# IDENTIFICATION OF PARAMETERS THAT HELP IN DIFFERENTIATING CROHN'S DISEASE FROM INTESTINAL TUBERCULOSIS

**A dissertation submitted in partial fulfillment of DM (Gastroenterology) course requirements of The Tamil Nadu Dr MGR Medical University, Chennai .**

# Certificate

This is to certify that this dissertation titled 'Identification of parameters that help in differentiating Crohn's disease from intestinal tuberculosis' is a bonafide work done by Dr Anoop K Koshy in partial fulfillment of rules and regulations for DM (Branch IV – Gastroenterology) examination of The Tamil Nadu Dr MGR Medical University, to be held in August 2010.

Guide and Head of the Department

Dr Ashok Chacko,
MD, MNAMS, DM, FRCP, FIMSA,
Professor and Head,
Department of Gastrointestinal Sciences,
Christian Medical College, Vellore.

# Declaration

I, Dr Anoop K Koshy, hereby declare that this dissertation entitled 'Identification of parameters that help in differentiating Crohn's disease from intestinal tuberculosis' has been prepared by me under the direct supervision and guidance of Dr Ashok Chacko, Professor and Head, Department of Gastrointestinal Sciences, Christian Medical College, Vellore being submitted to The Tamil Nadu Dr MGR Medical University in partial fulfillment of regulations for the award of DM degree in Gastroenterology examination to be held in 2010.

This dissertation has not been submitted by me either in part of in full on any previous occasion to any university or institution for the award of any degree or diploma.

Place: Vellore
Date:

Anoop K Koshy,
Postgraduate student,
Gastroenterology,
Christian Medical College,
Vellore.

# Acknowledgement

I take this opportunity to express my sincere gratitude to my guide, Dr Ashok Chacko, Professor, Department of Gastrointestinal Sciences, for his guidance, encouragement and constant support in undertaking and completing this project.

I express my sincere thanks to Dr Ashish Goel, Assistant Professor, Department of Gastrointestinal Sciences, for his support during the course of the study.

I am thankful to Dr A J Joseph, Assistant Professor, Department of Gastrointestinal Sciences, for his support in undertaking this project.

I thank Dr Amit Kumar Dutta, Assistant Professor, Department of Gastrointestinal Sciences, for his guidance during the course of the study.

I am thankful to Dr Anu Eapen, Professor, Department of Radiology, for all the help rendered in evaluation of the radiology images.

Special thanks to Mr Prasanna Samuel, Department of Biostatistics, for helping me with the statistical analysis.

Christian Medical College, Dr Anoop K Koshy
Vellore.

# Index

# Introduction

Crohn's disease (CD) and intestinal tuberculosis (ITB) are chronic diseases of the intestine. These diseases can present with similar clinical, radiologic, endoscopic and histopathologic findings. Hence differentiating these diseases from one another can be difficult. This affects the treatment. In event of misdiagnosis, treating Crohn's disease with anti tubercular drugs can result in the patient being exposed to the toxicity of these drugs as well as delay in treatment of Crohn's disease. On the other hand, treating a tuberculosis patient misdiagnosed as Crohn's disease with steroids can result in flare up or dissemination of tuberculosis which can be disastrous. These issues emphasize the need for a definite diagnosis before the start of therapy.

Two decades ago, Crohn's disease was rare in India while intestinal tuberculosis was common. During the past decade, there has been an emergence of Crohn's disease in India making differentiation of the two diseases an important issue[1]. Few studies have attempted to address this problem. Patel et al after an exhaustive histological and microbiological evaluation for intestinal tuberculosis could make a definite diagnosis in only 66.5% of patients [2]. Serological tests like anti-neutrophil cytoplasmic antibody (ANCA) and anti-Saccharomyces Cerevisiae antibody (ASCA) were not found useful in differentiation of Crohn's disease and intestinal tuberculosis [3, 4]. TB PCR was found highly specific for diagnosis of intestinal tuberculosis , but lacked sensitivity[5].

There are a few reports which suggest that differentiation of Crohn's disease from intestinal tuberculosis is possible on the basis of endoscopic [6] and histological characteristics [7-10]. Individual investigation results ( except presence of AFB or

caseating granulomas for tuberculosis ) are often found insufficient for diagnosis. There is therefore a need for a comprehensive study that can effectively differentiate intestinal tuberculosis from Crohn's disease.

# Aims.

- To analyze clinical, laboratory, radiologic, endoscopic and histological characteristics of intestinal tuberculosis and Crohn's disease and identify the parameters that differentiate the two diseases.
- To devise and validate a scoring system to help differentiate Crohn's disease from intestinal tuberculosis.

# Review of literature

Crohn's disease (CD) and tuberculosis (TB) are granulomatous disorders of the intestinal tract with similar clinical presentation. Differentiation between the two poses a dilemma to clinicians and pathologists but is essential for appropriate management. An increasing incidence of Crohn's disease in countries where tuberculosis continues to be highly prevalent has heightened the necessity for a clearer understanding of how to differentiate the two diseases [8, 11, 12]. The advent of AIDS and increased global travel make this a dilemma faced by gastroenterologists and pathologists in Western countries as well[13, 14] .

