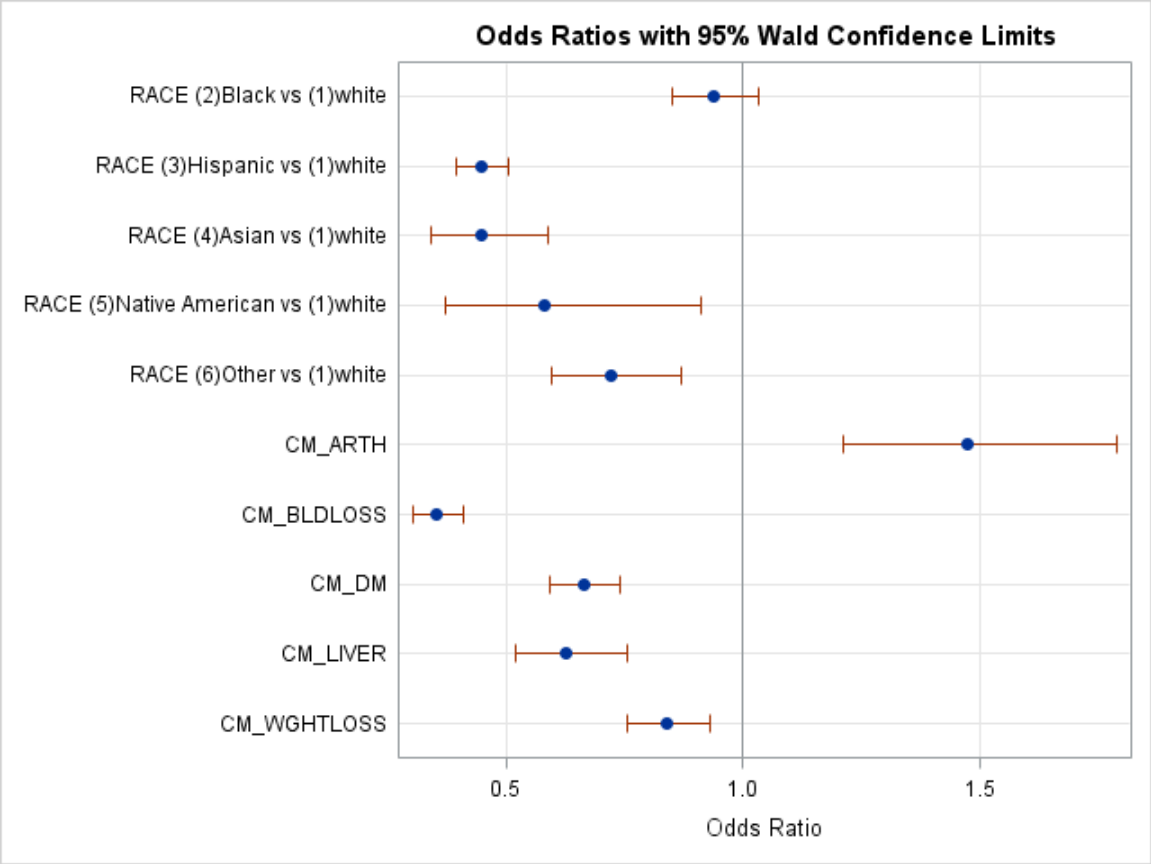


Figure 8: Odds Ratio Graph 2010

The LOGISTIC Procedure HCUP 2011

Model Information	
Data Set	WORK.MERGE2011ALL
Response Variable	Crohn’s
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	21262
Number of Observations Used	19136

Response Profile		
Ordered Value	**Crohn’s**	**Total Frequency**
1	1	11603
2	0	7533

Probability modeled is Crohn’s=1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	25657.841	25070.727
SC	25665.700	25094.305
-2 Log L	25655.841	25064.727

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	591.1138	2	<.0001
Score	598.7115	2	<.0001
Wald	580.2212	2	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.9908	0.0713	192.9981	<.0001
RACE	**(2)Black**		1	0.0197	0.0463	0.1812	0.6704
RACE	**(3)Hispanic**		1	-0.7836	0.0584	179.8100	<.0001
RACE	**(4)Asian**		1	-0.7222	0.1355	28.4242	<.0001
RACE	**(5)Native American**		1	0.0349	0.2693	0.0168	0.8968
RACE	**(6)Other**		1	-0.3551	0.0929	14.6111	0.0001
agecat	**(2)41-64**		1	-0.2031	0.1171	3.0076	0.0829
agecat	**(3) 65+**		1	-0.7692	0.5869	1.7179	0.1900
PAY1	**(1)medicare**		1	1.0848	0.1390	60.8740	<.0001
PAY1	**(2)medicaid**		1	0.1764	0.0880	4.0173	0.0450
PAY1	**(3) Private including HMO**		1	-0.2466	0.0760	10.5176	0.0012
PAY1	**(5)nocharge**		1	-0.4186	0.2097	3.9842	0.0459
PAY1	**(6)other**		1	-0.4413	0.1204	13.4282	0.0002
agecat*PAY1	**(2)41-64**	**(1)medicare**	1	-0.9741	0.1786	29.7462	<.0001
agecat*PAY1	**(2)41-64**	**(2)medicaid**	1	-0.3181	0.1458	4.7595	0.0291
agecat*PAY1	**(2)41-64**	**(3) Private including HMO**	1	-0.0912	0.1250	0.5316	0.4659
agecat*PAY1	**(2)41-64**	**(5)nocharge**	1	-0.2194	0.3754	0.3415	0.5590
agecat*PAY1	**(2)41-64**	**(6)other**	1	-0.0307	0.1962	0.0245	0.8755
agecat*PAY1	**(3) 65+**	**(1)medicare**	1	-1.4297	0.6004	5.6703	0.0173
agecat*PAY1	**(3) 65+**	**(2)medicaid**	1	-0.1873	0.7074	0.0701	0.7912
agecat*PAY1	**(3) 65+**	**(3) Private including HMO**	1	0.3147	0.5987	0.2763	0.5992
agecat*PAY1	**(3) 65+**	**(5)nocharge**	0	0	.	.	.
agecat*PAY1	**(3) 65+**	**(6)other**	1	0.5292	0.7237	0.5348	0.4646
CM_ARTH			1	0.2661	0.0866	9.4500	0.0021
CM_BLDLOSS			1	-0.9409	0.0715	173.0379	<.0001
CM_DM			1	-0.2835	0.0544	27.1734	<.0001
CM_LIVER			1	-0.3394	0.0852	15.8745	<.0001
CM_WGHTLOSS			1	-0.2037	0.0470	18.7615	<.0001