## Changing epidemiology of intestinal tuberculosis and Crohn's disease

Although tuberculosis remains a common problem in underprivileged areas of the world and less common in the developed world, the epidemiology of the disease is changing. For example, in North America, an increase in the number of cases of tuberculosis has been observed since the mid-1980s mainly attributable to immigration, human immunodeficiency virus and the development of multidrug-resistant strains of tuberculosis [15] . At the same time, the incidence of Crohn's disease in areas that are endemic for tuberculosis has increased. In a study from Saudi Arabia, the mean annual incidence of Crohn's disease over two decades changed from 0.32 / 100,000 to 1.66 / 100,000, representing more than a fivefold increase [16] and a similar observation was found in the pediatric population from the same area [17]. In a Lebanese study conducted

over the period from 2000 to 2004, the mean annual incidence was 1.4 / 100,000 [18] . Similar findings were also observed in Iran, South Asia and South Africa[12, 19, 20] . The epidemiology of Crohn's disease has changed over the years with increasing reports of Crohn's disease affecting the pediatric population as well as adults. In India there is an increase in the number of Crohn's disease cases reported [1] .

**Pathogenesis**

Intestinal tuberculosis is caused by mycobacterium tuberculosis whereas Crohn's disease has multifactorial etiology which includes genetic, immunological, environmental and microbial factors. Both trigger potent adaptive Th 1 cytokine responses which result in granuloma formation and are characterized by robust production of interferon gamma , IL 12 and IL 23.

The present evidence suggests that Crohn's disease results from abnormal immune response to commensal gut bacteria in genetically predisposed individuals. Normally gut inflammation is kept in check through immune tolerance. Tolerance is mediated in part by subsets of $CD4^+$ helper T cells that are generated in the intestinal mucosa and secrete the down-regulatory cytokines, transforming growth factor (TGF)-$\beta_1$ and interleukin (IL)-10. Two specific T cell populations—T regulatory 1 (Tr1) and T helper 3 (Th3) cells—appear to have similar roles in maintaining mucosal tolerance in the intestine [21]. Evidence points to an over-responsiveness of mucosal T cells to the enteric flora [22] in Crohn's disease. When an antigenic challenge occurs, or when tolerance is broken, the

immune response is skewed toward cell-mediated immunity via Th1 cell response. Th 1 response leads to elaboration of a variety of injurious and proinflammatory substances that cause tissue destruction and granuloma formation.

The interaction between T cells and macrophages is critical to the pathogenesis of Crohn's disease. Both cell types are found together in the earliest lesions of Crohn's disease. The antigens that perpetuate the inflammatory response are taken up by macrophages. Degradation of antigen within proteosomes in macrophages results in presentation of an epitope in the context of the class II major histocompatibility complex (MHC). Interaction between MHC class II and the T cell receptor (CD3) results in antigen-specific interaction between the macrophage and the $CD4^+$ T cell.

The sustained nature of the immune response in Crohn's disease may have diverse causes. Poor intestinal barrier function may permit continued exposure of lamina propria lymphocytes to antigenic stimuli from the lumen. Poor barrier function also may be a factor in the onset of Crohn's disease, because such patients have increased intestinal permeability preceding clinical relapse of disease [23]. Alternatively, a sustained exaggerated inflammatory reaction may result from an ineffective immune response—resulting from a variety of defects—to an ever-present stimulus, as occurs in a number of conditions in humans in which there is a known immunologic defect. Finally, the sustained nature of the inflammation may result from a programmed over-responsiveness to a persistent stimulus.

The principal cause of intestinal tuberculosis is Mycobacterium tuberculosis. Intestinal tuberculosis may be a primary infection, or secondary following reactivation, usually from a primary pulmonary focus. Assumed routes of infection of the gastrointestinal tract are ingestion, for example, of bacilli in sputum from an active focus in the lung, haematogenous spread from the lung, from infected lymph nodes and direct spread from adjacent organs.

## Genetics

The relative risk among first-degree relatives of Crohn's disease is 14 to 15 times higher than that of the general population [24]. The concordance rate among monozygotic twins is as high as 67% for Crohn's disease[25-27] . The presence of a locus on chromosome 16 (the IBD1 locus) had been confirmed repeatedly to be linked to Crohn's disease, indicating the presence of a Crohn's disease gene in this region [27].

IBD1 locus has been identified as the NOD2 (nucleotide-binding oligomerization domain 2) gene, also known as CARD15 (caspase-recruitment domain 15)[28, 29]. Persons with disease-associated allelic variants on both chromosomes have a 40-fold relative risk of Crohn's disease compared with those lacking variant NOD2/CARD15 genes, whereas heterozygous individuals have a sevenfold relative risk of Crohn's disease [29]. Nevertheless, the penetrance of NOD2/CARD15 is estimated to be less than 1% [30] ; that is, disease-related allelic variants of the gene may be found in a large number of individuals who do not have Crohn's disease. This strongly suggests that environmental

factors, as yet incompletely elucidated, play a significant role in the expression of the Crohn's disease phenotype.

The OCTN (organic cation transporter) gene, located at IBD5 locus on chromosome 5q31[31, 32] and the DLG5 gene , located on chromosome 10q23also have been associated with Crohn's disease.

In contrast to Crohn's disease, the contributions of genetic mutations in intestinal tuberculosis have not been found.

## Pathology

Focal intestinal inflammation is the hallmark pathologic finding in Crohn's disease.

The earliest characteristic lesion of Crohn's disease is the aphthous ulcer. The presence of granulomas , although highly characteristic of Crohn's disease, is neither unique to Crohn's disease nor universally found. Estimates of the prevalence of granulomas in Crohn's disease have varied greatly, ranging from 15% in endoscopic series [33] to as high as 70% in surgical series [34]. TNF is the key cytokine in the formation of granulomas. Appreciation of this fact led to the concept of anti-TNF therapies as a treatment for Crohn's disease. In contrast with the granulomas of tuberculosis, there is little or no central necrosis.

When the disease becomes chronic, aphthae may coalesce into larger ulcers with a stellate appearance. Linear or serpiginous ulcers may form when multiple ulcers fuse in a longitudinal direction. With linear and transverse coalescence of ulcers, the classic cobblestone appearance may result, as networks of ulcers surround areas of relatively

normal mucosa with prominent submucosal edema. Ulcers also may extend down to the muscularis propria.

Large ulcers, sinus tracts, and strictures are late features of Crohn's disease. Sinuses and fistulas represent extensions of fissures; sinus tracts end blindly, and fistulas enter epithelial-lined organs such as bowel, skin, bladder, or vagina.

With penetration of inflammation to the serosa, serositis may occur, resulting in adhesion of bowel to loops of small bowel, colon, or other adjacent organs. As a result of the chronicity of the inflammatory process, free perforation is much less common than walled-off perforation or contained intra-abdominal abscesses or fistula formation.

Fibrosis is another transmural aspect of the disease. Fibrosis may be evident grossly as irregular thickening of the bowel wall and, along with hypertrophy of the muscularis mucosa, may contribute to the development of strictures. One of the most characteristic findings of Crohn's disease is the presence of fat wrapping. This finding is highly characteristic of Crohn's disease and is referred to as "creeping" of mesenteric fat onto the serosal surface of the bowel.

In intestinal tuberculosis , the ileocaecal region is the most common site of involvement, although tuberculosis can have a focus at any site in the gastrointestinal tract, associated lymph nodes and/or peritoneum. Intestinal tuberculosis usually has one of the three forms: ulcerative, hypertrophic or ulcerohypertrophic, and fibrous [35].

Tuberculous granulomas initially form in the mucosa or Peyer's patches, whereas ulcers are relatively superficial, with a different appearance from those in Crohn's disease. Intestinal tuberculosis progresses slowly and presents late with complications, especially

acute or subacute obstruction due to mass (tuberculoma), stricture formation in the ileocaecal region or perforation leading to peritonitis.

**Clinical feaures**

Crohn's disease has a predilection for the distal small bowel and proximal large bowel. Nearly one half of all patients have disease affecting both ileum and colon. Another one third have disease confined to the small bowel, primarily the terminal ileum and in some cases including the jejunum as well [36]. From 20% to 25% of patients have disease confined to the colon.

Abdominal pain is a frequent and persistent complaint. Pain may be intermittent and colicky or sustained and severe and is attributable to obstruction, inflammation or abscess.

Constitutional symptoms, particularly weight loss and fever, or growth retardation in children, may be prominent and occasionally are the sole presenting features of Crohn's disease.

Disease of the ileum, often accompanied by involvement of the cecum, may present insidiously. Some patients present with a small bowel obstruction, perhaps precipitated by impaction of indigestible foods such as raw vegetables or fruit. Many years of subclinical inflammation may progress to fibrotic stenosis, with the subsequent onset of intermittent colicky pain, sometimes accompanied by nausea and vomiting.

Colonic disease may involve mainly the right colon or may extend distally to involve most or all of the colon (extensive or total colitis). In patients with Crohn's colitis,

tenesmus is a less frequent complaint than in patients with ulcerative colitis, because the rectum often is not involved or may be less severely inflamed than other colonic segments. The typical presenting symptom of colonic disease is diarrhea, occasionally with passage of obvious blood. The severity of the diarrhea tends to correlate with both the extent of colitis and the severity of inflammation, and the presentation may range from minimally altered bowel habits to fulminant colitis. Abdominal pain may be present to a greater extent than is seen in ulcerative colitis. Systemic manifestations such as weight loss and malaise also may be prominent.

Perianal disease is another common presentation of Crohn's disease. In as many as 24% of patients with Crohn's disease, perianal disease precedes intestinal manifestations with a mean lead time of 4 years [37]. More often, however, perianal disease occurs concomitantly with or after the onset of the symptoms of luminal disease. Perianal findings may be categorized as skin lesions, anal canal lesions, and perianal fistulas [38]. Skin lesions include maceration, superficial ulcers, and abscesses. Anal canal lesions include fissures, ulcers, and stenosis. The anal fissures of Crohn's disease tend to be placed more eccentrically than the usual idiopathic fissures, which generally occur in the midline.