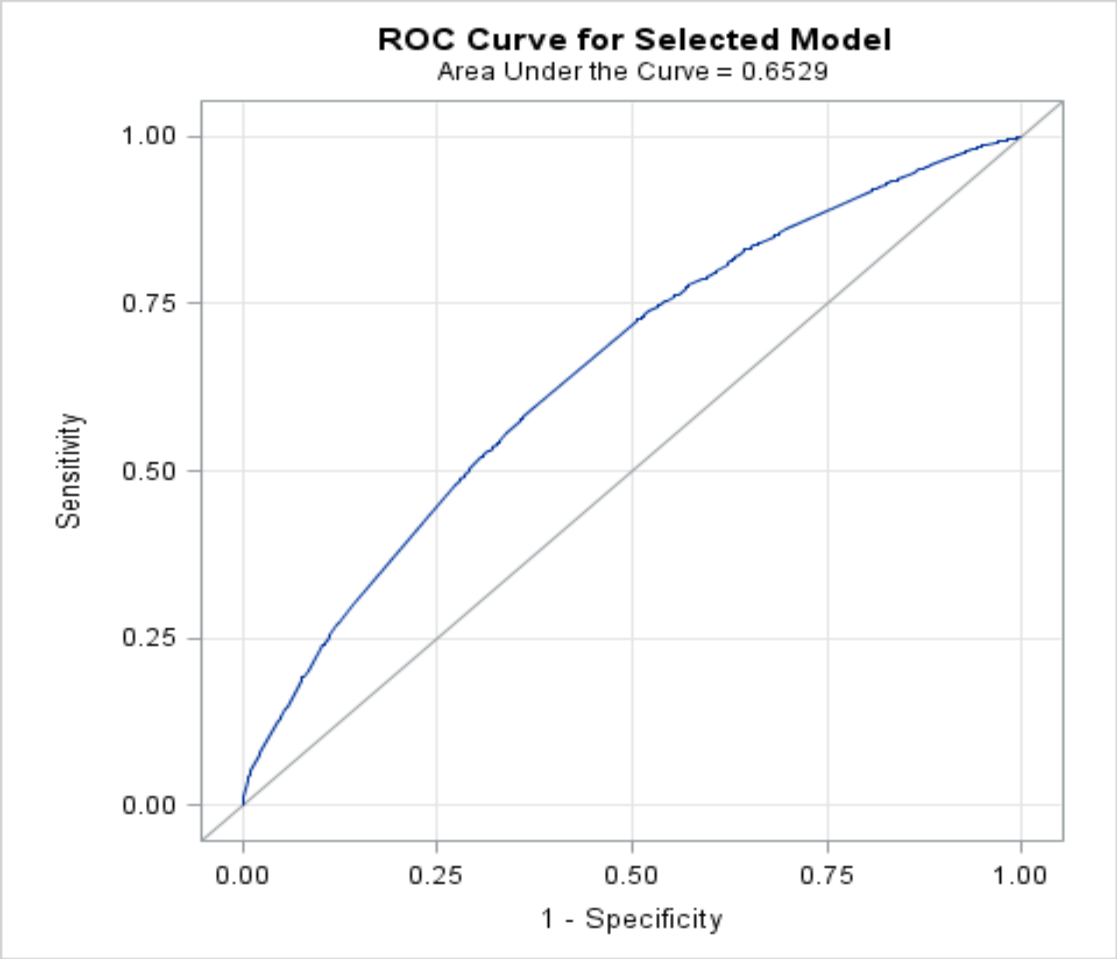


Figure 9: ROC Curve Logistic Regression Model with an area of 0.652 for 2011

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
RACE (2)Black vs (1)white	**1.0000**	1.020	0.931	1.117
RACE (3)Hispanic vs (1)white	**1.0000**	0.457	0.407	0.512
RACE (4)Asian vs (1)white	**1.0000**	0.486	0.372	0.633
RACE (5)Native American vs (1)white	**1.0000**	1.036	0.611	1.756
RACE (6)Other vs (1)white	**1.0000**	0.701	0.584	0.841
CM_ARTH	**1.0000**	1.305	1.101	1.546
CM_BLDLOSS	**1.0000**	0.390	0.339	0.449
CM_DM	**1.0000**	0.753	0.677	0.838
CM_LIVER	**1.0000**	0.712	0.603	0.842
CM_WGHTLOSS	**1.0000**	0.816	0.744	0.894

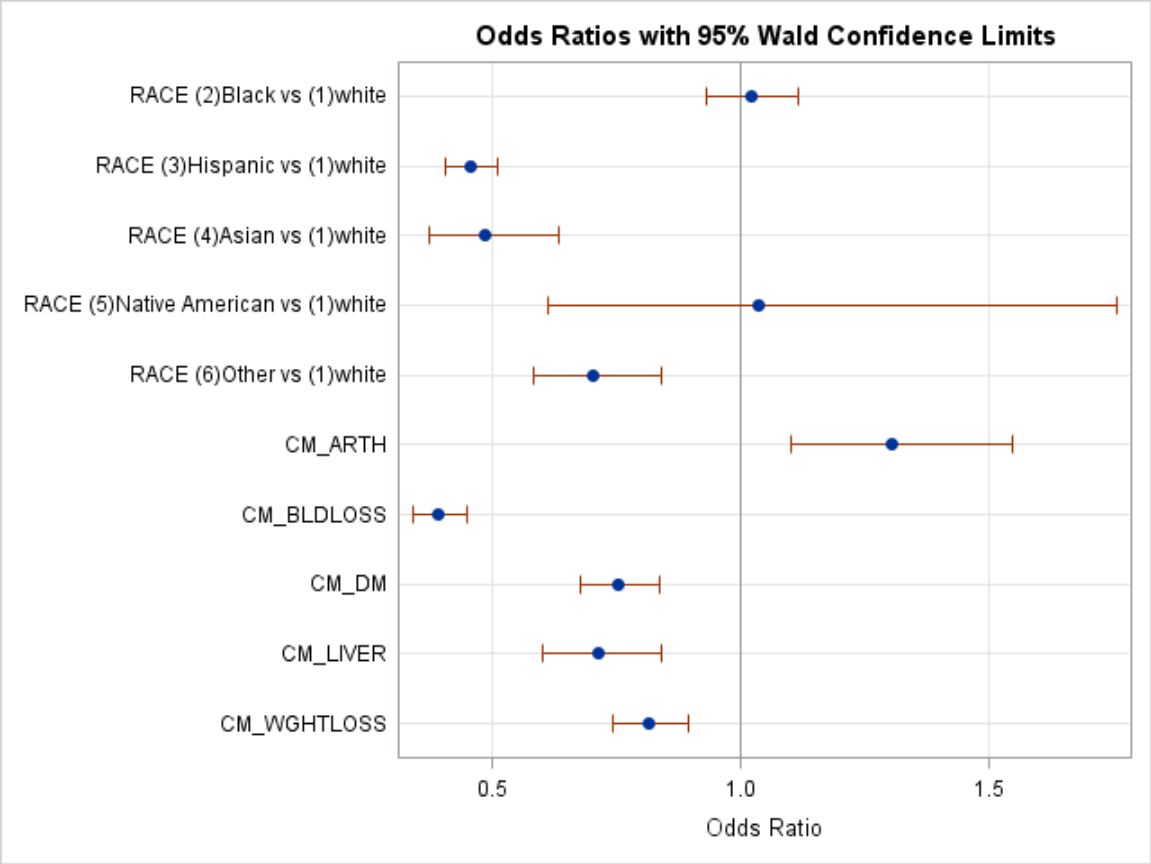


Figure 10: Odds Ratio Graph 2011

The LOGISTIC Procedure HCUP 2012

Model Information	
Data Set	WORK.MERGE2012ALL
Response Variable	Crohn’s
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	18952
Number of Observations Used	17892

Response Profile		
Ordered Value	**Crohn’s**	**Total Frequency**
1	1	11036
2	0	6856

Probability modeled is Crohn’s=1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	23819.947	23256.404
SC	23827.739	23279.780
-2 Log L	23817.947	23250.404

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	567.5432	2	<.0001
Score	578.8096	2	<.0001
Wald	558.5646	2	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.9362	0.0705	176.5093	<.0001
RACE	**(2)Black**		1	-0.0311	0.0487	0.4077	0.5231
RACE	**(3)Hispanic**		1	-0.8836	0.0622	201.5057	<.0001
RACE	**(4)Asian**		1	-0.6079	0.1361	19.9406	<.0001
RACE	**(5)Native American**		1	-0.4695	0.2479	3.5879	0.0582
RACE	**(6)Other**		1	-0.4616	0.0903	26.1343	<.0001
agecat	**(2)41-64**		1	-0.3186	0.1115	8.1704	0.0043
agecat	**(3) 65+**		1	-0.5800	0.6947	0.6970	0.4038
PAY1	**(1)medicare**		1	0.9584	0.1306	53.8924	<.0001
PAY1	**(2)medicaid**		1	0.2495	0.0878	8.0755	0.0045
PAY1	**(3) Private including HMO**		1	-0.1153	0.0762	2.2878	0.1304
PAY1	**(5)nocharge**		1	0.2434	0.2438	0.9969	0.3181
PAY1	**(6)other**		1	-0.3059	0.1207	6.4289	0.0112
agecat*PAY1	**(2)41-64**	**(1)medicare**	1	-0.4133	0.1706	5.8686	0.0154
agecat*PAY1	**(2)41-64**	**(2)medicaid**	1	0.00183	0.1433	0.0002	0.9898
agecat*PAY1	**(2)41-64**	**(3) Private including HMO**	1	0.0677	0.1209	0.3139	0.5753
agecat*PAY1	**(2)41-64**	**(5)nocharge**	1	-0.6955	0.3883	3.2071	0.0733
agecat*PAY1	**(2)41-64**	**(6)other**	1	0.1699	0.1919	0.7839	0.3760
agecat*PAY1	**(3) 65+**	**(1)medicare**	1	-1.3668	0.7046	3.7629	0.0524
agecat*PAY1	**(3) 65+**	**(2)medicaid**	1	-0.5224	0.7940	0.4329	0.5106
agecat*PAY1	**(3) 65+**	**(3) Private including HMO**	1	-0.2391	0.7066	0.1145	0.7351
agecat*PAY1	**(3) 65+**	**(5)nocharge**	1	10.3152	96.7833	0.0114	0.9151
agecat*PAY1	**(3) 65+**	**(6)other**	1	0.6596	0.8629	0.5843	0.4446
CM_BLDLOSS			1	-0.9863	0.0760	168.4112	<.0001
CM_DM			1	-0.3237	0.0561	33.2812	<.0001
CM_LIVER			1	-0.2612	0.0899	8.4471	0.0037
CM_WGHTLOSS			1	-0.2637	0.0498	28.0096	<.0001