Upper gastrointestinal tract Crohn's disease is uncommon in the absence of disease beyond the ligament of Treitz. Approximately one third of patients with proximal Crohn's disease do not have evidence of distal Crohn's disease at the time of diagnosis, but virtually all develop distal disease in time [39].

Esophageal Crohn's disease is rare, occurring in less than 2% of patients. The presenting symptoms may include dysphagia, odynophagia, substernal chest pain, and heartburn.

These symptoms may be progressive and lead to profound weight loss [40]. Aphthous ulcers may sometimes be found in the mouth and posterior pharynx.

Disease behavior in Crohn's disease may be divided roughly into two categories: aggressive fistulizing disease and indolent cicatrizing disease denoted by fibrostenotic stricture [41]; a third subset of patients appear to develop neither behavior over long periods of observation. Moreover, these categories of disease can overlap wth both fistula and stricture occurring simultaneously in the same patient or at different times.

Fistulas are frequent manifestations of the transmural nature of Crohn's disease. Immune activation triggers the release of a variety of proteases and matrix metalloproteinases [42] that may contribute directly to tissue destruction, sinus tract formation, and, finally, penetration to adjacent tissues. Perianal fistulas are common and are estimated to occur in 15% to 35% of patients. One fourth of all patients with Crohn's disease will present with an intra-abdominal abscess at some time in their lives [43].

The classic presentation of an intra-abdominal abscess is that of a patient with spiking fevers and focal abdominal tenderness or localized peritoneal signs. Unfortunately, many of the patients at highest risk for perforation or abscess also are on glucocorticoids, which are notorious for suppressing peritoneal signs and fever and masking the presentations of infection. Therefore, a high level of suspicion must be maintained.

Stricture is another characteristic complication of Crohn's disease. Strictures represent long-standing inflammation and may occur in any segment of the gastrointestinal tract in which inflammation has been active. Strictures do not develop in all patients with inflammatory disease but are likely to recur, most often at the anastomosis, in patients who undergo bowel resection because of a stricture. One fourth of all patients with

Crohn's disease will have an extraintestinal manifestation of inflammatory bowel disease. [44].

The clinical features of intestinal tuberulosis are nonspecific. The predominant symptom is abdominal pain noted in upto 90% of cases. . Intestinal tuberculosis patients often have fever, night sweats, anorexia , weight loss and diarrhea [45]. If the abdominal cavity is involved, there may be ascites. Sometimes obstruction can lead to proximal bacterial overgrowth leading to malabsorption.

In intestinal tuberculosis , all regions from the oesophagus to the rectum may be involved. Oesophageal tuberculosis is very uncommon and mimics oesophageal carcinoma. Gastroduodenal tuberculosis may mimic peptic ulcer disease or present with symptoms of pyloric obstruction, thus being confused with adenocarcinoma. Ileocaecal tuberculosis presents with abdominal pain, a right iliac fossa mass, altered bowel habits and bleeding, which mimics Crohn’s disease, carcinoma, amoebiasis, enteric fever or Yersinia enterocolitica. Colonic tuberculosis occurs in about 10% of cases, and may mimic carcinoma or, more rarely, ulcerative colitis. In rectal tuberculosis the predominant symptom is bleeding, and in anal tuberculosis fistulae are common, both mimicking carcinoma or Crohn’s disease [46] .

In children, the presenting features of intestinal tuberculosis are similar with abdominal pain, fevers and ascites[47, 48] . Malnutrition is a common feature of intestinal tuberculosis in children. Some cases may have a right iliac fossa mass. The nonspecific laboratory abnormalities which can be seen are anemia, hypoalbuminemia and an elevated ESR.

## Diagnosis

A single gold standard for the diagnosis of Crohn's disease is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations (ECCO consensus statement) [49]. Crohn's disease is a heterogeneous entity comprising a variety of complex phenotypes[41, 50-52] .

Anemia, hypoalbuminemia, an elevated C-reactive protein or erythrocyte sedimentation rate, although not specific for IBD, may prompt further investigation. As there is no single way to diagnose Crohn's disease, Lennard-Jones et al have defined macroscopic and microscopic criteria to establish the diagnosis. The macroscopic features include physical examination, endoscopy, radiology, and examination of an operative specimen. Microscopic features can be only partly assessed on mucosal biopsy, but completely assessed on an operative specimen. The diagnosis depends on the finding of discontinuous and often granulomatous intestinal inflammation [53]. The current view is that the diagnosis is established by a nonstrictly defined combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings.

A small bowel follow-through study is the primary modality to evaluate for small bowel disease. Early findings include aphthous ulcers, a coarse villous pattern of the mucosa, and thickened folds. Submucosal edema may be evident as thickening or flattening of the valvulae conniventes, whereas transmural edema manifests as widening of the separation

between loops of bowel. Ulcers most often occur on the mesenteric border with consequent pseudosacculation of the antimesenteric border because of shortening of the mesenteric border [54]. Later findings include a cobblestone appearance resulting from edema in relatively spared islands of mucosa that are separated by longitudinal and transverse knife-like clefts of ulceration [54]. Still later, one may discern fistulas, sinus tracts, and fixed strictures.

The features suggestive of Crohn's disease on CT scan of the abdomen are mesenteric lymphadenopathy, transmural thickening of the bowel and fibrofatty proliferation of the mesentery. CT is the investigation of choice for identifying suppurative complications of Crohn's disease, such as intra-abdominal and retroperitoneal abscess

Colonoscopy shows aphthous ulcers, mucosal edema, cobblestoning. Discontinuous segmental nature of the disease and rectal spaing are characteristic [55]. In a prospective endoscopic study of patients with Crohn's disease who were about to start a course of prednisone, the incidence of endoscopic findings was as follows:superficial erosions, 93%; deep erosions, 74%; mucosal edema, 48%; erythema, 44%; pseudopolyps, 41%; aphthous ulcers, 10%; ulcerated stenosis, 8%; and non-ulcerated stenosis, 2% [56]. In another study of 44 patients of Crohn's disease , aphthous ulcers were seen in 81.8% , cobble stone appearance in 34.1% , pseudopolyps in 27.3% , longitudinal ulcers in 40.9%, transverse ulcers in 25% [6].

In Crohn's disease granulomas can be found in histopathology- they are usually sparse, scattered, not well formed with little or no central necrosis, and acid-fast stains for AFB and mycobacterial cultures are negative. Other features include focal crypt

inflammation, focal areas of marked chronic inflammation, the presence of aphthae and ulcers on a background of little or no chronic inflammation, and the interspersing of segments of involved bowel with segments of uninvolved bowel. Transmural involvement and presence of lymphoid aggregates in both the submucosa and external to the muscularis propria are other suggestive features on biopsy.

For diagnosing intestinal tuberculosis the main diagnostic utilities are imaging, biopsy for histology and culture. Intestinal tuberculosis can be diagnosed if there is clinical, colonoscopic, and/or radiologic evidence of intestinal tuberculosis with histologic demonstration of acid fast bacilli or growth of Mycobacterium tuberculosis on tissue culture or histologic evidence of caseating granulomas or evidence of proved tuberculosis elsewhere [6].

An abdominal radiograph yields no specific information for identifying intestinal tuberculosis but may reveal obstruction or perforation and calcified mesenteric lymph nodes. Barium studies are particularly useful in demonstrating mucosal lesions. The main imaging techniques are small bowel follow through and CT abdomen. The common imaging features that may be seen in intestinal tuberculosis are as follows: (1) enlarged para-aortic nodes, (2) asymmetric bowel wall thickening, (3) ascites, (4) inflammatory mass of bowel wall lymph nodes and omentum, (5) narrowing of the terminal ileum with thickening and gaping of the iliocaecal valve, (6) 'white bowel' sign due to lymphatic infiltration and (7) 'sliced bread sign' due to fluid surrounding bowel caused by inflammation of the bowel wall [46].

Colonoscopy shows nonspecific findings. In a study of intestinal tuberculosis patients the findings on colonoscopy were patulous ileocecal valve (40%), transverse ulcers (65.9%), longitudinal ulcers (2.3%), cobblestone appearance (6.8%), pesudopolyps (52.3%) [6].

The histopathologic features seen in intestinal tuberculosis are chronic inflammation, ulceration, granulomas, caseation [9]. Other features such as cryptitis and crypt abscess may also be found. Histopathologic sections may reveal acid fast bacilli which is specific for the diagnosis of tuberulosis.

**Differentiating Crohn's disease from intestinal tuberculosis.**

Both intestinal tuberculosis and Crohn's disease are chronic granulomatous disorders [10] with similarities that make the differentiation between these two entities very difficult but at the same time crucial, as the repercussions of a misdiagnosis carry grave consequence. There have been reports of misdiagnosing intestinal tuberculosis as Crohn's disease for as long as 7 years before the correct diagnosis was reached [57].

Distinguishing Crohn's disease from intestinal tuberculosis especially in highly endemic areas for tuberculosis is challenging, and a diagnosis of Crohn's diseae in individuals from such areas should be made after careful evaluation of all diagnostic modalities [58, 59] . At the same time, it should not cause the clinicians to delay the diagnosis of Crohn's disease, as this would delay definitive treatment of the disease.

## Clinical Presentation

The symptoms and signs of intestinal tuberculosis are nonspecific and may closely resemble Crohn's disease. A high index of suspicion is required as otherwise the diagnosis may be missed or delayed, and the institution of immunosuppressive therapy would result in an increase in morbidity and mortality in patients with intestinal tuberculosis. Most of the intestinal tuberculosis patients usually present with symptoms ranging from 1 month to 1 year. Pain is the most common presentation in about 85 % , weight loss in 66 % , fever in 35 – 50 % and diarrhea in only 20 % of patients [15] . On physical examination, abdominal tenderness is found in most patients and an abdominal mass, usually in the right lower quadrant, in 25 to 50 % of patients. A majority of these patients present with obstruction like symptoms or with fistulisation [60] and intussusception [61] but occasionally they may present with recurrent significant gastrointestinal tract blood loss [62] .Unusual presentations include bowel perforation and dysentery, and thus intestinal tuberculosis should always be considered in the differential diagnosis of unusual gastrointestinal presentations especially in highly endemic areas [63] . Furthermore, intestinal tuberculosis has been identified in asymptomatic patients who undergo colonoscopies for other reasons [64] .