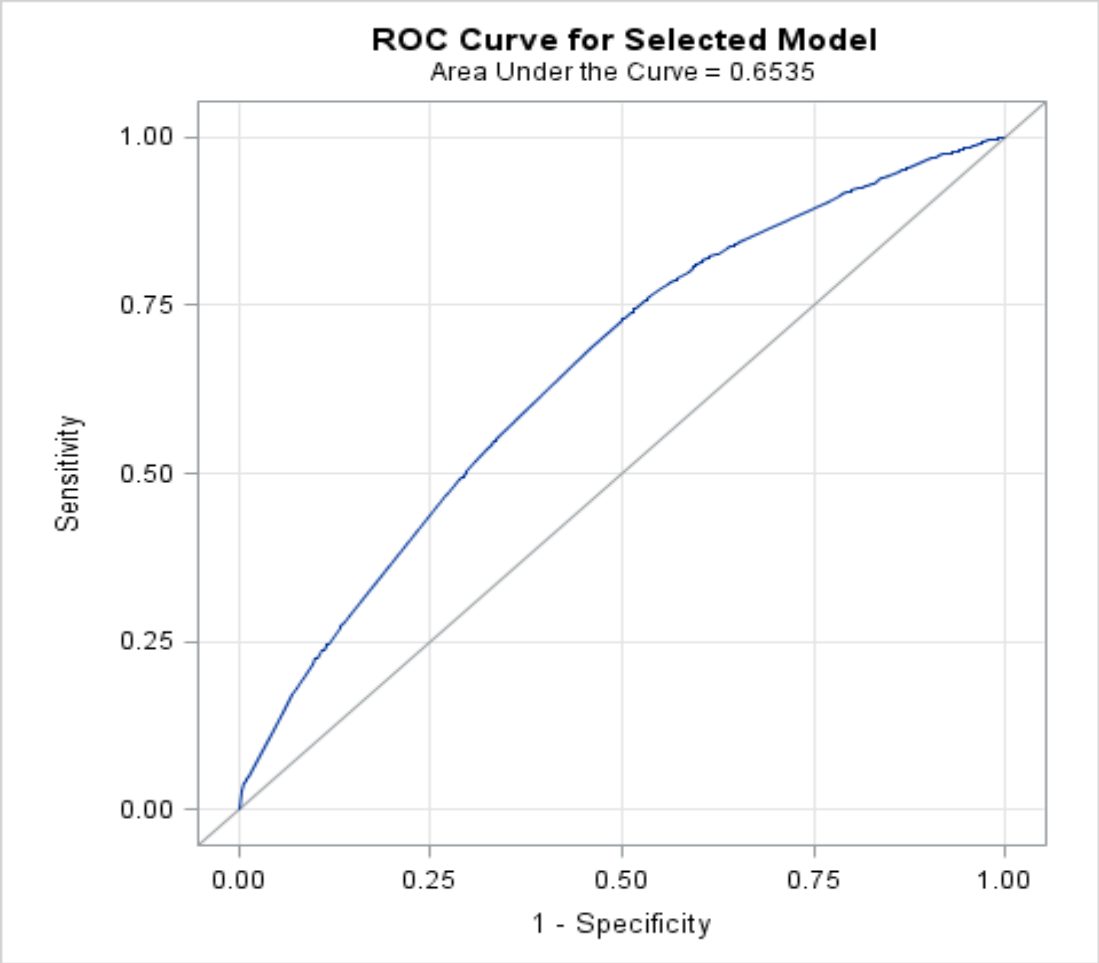


Figure 11: ROC Curve Logistic Regression Model with an area of 0.653 for 2012

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	**Unit**	**Estimate**	**95% Confidence Limits**	
RACE (2)Black vs (1)white	**1.0000**	0.969	0.881	1.066
RACE (3)Hispanic vs (1)white	**1.0000**	0.413	0.366	0.467
RACE (4)Asian vs (1)white	**1.0000**	0.544	0.417	0.711
RACE (5)Native American vs (1)white	**1.0000**	0.625	0.385	1.016
RACE (6)Other vs (1)white	**1.0000**	0.630	0.528	0.752
CM_BLDLOSS	**1.0000**	0.373	0.321	0.433
CM_DM	**1.0000**	0.724	0.648	0.808
CM_LIVER	**1.0000**	0.770	0.646	0.918
CM_WGHTLOSS	**1.0000**	0.768	0.697	0.847

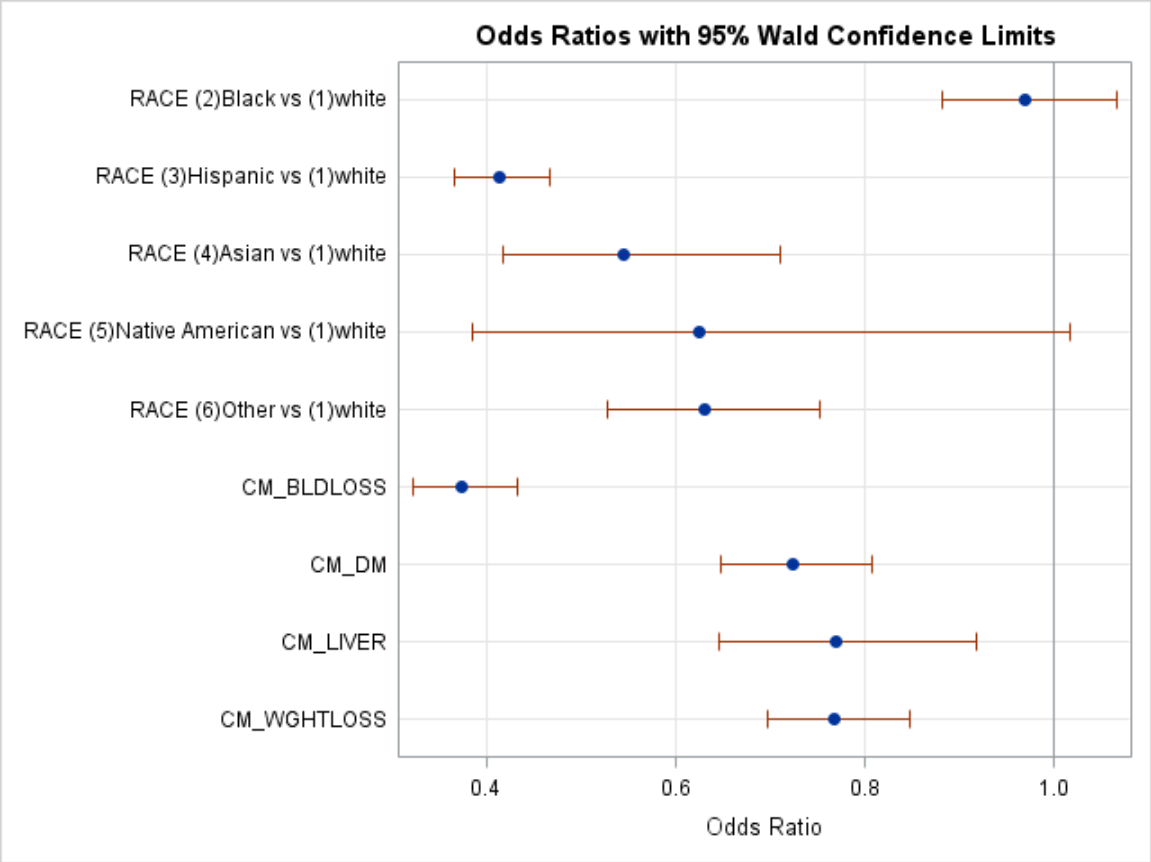


Figure 12: Odds Ratio Graph 2012

4.4 Results of Analysis of Variance

The results of the ANOVA analysis (analysis of variance) are presented in this section. We were interested to understand if the study variables (Race, Pay1, Female and Agecat) impact the null hypothesis for Length of stay (LOS) and total charge for hospitalization (TOTCHG).

Analysis of variance is a statistical method used for testing the hypothesis that there is no difference between two or more population means and often used for testing the hypothesis that there is no difference between a number of outcomes. In this section results from HCUP data 2008-2012 are presented. The variance analysis compares the data of length of stay in the hospital for the years 2008-2012 as the outcome variable versus the independent variables (Pay1, Race, Female, Agecat) being studied in this thesis. Total hospital charge is also assessed for differences within the means of each of the independent variable for the years 2008-2012.

The results of this study model indicate that *F ratio* across 2008-2012 varies with length of stay. More specifically, for 2008 the *F ratio* is 15.36, 2009 13.01, 2010 12.97, 2011 12.84 and 2012 0.50. But when looking closely at each variable we do see a difference. In 2008-2011 data we see that race, female (gender), pay1 and agecat do show differences in their means. Table 15A-B, 16A-B, 17A-B, 18A-B represent the findings respectively.

For race, pay1, female and agecat their respective *F value* is much higher than the *p value*. Therefore, based on this indication the null hypothesis is rejected and the above variables do impact the LOS for patients with Crohn's disease hospitalization. For 2012 data we don't see any differences among the variables impacting the LOS. Table 19A-B, represent these findings respectively. Therefore, the null hypothesis is accepted that these variables do not impact a change in LOS for 2012.

In the second class variable of total charge (TOTCHG) we see very similar results to that of LOS. For the years 2008-2011 the *F value* for the variables indicate a greater value than the *p value* where the null hypothesis is rejected based on the value being greater than the *p value*. However, in 2012 the variables do impact the model and the results yield *F values* that are lower than the *p value*. Therefore, the null hypothesis in this case is accepted and the variables do not impact change in TOTCHG for 2012.

The GLM Procedure 2008

Dependent Variable: LOS Length of stay

Table 15 A: Results of Analysis of Variance LOS vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	7172.4260	551.7251	15.36	<.0001
Error	16299	585537.7106	35.9248		
Corrected Total	16312	592710.1366			

Table 15 B: Independent Variables vs LOS

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	372.594381	74.518876	2.07	0.0654
PAY1	5	980.416016	196.083203	5.46	<.0001
FEMALE	1	462.269875	462.269875	12.87	0.0003
AGECAT	2	2098.593961	1049.296980	29.21	<.0001

Dependent Variable: TOTCHG Total charge

Table: 15 C: Results of Analysis of Variance TOTCHG vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	412659020511	31743001578	13.81	<.0001
Error	16020	3.6819215E13	2298328041		
Corrected Total	16033	3.7231874E13			

Table 15 D: Independent Variables vs TOTCHG

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	92211569433	18442313887	8.02	<.0001
PAY1	5	67638081524	13527616305	5.89	<.0001
FEMALE	1	72131983720	72131983720	31.38	<.0001
AGECAT	2	88998488235	44499244117	19.36	<.0001

The GLM Procedure 2009

Dependent Variable: LOS Length of stay

Table 16 A: Results of Analysis of Variance LOS vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	5629.2524	433.0194	13.01	<.0001
Error	15868	528255.5898	33.2906		
Corrected Total	15881	533884.8422			

Table 16 B: Independent Variables vs LOS

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	681.304207	136.260841	4.09	0.0010
PAY1	5	459.934861	91.986972	2.76	0.0169
FEMALE	1	339.756248	339.756248	10.21	0.0014
AGECAT	2	1790.614861	895.307431	26.89	<.0001

Dependent Variable: TOTCHG Total charge

Table: 16 C: Results of Analysis of Variance TOTCHG vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	370374954880	28490381145	12.74	<.0001
Error	15645	3.4973242E13	2235426167		
Corrected Total	15658	3.5343617E13			

Table 16 D: Independent Variables vs TOTCHG

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	110617774191	22123554838	9.90	<.0001
PAY1	5	47321178603	9464235720.6	4.23	0.0008
FEMALE	1	62366251163	62366251163	27.90	<.0001
AGECAT	2	102007300950	51003650475	22.82	<.0001

The GLM Procedure 2010

Dependent Variable: LOS Length of stay

Table 17 A: Results of Analysis of Variance LOS vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	6114.6299	470.3561	12.97	<.0001
Error	17216	624240.3106	36.2593		
Corrected Total	17229	630354.9405			

Table 17 B: Independent Variables vs LOS

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	471.283053	94.256611	2.60	0.0234
PAY1	5	1438.105636	287.621127	7.93	<.0001
FEMALE	1	94.177884	94.177884	2.60	0.1071
AGECAT	2	1660.134982	830.067491	22.89	<.0001

Dependent Variable: TOTCHG Total charge

Table: 17 C: Results of Analysis of Variance TOTCHG vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	370084526893	28468040530	11.17	<.0001
Error	16912	4.3110204E13	2549089667		
Corrected Total	16925	4.3480289E13			

Table 17 D: Independent Variables vs TOTCHG

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	75080616611	15016123322	5.89	<.0001
PAY1	5	93047234736	18609446947	7.30	<.0001
FEMALE	1	35769557264	35769557264	14.03	0.0002
AGECAT	2	89013640690	44506820345	17.46	<.0001

The GLM Procedure 2011

Dependent Variable: LOS Length of stay

Table 18 A: Results of Analysis of Variance LOS vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	4631.8388	356.2953	12.84	<.0001
Error	19120	530392.2988	27.7402		
Corrected Total	19133	535024.1376			

Table 18 B: Independent Variables vs LOS

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	147.179258	29.435852	1.06	0.3798
PAY1	5	1612.076611	322.415322	11.62	<.0001
FEMALE	1	76.721364	76.721364	2.77	0.0963
AGECAT	2	603.343035	301.671518	10.87	<.0001

Dependent Variable: TOTCHG Total charge

Table: 18 C: Results of Analysis of Variance TOTCHG vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	325799964878	25061535760	10.47	<.0001
Error	18736	4.4832304E13	2392842870.8		
Corrected Total	18749	4.5158104E13			

Table 18 D: Independent Variables vs TOTCHG

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	5	60966586977	12193317395	5.10	0.0001
PAY1	5	98842460258	19768492052	8.26	<.0001
FEMALE	1	32326890950	32326890950	13.51	0.0002
AGECAT	2	63863210247	31931605123	13.34	<.0001

The GLM Procedure 2012

Dependent Variable: LOS Length of stay

Table 19 A: Results of Analysis of Variance LOS vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	174.993135	14.582761	0.50	0.9118
Error	87	2557.116865	29.392148		
Corrected Total	99	2732.110000			

Table 19 B: Independent Variables vs LOS

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	4	77.23537374	19.30884344	0.66	0.6236
PAY1	5	87.40394424	17.48078885	0.59	0.7040
FEMALE	1	1.70856380	1.70856380	0.06	0.8100
AGECAT	2	5.17291165	2.58645582	0.09	0.9158

Dependent Variable: TOTCHG Total charge

Table: 19 C: Results of Analysis of Variance TOTCHG vs Independent Variables

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	9059155167	754929597	1.51	0.1342
Error	87	43362999854	498425286		
Corrected Total	99	52422155021			

Table 19 D: Independent Variables vs TOTCHG

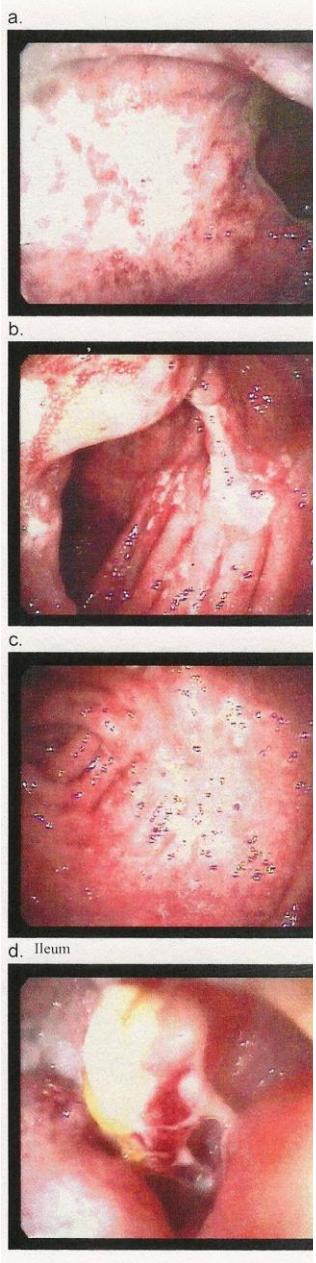
Source	DF	Type III SS	Mean Square	F Value	Pr > F
RACE	4	6550012681	1637503170	3.29	0.0148
PAY1	5	738198432	147639686	0.30	0.9138
FEMALE	1	1490252621	1490252621	2.99	0.0873
AGECAT	2	203983430	101991715	0.20	0.8153

4.5 Crohn's Disease Case Study

The clinical diagnosis of classic Crohn's disease (CD) of the small-bowel is based on a typical history, tender right lower quadrant fullness or mass, and characteristic radiographic findings of the terminal ileum. At time these symptoms may be confused with appendicitis. I herein describe a case of a male in his early 20s having been diagnosed with a severe case of Crohn's disease. This information provided here was diagnosed and reviewed by a gastroenterologist.