Some of the features on history and physical examination that favor the diagnosis of Crohn's disease are younger age, oral ulcers, perianal disease, enteric fistulae and extraintestinal manifestations of Crohn's disease[10, 65] , although intestinal tuberculosis involvement of the lower limb joints, skin, eye and liver may mimic extraintestinal Crohn's disease[66, 67]. In addition, bleeding per rectum, diarrhea and shorter duration

of symptoms may favor Crohn's disease rather than intestinal tuberculosis [68, 69]. Fever is seen in both Crohn's disease and intestinal tuberculosis, but a high swinging fever (>38.5 ° C) favors intestinal tuberculosis in the absence of any intra-abdominal abscess. Peritoneal involvement with ascites would also favour a diagnosis of intestinal tuberculosis but as it is often absent it is not very discriminatory [70] .

**Serological Tests And Cultures**

The laboratory diffeerentiation between intestinal tuberculosis and Crohn's disease has not had great success. Routine routine blood tests looking at the cell counts and fractionation of white blood cells and other conventional tests, such as the erythrocyte sedimentation rate and C-reactive protein, are too nonspecific and do not aid in the work-up of these patients. A recent series of studies showed that the use of different serological markers, such as the anti-neutrophil cytoplasmic antibodies, the peri-nuclear and the cytoplasmic variants (p-ANCA and c-ANCA), and the IgA and IgG subtypes of anti-Saccharomyces cerevisiae antibodies, had no significant diagnostic value[3, 4, 69] in discriminating between intestinal tuberculosis and Crohn's disease. These tests should not therefore be relied upon for distinguishing intestinal tuberculosis from Crohn's disease.

The most reliable differentiation method is to find evidence of M. tuberculosis in the intestinal tissues. Unfortunately, acid-fast bacilli staining lacks sensitivity. In addition, the biopsy culture for M. tuberculosis is time consuming (3 – 8 weeks) and results are

frequently negative (accuracy ranging from 25 to 35 % ) [69] . The most promising new approach to this problem is the PCR assay. The TB polymerase chain reaction assay (TB PCR) on either endoscopic or surgical sections from patients ' with intestinal tuberculosis has been found to have a high accuracy for diagnosing intestinal tuberculosis [59] . This test is based on augmenting oligonucleotides found in the M. tuberculosis chromosome that are highly specific for the organism, thus increasing its detection rate. PCR assay showed a specificity of up to 95 % [5] and an accuracy of 82.6 % for diagnosing intestinal tuberculosis [69] . In a study by Pulimood et al which did Mycobacterium tuberculosis PCR in mucosal biopsy specimens of 20 patients each of intestinal tuberculosis and Crohn's disease , it was positive in 6 intestinal tuberculosis and 1 Crohn's disease specimens [71]. Some studies found no variation in the performance of the PCR assay whether the histology showed granuloma or not, and whether granulomas showed caseation or not. One of the benefits of using the PCR assay is the speed at which the diagnosis can be made. In one study, a definite diagnosis of intestinal tuberculosis was concluded in 3 days [72] .

**The Tuberculin Skin Test**

The PPD skin test has been extensively studied in cases of pulmonary tuberculosis. The value of this test is unknown for intestinal tuberculosis, but from these studies we can conclude that diagnostic value of this test varies according to the population that is being tested. In communities with a moderate to high prevalence of smear positive pulmonary tuberculosis (>20 per 100,000 per year), a positive tuberculin skin test (TST) is more

likely to indicate a true tuberculosis infection. However, in areas with a very low incidence of active tuberculosis ( < 10 per 100,000 per year), a positive TST will more likely be a false positive, and the false-positive rate is very high in areas of the world where the bacillus Calmette – Gu é rin (BCG)vaccination is still given [73] . Furthermore, anergy in human immunodeficiency virus, primary tuberculosis and disseminated tuberculosis further limits the diagnostic utility of this test [74] . Use of corticosteroids and immunosuppressive drugs may also limit diagnostic utility of TST.

**Quantiferon-Tb Gold**

Quantiferon-TB gold (QFT-G) is a blood test that uses an interferon- gamma -release assay that measures the release of interferon after stimulation in vitro by M. tuberculosis antigens. The main advantage of this assay with respect to the TST is the lack of cross reaction with BCG and most nontuberculous mycobacteria. QFT-G also eliminates the need for the patient to return for test reading in 48 – 72 h[75, 76]. It has also been used to identify false-positive TSTs given its high specificity[77, 78]. Most of the studies on this test have been performed on pulmonary tuberculosis. Although there is a report describing the use of QFT-G in the diagnosis of two cases with intestinal tuberculosis [79] , its value has not been formally studied in intestinal tuberculosis. Such studies of QFT-G in intestinal tuberculosis are urgently required.