In this case I describe an unique therapeutic agent, camel milk, which potentially may affect the outcome of patients suffering from Crohn's disease. The patient in this study is a 22 year-old white male who presented with watery diarrhea and left sided abdominal pain. Stool cultures were negative. Some blood was seen in the stool. CDAI score was 400. Flagyl and Cipro had been given in the emergency room. A CT scan of the abdomen/pelvis revealed diffused long segment thickening of the terminal ileum and mild thickening of the cecum. The pain location did not match the CT findings but the colonoscopy in fact showed pancolitis. A CBC revealed a white blood count of 11.4 and was otherwise normal. SMA 12 was normal. A C-reactive protein was normal (1.0). pANCA was 1:320 and cANCA was negative.

On physical examination he was a well-developed male in no distress, 139 lb. His heart and lungs were normal. His abdomen revealed left lower quadrant tenderness. A colonoscopy revealed moderate to severe pancolitis, ulcerations, and cobblestoning of the terminal ileum. Biopsies revealed chronic active colitis, crypt abscesses and chronic active ileitis. No granulomas were seen. Entocort 9 mg/d was given and patient improved. Humira was suggested but the family decided to use camel milk 8 oz, tid instead. Entocort was stopped approximately 1 week later. The patient's symptoms totally abated while on camel milk except for a short bout of self-limited right hip arthritis. A repeat colonoscopy a year later showed much improvement, and shallower terminal ileum ulcerations. Inflammation was now limited to the cecum with pseudopolyp in the ascending colon. The patient was entirely asymptomatic and weighed 150 lb.



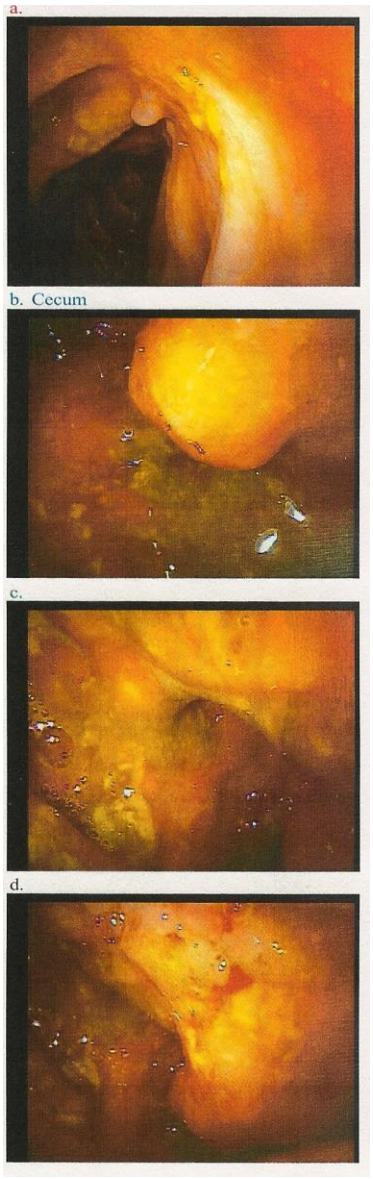
Transverse Colon Ulcerations

Ascending Colon Aphthous Ulcers

Cecum

Ileum Cobble Stoning

Figure 13. A colonoscopy in May 2011 revealed moderate to severe pancolitis, ulcerations, and cobblestoning of the terminal ileum consistent with Crohn's disease.



Ascending Colon Pseudopolyp

Cecum

Transverse Colon

Ileum

Figure 14. A follow-up colonoscopy in March 2012 after a regimen of camel milk 8 oz tid demonstrated healing of the colonic mucosa and ileum. Inflammation was now limited to the cecum with pseudopolyp in the ascending colon. The patient is entirely asymptomic.

CHAPTER V

DISCUSSION AND LIMITATIONS

DISSCUSSION

The objective to this study was to understand how medical comorbidities affect the outcomes of Crohn's disease hospitalization in various regions of the United States between the years of 2008-2012. This was accomplished by using the Healthcare Cost Utilization Project (HCUP) dataset by comparing medical comorbidities for patients with CD, UC and IBD across defined regions within the United States during the years 2008-2012. The study also focused on age, race, gender and payer information. The study sample of close to 100,000 Americans, between the years of 2008-2012 have been diagnosed and hospitalized with a form of inflammatory bowel disease (IBD). More specifically, approximately 61,000 of those patients hospitalized and diagnosed from 2008-2012 suffer from crohn's disease (CD) respectively. Adults between the ages of 18-40 showed the largest prevalence rate of hospitalization due to crohn's disease in the United States from 2008-2012. There was a slight female predominance of CD in the population of 18-40 years old adults. The prevalence of IBD and ulcerative colitis (UC) was very consistence across the age group of 18-40 and female leading with the hospitalization and diagnosis of those diseases. One item important to note that CD appears to be more common in commercially insured individuals, compared with those insured by managed Medicare. This difference was particularly prominent in the adult age group of 41-64. Overall, there were some regional differences in the prevalence of crohn's disease, with the highest observed in the South region followed by Northeast, Midwest and West respectively.

This study includes a relatively small sample size, for hospitalization data from the HCUP NIS database related to IBD compared to other claims databases that are used to capture more specific data relating to IBD in the United States. However, this dataset does include a geographically diverse population. Thus, we report the most representative prevalence estimates

of IBD in the United States to be able to describe differences by geography, age, sex, socioeconomic status and more importantly medical comorbidities relating to IBD.

Our overall data represents estimates of crohn's disease which are similar but slightly lower than those reported from the Olmstead County, Manitoba[1,4,9]. The lower prevalence reported in this study for 2008-2012 may be owing to the geographic diversity of our sample size, which potentially includes regions of relatively low prevalence such as the west, as well as ways in which the hospitals capture and reports crohn's disease related hospitalization. We also observed in this study that across the years the hospitalization related to crohn's disease was consistent.

In this study we observed that the largest number of hospitalization was within the age group of 18-40 in 2008. In 2009-2012 we a observed a slight decrease in hospitalization due to CD. The increasing of crohn's disease within the age group 18-40 is consistent with previous literature. We also absorbed a female to male predominance in CD, as compared to IBD and UC across all the years under study. The most unexpected finding was a dramatic difference in the prevalence of CD and UC among individuals with private insurance HMO compared to Medicare and Medicaid. This association may reflect underdiagnoses or poorer access to care for IBD among insured by Medicaid. Another possible explanation to this finding is that patients who were diagnosed and hospitalized under Medicaid insurance possibly switched their insurance type and was not captured at time of hospitalization. The data may also suggest that more patients with commercial type of insurance were better diagnosed or had more access to better healthcare. It even has been suggested that the effect of socioeconomic status on the development of IBD may be caused by decreased exposure to infectious agents as a consequence of higher socioeconomic status.[96-97] In the end, the data noted here are based on relative small numbers of patients hospitalized based on a primary diagnosis of CD, UC and IBD. The majority of patients represented in the data set for 2008-2012 are enrolled in some type of commercial insurance. Furthermore, it is important to point out that the majority of the patients in this study whom are diagnosed and hospitalized for CD, IBD and UC are of a Caucasian background based on our

descriptive analysis data for 2008-2012. This finding is followed by Black, Hispanic, Asian, Native American and Other respectively.

In an era of evidence-based medicine, decision makers need high-quality data to support decisions about whether or not a medical condition can affect the outcomes decisions. The odds ratio is used in statistic in epidemiology, to express the strength of association between exposure and disease. The logistic regression results offers an understanding how study variables effect the outcomes understudy. Logistic regression can be used to construct decision rules, reflecting the combined diagnostic value of a number of diagnostic variables.[98] The odds ratio used as a measure of test performance combines the strengths of the sensitivity and specificity, as prevalence independent indicators, with the advantage of accuracy as a single indicator.

We compared several variables of medical comorbidities to better understand how these impact the overall logistic model inpatients diagnosed and hospitalized with CD, IBD and UC. For 2008, 2010 and 2012 we did not observed a difference in odds ratio among white vs black patients diagnosed and hospitalized with CD. This finding is not consistent with what is reported in literature. In literature we observed that CD is a disease that predominantly present in a Caucasian population. Our data for 2009 does align with the literature findings. For 2011, data we don't observed a difference. This is also not in line with what is reported in literature. One can conclude that there are some differences in how data is captured across US hospitals with the specific ICD-9-CM diagnosis code for CD. Our logistic regression model shows that CD patients which are diagnosed with arthritis have a higher probability of having CD as part of their underlining diagnosis. We see this results being consistent across 2008, 2010 and 2011 data. For 2009 and 2012 we don't observe the same results which again would suggest that there is a probability that arthritis is not present in the population of patients diagnosed and recorded having CD. Some of the other medical comorbidities that we added to our model did not show specificity for the underlining condition of CD. One can argue that these comorbidities (ie, arthritis, blood loss, diabetes, liver disease and weightless) can impact patients with CD.