## Imaging Studies

A chest X-ray shows radiographic features suggestive of tuberculosis in up to 32 % of patients with intestinal tuberculosis [80] . A negative chest X-ray does not exclude intestinal tuberculosis. Although the intestinal radiographic features of Crohn's disease and intestinal tuberculosis can be similar [69] , there are findings on imaging that can help to differentiate them. Barium studies have not been found to be helpful in differentiating the two diseases[81]. Computerized tomography scans have become an essential tool because it can show the location of the disease, but it also has the advantage of evaluating the extent of the inflammatory process and involvement of the intestine, mesentery, peritoneum, lymph nodes, solid organs and retroperitoneal disease [82] . In a study, asymmetric thickening of the colonic wall and enlarged necrotic lymph nodes were highly suggestive of intestinal tuberculosis [83] . In intestinal tuberculosis, the lymph nodes were noted to be larger and one-third had necrotic centers. Bowel loop displacement was more often due to lymphadenopathy in intestinal tuberculosis, whereas in Crohn's disease it was frequently due to fibrofatty changes. In Crohn's disease, the wall thickening usually is symmetric and concentric and there is mural stratification (target sign)[84]. Magnetic resonance imaging is not helpful in discriminating Crohn's disease from intestinal tuberculosis.

## Endoscopic Features

Endoscopic features of intestinal tuberculosis and Crohn's disease have a lot of similarities, as the mucosal inflammatory response in both disease processes are the same [85] . The majority of both intestinal tuberculosis and Crohn's Disease diseases involve the ileo-colonic region, and so ileo-colonoscopy is crucial for the diagnosis of both diseases. Rapid diagnosis of intestinal tuberculosis is possible if acid-fast bacilli or caseating granulomas are seen on the biopsied tissue. When intestinal tuberculosis affects the colon, it can present in different ways, the most common being segmental ulcers and colitis, inflammatory strictures or hypertrophic lesions resembling polyps and masses [3, 45, 64, 86-93] . Colonic tuberculosis also can present as a diffuse colitis that might resemble to a great degree the appearance of ulcerative colitis[15, 45, 86, 90]. In tuberculous colitis, the mucosa surrounding an ulcer exhibit feature of inflammation, such as erythema, nodularity or edema, but the rectum is rarely involved in intestinal tuberculosis [45]. . Lee et al in the first systematic prospective analysis evaluated endoscopic findings in 44 patients with intestinal tuberculosis and 44 patients with Crohn's Disease. They found that anorectal involvement, longitudinal ulcers, aphthous ulcers and a cobblestone appearance were all significantly more common in patients with Crohn's disease than in patients with intestinal tuberculosis. In contrast, intestinal tuberculosis usually has less than four segments involved, a patulous ileocecal valve, transverse ulcers and more scars[6]. Table 1 shows comparison of endoscopic findings between Crohn's disease and intestinal tuberculosis.

**Table 1. Endoscopic Features of intestinal tuberculosis and Crohn's Disease**

| Intestinal tuberculosis | Crohn's disease |
|---|---|
| Ulcers have circumferential orientation | Longitudinal orientation |
| Surrounding mucosa inflamed/nodular | Surrounding mucosa normal |
| Apthous ulcers uncommon | Apthous ulcers common |
| Hyperaemic nodules-isolated or in clusters | Cobblestoning |
| Pseudopolyps | Multiple skip lesions |
| Hypertrophic mucosa | Anorectal lesions |
| Strictures | Strictures |
| Destruction of ICV and/or caecum | Preservation of ICV |

One of the great advantages of endoscopic examination is obtaining biopsy samples, which should be taken from ulcer margins. The optimal number of biopsy samples has not been established, but one study suggested taking at least 6 samples. Samples should be routinely sent for culture. A larger number of biopsies would increase the chance of studying granuloma morphology well and identifying Mycobacteria.

## Pathological Features

Differentiation between intestinal tuberculosis and Crohn's Disease usually hinges on the biopsy specimens obtained at endoscopic examination. Apart from finding acid-fast bacilli, which is only found in a fraction of these patients, the differentiation can present a great challenge for the pathologist. Pulimood et al identified nine histological parameters helpful in distinguishing Crohns disease from intestinal tuberculosis. Features favouring intestinal tuberculosis are large granulomas, > four sites of granulomatous inflammation, caseation, band of epithelioid histiocytes in ulcer base and granulomatous inflammation in caecum.

Features favouring Crohn's Disease are non-tuberculous granulomas, mucosal changes distant to sites with granulomas, focal crypt-related inflammation, granulomas in sigmoid or rectum.

In a South African study that compared 25 patients with Crohn's Disease to 18 with intestinal tuberculosis, the histological features that were only detected in cases with intestinal tuberculosis were confluent granulomata, 10 or more granulomata per biopsy site and caseous necrosis. Other features seen in intestinal tuberculosis more often than Crohn's Disease were granulomata exceeding 0.05 mm, ulcers lined by conglomerate epithelioid histiocytes and disproportionate submucosal inflammation[8, 10].

Table 2 shows comparison of histological findings in patients with intestinal tuberculosis and Crohn's disease.