The addition of all the variables that were entered into the model was confirmed by the logistic regression ROC curves' analysis, which implied that variables, such race, agecat, pay1,

agecat*pay1, CM_ARTH, CM_BLDLOSS, CM_LIVER, CM_WGHTLOSS, CM_ANEMDEF can predict the odds ratio that patients diagnosed and hospitalized with CD have other underlining medical conditions which are potentially associated with CD. For years 2008, 2009, 2010, 2011, and 2012 the *c*-statics values for the ROC curve are as follows 0.6557, 0.6461, 0.6617, 0.6522, and 0.6530. This percentage refers to all the outcomes pairs are correctly predicted by the model. Given a high value for *c*-statics suggests that the model does not predict the outcomes randomly but in a more positive outcome as seen with the following *c*-statics values of 65.5%, 64.5%, 66.1%, 65.2% and 65.3% respectively. Based on our results 2008 HCUP data confirms this findings and conclusion. These results are indifferent from other reported studies in literature. Typically, patients diagnosed with CD tend to have some of these medical comorbidities as part of their overall CD diagnosis. One explanation that we do not see it in our datasets for following years 2009-2012 is potentially how physicians report and record hospitalization cause due to other medical matters. Another explanation is part of what the patient reports as his or her medical history.

5.1 Impact of Crohn's Disease on Hospitalization

The data set used in this thesis produced a sample size of ~ 100,000 patients hospitalization with crohn's disease between the years 2008-2012 across the United States. This sample size it relative low. Looking at combined sample size of hospitalization including crohn's disease, inflammatory bowel disease and ulcerative colitis is approximately, ~ 80,000 patients for years 2008-2012. The datasets produced a relative low number of patient hospitalizations. Since this is a hospitalization database crohn's disease and its relatives are not a disease that calls for a large number of hospitalizations.

Closely examining each year within the study we see a consistent number of crohn's hospitalizations with the age group of 18-40. This result is in line with what is reported in literature. Crohn's disease is a disease of the young. It's typically diagnosed within the age group of 18-40.[85]

The most unexpected finding was the dramatic difference in prevalence of crohn's disease and ulcerative colitis among patients with commercial HMO insurance compared with

those with Medicare insurance. This association may reflect and in line with reported literature that crohn's disease tends to occur in a much younger population, which have commercial insurance whereas patients on Medicare are older population where the disease is not as prevalent as it is in a younger population. Another possible explanation for this finding is that patients with Medicare insurance switch to commercial insurance after a diagnosis of crohn's. Alternately, these differences may be related to the presence of unmeasured confounders. In the end, the effects noted here are relatively small numbers of patients enrolled in commercial insurance plans. Future studies that measure differences in biologically plausible exposures and disease incidence between different socioeconomic classes are necessary to confirm the association between socioeconomic status and crohn's and elucidate the contribution of environmental factors to disease pathogenesis.

5.2 Alternative Treatment for Crohn's Disease

The typical first line of treatment for Crohn's disease includes various medications, which may offer some relief or no relief. More patients as with any disease are looking for other alternative treatments which can ease their symptoms. Treatments outside of the conventional medicines are often referred to as alternative, complementary, or integrative medicines. The alternative treatments refer to nonmainstream treatment, nontraditional approach. Integrative medicine means you are using a nonmainstream treatment and a conventional treatment in a complimentary way.

We examined the use of camel's milk as an alternative method to potentially treat CD. The results presented in this case study may potentially offer an alternative method of treatment to the conventional treatment that is being used to treat the disease. It is important to note that further studies are needed to support the claim that camel's milk may offer an alternative treatment. The claims that are made in this thesis are based on one case study in which the patient showed significant improvement in his disease stage. Further, clinical studies are needed to support any claims that camel's milk may potentially be used as an alternative therapy for CD.
In our work we discussed one case of a young patient who was diagnosed with CD and used camel's milk as a first line of defense. Interestingly, enough the patient achieved a decrease in

CD symptoms and is asymptomatic. The mechanism of action how camel's milk works on the human intestine is unknown. One theory is that the camel's milk contains billions of good bacteria that when it interacts with the internal gut bacteria changes the composition of the microbiome within the human intestine by activing a cascade of an immune reaction which in turn begins a healing and rebuilding process of infected epithelial tissue within the intestine.

Camel milk contains high antibodies IgA which is able to synthesize high concentration of such type of immunoglobulin and acts as a defense factor. It also has been found that lysozyme within the camel milk increases antibacterial activity of lactoferrin. The lactoferrin protein is one component of the immune system of the human body; it has antimicrobial activity and is part of the innate defense, mainly mucosa. More, studies are needed to understand by which mechanism the milk works on the intestine.

5.3 Study Limitations

This study generated results, however, we also need to consider that there are limitations that need to be discussed and highlighted as part of extending this study into other databases. Limitations in Nationwide Inpatient Sample (NIS) data a part of the Healthcare Cost and Utilization Project (HCUP) available published data should also be noted. The main limitation of this study inherent to administrative data is potential misclassification of diagnosis based on diagnosis codes from a single hospitalization. Because the NIS data cannot be linked to medical records, I cannot validate ICD-9-CM coding for Crohn's disease diagnosis in the NIS dataset.

Datasets are only valuable if the information that is entered is controlled and is audited for accuracy. Since crohn's disease is not the type of disease that majority of patients are hospitalized as a primary diagnosis the overall reported data within maybe exposed to bias. This study generated results that are very consistent with what is reported in literature relating to the descriptive analysis there is a small probability to bias. This study examines comorbidities, which are related to crohn's disease however; there is a potential bias, which might be interrupted as an unknown. Some of the common symptoms relating to the disease are also noted for other diseases and therefore might be reported otherwise. The data used in this work potentially can change the model outcome due to bias and incomplete data reporting.

Another significant limitation inherent to the studies using the nationwide sample data is the inability to measure relationship of crohn's disease and its comorbidities. Ideally, we should be able to assess the level of disease and its appropriateness in the context of underlying crohn's disease. However, as previously mentioned, the implications of misclassification bias attribute to diluting the results. Given the dataset that I was working with I took into consideration that bias can play a major role in limiting factors and therefore my analysis can potentially skew in one ore more direction from the overall objective.

An inherent limitation of using hospital administrative data for epidemiologic studies is that the study population is not random sample of the US population. In this study we included a population that included patients with commercial insurance as well as managed care Medicaid and Medicare, and therefore may not be generalizable to the uninsured population in the United States. Similarly, Medicare patients, and thus the elderly, were underrepresented in our data source. In addition, hospital claims data lack sufficient clinical detail to confirm each case, resulting in some degree of diagnostic misclassification. A final limitation to this study is that health plans do not routinely collect detailed demographic information about each patient, such as race/ethnicity. Therefore, based on some of the results which we obtained in this study we were unable to analyze whether the prevalence of IBD varies by racial or ethnic group. Similarly, detailed geographic information other than US census region (ie, city/state of residence) was not provided to protect the identity of individual health plans. Nevertheless, we believe that the size and diversity of this database outweigh these limitations.

Despite the limitations of this NIS dataset, it allows a comprehensive and national perspective on trends in the delivery of crohn's inpatient care and its potential impact on health outcomes. The nature of these data is exploratory and certainly not sufficient to advocate regionalization of crohn's healthcare, as has been done for other acute conditions. However, these findings should prompt further investigation using primary and prospective data to determine the specific mechanism of crohn's disease differences between inflammatory bowel disease and ulcerative colitis.

CHAPTER VI

SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 Summary and Conclusions

This chapter of the dissertation will focus on summarizing all the previous sections including the goals of this study. Additionally, recommendations will be made that can be further examining the work that was proposed for this dissertation. Lastly, a section on future work and /or direction will be discussed for potential future analysis to be done.

In conclusion, using the HCUP dataset for 2008-2012, this dissertation was intended to gain an insight to hospitalization data relating to medical comorbidities impacting CD patients. We also set out to get a better understanding on patient demographics across several years' worth of hospital data across the Unites States. To achieve these goals we devised series of questions, which was analyzed via several statistical methods. Using descriptive analysis we gained valuable information to the patient demographics as well as patient health insurance information across several years' worth of data. Our findings from the logistic regression analysis suggested that there were statistically significant predictive associations between CD patients and medical comorbidity of arthritis. The determination of the logistic regression models were confirmed by the ROC curve and the goodness-of-fit test both of which showed that the logistic regression models were a good fit for the HCUP dataset for years 2008-2012 and showed that the predictive outcomes were not randomly presented.

6.2 Recommendations

The main purpose of this dissertation is to evaluate and understand the impact of hospitalization of patients diagnosed with Crohn's disease and to potentially use alternative method of treating the disease. In this section, I will address critical recommendations that can be potentially offer alternative solutions and treatment for Crohn's disease that can reduce the burden on hospitalization.

HCUP dataset, needs to develop a link between the hospitalization data and electronic medical record (EMR). This will help with getting the accurate ICD-9-CM codes and avoid any misclassifications relating to the disease and its stage categorization. The medical community needs to explain alternative methods of treating the disease.

The alternative method mentioned in this thesis can be potentially the groundwork for a new class of treatment to treat disease symptoms, which in turn can reduce the burden of disease on the healthcare system (i.e. hospitalization).

Currently, ongoing clinical trials will help determine whether the alternative method of treating Crohn's disease with camel's milk can potentially help patients with their disease symptoms and reduce the burden on the healthcare system as a whole.

6.3 Future Work

The preliminary results of the descriptive analysis show that the data for 2008-2012 tend to be consistent for the four years in this study. The data needs to be cleaned up by removing outliers and focusing on the burden of disease. Once the data is clean up, a series of regressions will be done in order to understand the correlation between the variables that were examined in this thesis. If correlations are found this will explain what the factors that affects Crohn's disease are. Understanding, variation between various healthcare plans that enable patients to get the best medical care to treat Crohn's disease is also a key in the future of hospitals will treat patients with Crohn's disease. It will determine what in depth tests can be done that is not just within the guidelines of disease diagnosis and treatment. Understanding what drives disease progression in various demographic regions within the United States is a key to understand where the disease is more prevalent and what can be done to help reduce disease progression.

As mentioned in the previous section the continuation of exploring the alternative methods for treating Crohn's disease and in this case camel's milk can potentially, open new avenue for treating the disease and minimizing adverse events which in turn might change patients quality of life. Another important point worth mentioning is the reduction on healthcare system as a whole.

REFERENCES

1. Sonnenberg, A., et al. Geographic variation in the incidence of and mortality from inflammatory bowel disease. *Dis Colon Rectum.* 1986; 29:854-861.
2. Packey, C.B., et al. Commensal bacteria, traditional and opportunistic pathogens, dysbiosis and bacterial killing in inflammatory bowel disease. *Curr opin Infect Dis* 2009, 22:292-301.
3. Glick, S.N., Crohn's disease of the small intestine. *Radiol Clin North Am* 1987; 25(1):25-45.
4. Thia, K., et al. The evolution of Crohn's disease (CD) behavior in population-based cohort [abstract 1135]. *Am J Gastroenterol.* 2008; 103 Suppl 5:S443-S444.
5. Fiocchi, C., Susceptibility genes and overall pathogenesis of inflammatory bowel disease: Where do we stand? *Dig Dis* 2009; 27:226-235.
6. Behr M.A., et al. The evidence for Mycobacterium paratuberculosis in Crohn's disease. *Curr Opin Gastroenterol* 2008; 24:17-21.
7. Pierce, E., Ulcerative colitis and Crohn's disease: is *Mycobacterium avium* subspecies *paratuberculosis* the common villain? 2010; 2:1-11.
8. Loftus, Ev., et al. Crohn's disease in Olmsted County , Minnesota, 1940-1993:incidence, prevalence and survival. *Gastroenterology* 1998; 114:1161-68.
9. Monk, M., et al. An epidemiological study of ulcerative colitis and regional enteritis among adults in BaltimoreI. Hospital incidence and prevalence. *Gastroenterology* 1987; 53:198-210.
10. Sawczenko, A., et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet* 2001; 357:1093-1094.
11. Sewell G.W., et al. The immunopathogenesis of Crohn's disease: a three-stage model. *Curr Opion Immunol* 2009; 21:506-513.
12. Marks, D.J.B., Defective innate immunity in inflammatory bowel disease: a Crohn's disease exclusivity? *Curr Opion Gastroentro* 2011; 27:328-334.
13. Marks, D.J., et al. Defective acute inflammation in Crohn's Disease: A clinical investigation. *Lancet* 2006; 367:668-678.
14. Smith A.M., et al. Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease. *J Exp Med* 2009; 206:1883-1897
15. Casanova J.L., et al. Crohn's disease as a primary immunodeficiency of macrophages. *J Exp Med* 2009; 206:1839-1843.
16. Rutgeerts, P., A critical assessment of new therapies in inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; 17 Suppl: S176-185.
17. Knutson, D., et al. Management of Crohn's Disease A Practical Approach. *American Family Physican* 2003; 68(4):707-714.
18. Feller, M., et al. Mycobactrium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. *The Lancet Infectious disease* 2007; 7:607-613
19. Abubakar, I., et al. Detection of Mycobactrium avium subspecies paratuberculosis from patients with Crohn's disease usinf nucleic acid-based techniques: a systematic review and meta-analysis. *Inflammatory bowel disease* 2008; 14:401-410.
20. Bernstein, C.N., Population-based case control study of seroprevalence of Mycobactrium paratuberculosis in patients with Crohn's disease and ulcerative colitis. *J Clin Microbiol* 2004; 42:1129-1135.
21. Naser S.A., et al. Specific Seroreactivity of Crohn's disease against p35 and p36 antigens of *M. avium subsp. Paratuberculosis.* Vet Microbiol 2000; 77:497-504.
22. Polymeros D., Does cross-reactivity between mycobacterium avium paratuberculosis and human intestinal antigens characterize Crohn's diseas? *Gastroenterology* 2006; 131:85-96.
23. Sherris J.C., et al. Medical microbiology: an introduction to infectious diseases. *Elsevier* New York 1984.

24. Patel, D., et al. The ability of Mycobacterium avium subsp. Paratuberculosis to enter bovine epithelial cells is influenced by preexposure to a hyperomolar environment and intracellular passage in bovine mammary epithelial cells. *Infect Immun* 2006; 74:2849-2855.
25. Bernstein C.N., et al. A prospective comparison study of MRI versus small bowel follow-through in reccurent Crohn's disease. *Am J. Gastroenterol* 2005; 100(11):2493-2502.
26. Chernish S.M., et al. Evaluation of the small intestine by enteroclysis for Crohn's disease. *Am J Gastroenterol* 1992; 87(6):696-701.
27. Mudter, J., Diagnostics in inflammatory bowel disease: Ultrasound. *World J gastroenterology* 2011; 27(17):3192-3197.
28. Fraquelli M., et al. Role of US in detection of Crohn disease: Meta-analysis. *Radiology* 2005; 236:95-101.
29. Monkemuller, K., et al. Advanced endoscopic imaging methods for colon neoplasia. *Digestive Diseases* 2010; 28(4-5):629-640.
30. Monkemuller, K., et al. Small-bowel endoscopy, *Endoscopy* 2009; 41(10):872-877.
31. Mishkin, D.S., et al. ASGE Technology Status Evaluation Report: wireless capsule endoscopy. *Gastrointestinal Endoscopy* 2006; 63(4):539-545.
32. Neumann, H., Confocal laser endomicroscopy: technical advances and clinical applications. *Gastroenterology* 2010; 139(2):388.
33. Kiesslich, R., Methylene blue aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003; 124(4):880-888.
34. Kiesslich, R., Chromoscopy Guided Endomicroscopy Increases the Diagnostic Yield of Intraepithelial Neoplasia in ulcerative colitis. *Gastroenterology.* 2007; 132(3):874-882.
35. Hurlstone, D.P., Confocal endomicroscopy in ulcerative colitis: differentiating dysplasia-associated lesional mass and adenoma-like mass. *Clinical Gastroenterology and Hepatology.* 2007; 5(10):1235-1241.
36. Neumann, H., Review article: in vivo imaging by endocytoscopy. *Alimentary Pharmacology and Therapeutics*. 2011; 33(11):1183-1193.
37. Neumann, H., et al. In vivo diagnosis of small-cell lung cancer by endocytoscopy. *Journal of Clinical Oncology.* 2011; 29(6):131-132.
38. Pohl, H., et al. Endocytoscopy for the detectionof microstructural features in adult patients with celiac sprue: a prospective, blinded endocytoscopy-conventional histology correlation study. *Gastrointestinal Endoscopy.* 2009; 70(5):933-941.
39. Podolsky D.K., Inflammatory bowel disease. *New England Journal of Medicine* 1991; 324:928-37.
40. FussI.J., et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease Crohn's disease LP cells manifest increased secretion og INF-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J. Immunol.* 1996; 157:1261-1270.
41. Trinchieri G. Interleukin-12 and the reqgulation of innate resistance and adaptive immunity. *Nat Rev Immunol* 2003; 3:133-146.
42. MacDermott R.P., Alterations of the immune system in ulcerative colitis and Crohn's disease. *Adv Immunol* 1988; 42:285-328.
43. Burgio V.L., et al. Peripheral monocyte and naïve T-cell recruitment and activation in Crohn's disease. *Gastroenterology* 1997; 113:118-26.
44. Trinchieri G. Interleukin-12: a cytokine produced by atigen-presenting cells with immunoregulatory functions in the generation of T-Helper cells type 1 and cytotoxic lymphocytes. *Blood* 1994; 84:4006-27.
45. Furukawa, A., Cross-sectional imaging in Crohn's Disease. *Radiographics* 2004; 24:689-702.
46. Parronchi P., et al. Type 1 T-helper cell predominance and interlukin-12 expression in the gut of patients with Crohn's disease. *Am Journal of Pathology.* 1997; 150:823-32.
47. Fidler, J., MR imaging of the small bowel. *Radiol Vlin North Am* 2007; 45:317-331.
48. Low, R.N., Crohn's disease evaluation: Comparison of contrast-enhanced MR imaging and single-phase helical CT scanning. *JMagn Reson Imaging* 2000; 11:127-135.

49. De Groot V., et al. Hoe to measure comorbidity. A clinical review of available methods. *J. Clinical Epidemiology* 2003; 56:221-229.
50. Perkins AJ., et al. Common comorbidity scales were similar in their ability to predict health care costs and mortality. *J. Clinical Epidemiology* 2004; 57:1040-1048.
51. Janke KH., et al.Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; 11:272-286.
52. Desilva S., et al. Predictors of complications following a colectomy for ulcerative colitis patients: A population based study. *Gut* 2009;58(Suppl II): A457
53. Gisbert JP., et al. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. *Inflamm Bowel Dis* 2007; 13:1106-1114.
54. Knight C., et al. Hepatobiliary associations with inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2009; 3:681-691.
55. Marine Guillem M., et al. Should the possibility of celiac disease be investigated in all patients with Crohn's disease?. *Gastroenterol Hepatol* 2009; 32:169-170.
56. Warrington TP., et al. Psychiatric adverse effects of corticosteroids. *Mayo Clin Pro* 200; 81:1361-1367.
57. Merino O., et al. Association between inflammatory bowel disease ad celiac disease. *Gastroenterol Hepatol* 2008; 31:165.
58. Mittermaier C., et al. Impact of depressive mood on relapse in patients with immflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med* 2004; 66:79-84.
59. Levenstein S., et al. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000; 95:1213-1220.
60. Van Kruiningen, H.J. Lack of support for a common etiology in Johne's disease of animals and Crohn's disease in humans. *Inflammatory Bowel Dis* 1999;5(3):183-191.
61. Momotani, E., et al. Role of M cells and macrophages in the entrance of *M. paratuberculosis* into domes of ileal Peyers patches in calves. 1988; *Vet Path* 25:131-137.
62. Collins, M.T., Diagnosis of *paratuberculosis* The veterinary Clinics of North America: Food Animal Practice 1996; 12(2):357-370.
63. Sweeny R.W., et al. Evaluation of a commercial enzyme linked immunosorbent assay for the diagnosis of *paratuberculosis* in dairy cattle. *J. Vet Diagn Invest.* 1995; 7:488-493.
64. Mottet, N.K., Histopathologic spectrum of regional enteritis and ulcerative colitis *Major Problems in Pathology Series.* 1971; 2:1-25.
65. Hanauer, S.B., et al. Management of Crohn's disease in adults. *Am J Gastroenterol* 2001; 96:635-43.
66. Tromm, A., et al. Oral mesalazine for the treatment of Crohn's disease: clinical efficacy with respect to pharmacokinetic properties. *Hepatogastroenterology* 1999;46:3124-35.
67. Loftus, E.V. Jr., Incidence, prevalence, and survival. *Gastroenterology* 1998; 114:1161-68.
68. Preiss, J.C., et al. Use of Methotrexate in patients with inflammatory bowel disease. *Clin Exp Rheumatol.* 2010; 28(5):151-155.
69. Schirbel, A., et al. Inflammatory bowel disease: Established and evolving considerations on its etiopathogenesis and therapy. *J Dig Dis.* 2010; 11(5):266-276.
70. Lim W.C., et al. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Sys Rev.* 2010; (12):CD008870.
71. Ito, K., et al. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol.* 2006;117(3):522-543.
72. Jharap, B., Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-yearintercept cohorts. *Inflamm Bowel Dis* 2010;16(9):1541-1549.
73. Ramasundara, M., et al. Defensins and inflammation: the role of defensins in inflammatory bowel disease. *J Gastroenterol Hepatol.* 2009; 24(2):202-208.
74. Ursing, B., et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. *Gastroenterology* 1982; 83(3):550-562.

75. Ambrose, N.S., et al. Antibiotic therapy for treatment in relapse of intestinal Crohn's disease. A prospective randomized study. *Dis Colon Rectum.* 1985; 28(2):81-85.
76. Sutherland, L., et al. Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991; 32(9):1071-1075.
77. Triantafillidis, J.K., et al. Ornidazole in treatment of active Crohn's disease: short-term results. *Ital J Gastroenterol.* 1996; 28(1):10-14.
78. Flanagan, J.C., A research approach to improving our quality of life. *Am Phsychol* 1978; 33: 138-147.
79. Fitzpatrick R., et al. Quality of life measures in health care. I: appliations and issus in assessment. *BMJ* 1992; 305:1074-1077.
80. Wilson I.B., et al. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *JAMA* 1995; 273:59-65.
81. Greenbloom, S.L, et al. Combination ciprofloxacin and metronidazole for active Crohn's disease. *Can J Gastroenterol* 1998; 12(1):53-56.
82. Obaid Ulah BEG., et al. The primary structure of α-lactalbumin from camel milk. *Eur. J. Biochem*. 1985 147,233-239.
83. Ferguson A., et al. Morbidity of juvenile onset inflammatory bowel disease: effects on education and employment in early adult life. Gut 1994; 35:665-668.
84. Longobardi T., et al. Work losses related to inflammatory bowel disease in Canada: results from a National Population Health Survey. Am J. Gastroenterol 2003;98:844-849.
85. Leiper, K., et al. Clinical trial: randomized study of clarithromycin versus placebo in active Crohn's disease. *Aliment Pharmacol Ther.* 2008; 27(12):1233-1239.
86. Greenber, G.R., Antibiotics should be used as first-line therapy for Crohn's disease. *Inflamm Bowel Dis.* 2004; 10(3):318-320.
87. William N.T., Probiotics. *Am J Health Syst Pharm.* 2010; 67(6):449-458.
88. Garcia, V.E., et al. Influence of Saccharomyces boulardii on the intestinal permeability of patients with Crohn's disease in remission. *Scand J Gastroenterol.* 2008; 43(7):842-848.
89. Lichtenstein, G.R., et al. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol.* 2004; 99(1):91-96.
90. Colombel, J.F., Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010; 362(15):1383-1395.
91. Sandborn, W.J., et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med.* 2007;146(12):829-838.
92. Stallmach A., et al. Adverse effects of biologics used for treating IBD. *Best Pract Res Clin Gastroenterol.* 2010; 24(2):167-182.
93. Fiorino, G., et al. Emerging biologics in the treatment of inflammatory bowel disease: What is around the corner? *Curr Drug Targets.* 2010;11(2):249-260.
94. Reynolds, E.C., et al. Effects of casein and whey protein solutions on the caries experience and feeding patterns of the rat. *Archives of Oral Biology* 1984; 29:927-933.
95. Kappleman, M.D., The prevalence of geographic distribution of crohn's disease and ulcerative colitis in the United States. *Clinical Gastroenterology and Hepatology* 2007; 5:1424-1429.
96. Armitage EL., et al. Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. *Gastroenterology* 2004; 127:1051-1057.
97. Weiss St., Eat dirt-the hypothesis and allergic disease. *N Engl J Med* 2002; 347:930-931.
98. Glas A.S., et al. The diagnostic odds ratio: a single indicator of test performance. *Journal of Clinical Epidemiology* 2003; 56:1129-1135.