**Table 2. Prevalence of Selected Histological Parameters in Patients with Intestinal Tuberculosis (ITB) and Crohn's Disease (CD): A Comparison of Three Similar Studies (values are in %)**

| | Pulimood et al. (1999) Southern India [8] | | Pulimood et al. (2005) Southern India [9] | | Kirsch et al. (2006), Cape Town, South Africa [10] | |
|---|---|---|---|---|---|---|
| | ITB (n = 20) | CD (n = 20) | ITB (n = 33) | CD (n = 31) | ITB (n = 18) | CD (n = 25) |
| **Caseous necrosis** | 40 | 0 | 36 | 0 | 22 | 0 |
| **Confluent granulomas** | 60 | 0 | 42 | 3 | 50 | 0 |
| **≥5 granulomas/biopsy site** | 40 | 0 | 45 | 0 | 44 | 24 |
| **≥10 granulomas/biopsy site** | -- | -- | -- | -- | 33 | 0 |
| **Large granulomas** | Diameter > 200 µm | | Diameter > 400 µm | | Area > 0.05 $mm^2$ | |
| | 90 | 5 | 51 | 0 | 67 | 8 |
| **Submucosal granulomas** | 45 | 5 | 39 | 6 | 44 | 12 |
| **Ulcers lined by bands of epithelioid histiocytes** | 45 | 5 | 61 | 0 | 61 | 8 |
| **Disproportionate submucosal inflammation** | 65 | 5 | -- | -- | 67 | 10 |
| **Architectural distortion distant to granulomatous inflammation** | -- | -- | 0 | 62 | -- | -- |

# Materials and methods

Case records of patients with definite diagnosis of intestinal tuberculosis and Crohn's disease were analysed using uniform structured data forms with respect to clinical, laboratory, radiologic, endoscopic and histological parameters.

**Inclusion Criteria**

Patients with definite diagnosis of intestinal tuberculosis or Crohn's disease.

Diagnostic criteria of intestinal tuberculosis [6]

Clinical, colonoscopic, and/or radiologic evidence of intestinal tuberculosis with one of the criteria shown below.

- Histological demonstration of acid fast bacilli.
- Growth of Mycobacterium tuberculosis on tissue culture.
- Histological evidence of caseating granulomas
- Proved tuberculosis elsewhere in the body.
- Sustained response to ATT.

Diagnostic criteria of Crohn's disease [6]

Positive response to therapy for Crohn's disease with any of the two criteria as shown below.

- Clinical history of chronic diarrhoea, abdominal pain, weight loss, and/or rectal bleeding.

- Endoscopic findings of mucosal cobblestoning, linear ulceration or skip areas.
- Radiologic findings of stricture, fistula, mucosal cobblestoning or ulceration.
- Histological findings of chronic inflammation/ granulomas.
- Macroscopic appearance of bowel-wall induration, mesenteric lymphadenopathy, and "creeping fat" at laparotomy.

**Statistical methods**

Sample size was calculated based on the following assumptions. From the previous studies , the prevalence of deep linear ulcer in the Crohn's disease group was 57% and in the intestinal tuberculosis group was 23%[69]. To find a 35% difference in the prevalence of deep linear ulcer between Crohn's disease and intestinal tuberculosis with a power of 80% and 5% level of significance, the sample size was calculated as 56 in each group.

Continuous data is presented as mean with standard deviation and categorical data as proportions. Univariate analysis was done to identify the significantly different characteristics between the two diseases. The categorical variables were compared using chi square test and the continuous variables using t test. A p value of $< 0.05$ was taken as significant; the significant parameters were included in multivariate analysis using logistic regression method. The data was analyzed using STATA software.

**Development of scoring system**

After logistic regression analysis, each of the regression coefficients of the final significant parameters was multiplied by 10 and rounded off to the nearest integer. A total score was calculated for each patient by summing up the individual coefficients expressed in integers. The total score was plotted on ROC curve [94] to derive the cut off score to differentiate intestinal tuberculosis from Crohn's disease . The model was validated using bootstrapping method [95].

The bootstrap analysis involves drawing 1000 samples from the original dataset. For each sample, the logistic regression model is performed using the variables which are significant in the univariate analysis. The number of times each of the final variables appear in the repeated models indicates stability or consistency of the variable. If the variable in model occurs in more than 50% ( >500) of the bootstrap samples, then the variable in the final model is considered good.

# Results

A total of 110 patients with intestinal tuberculosis (ITB) and 103 patients with Crohn's disease (CD) were identified for the study. In the intestinal tuberculosis group there were 65 (59.09%) males and 45 (40.91%) females, while in the Crohn's disease group there were 61 (59.22%) males and 42 (40.78%) females.

The mean age of the patients with intestinal tuberculosis [35.2 $\pm$ 13.14 years(range 8-66)] was similar to the patients with Crohn's disease [33.2 $\pm$ 12.70 years (range 9-68)].

**Clinical features**

The frequency of clinical symptoms and signs in patients with intestinal tuberculosis and Crohn's disease are shown in Table 1.

**Table 1: Clinical features**

| Parameter | TB (n=110) | CD (n=103) | P value |
|---|---|---|---|
| **Blood in stools** | **17 (15.5)** | **38 (36.89)** | **<0.001** |
| **Diarrhea** | **34 (30.91)** | **55 (53.40)** | **0.001** |
| **Abdominal pain** | **97 (88.18)** | **76 (73.79)** | **0.007** |
| **Anorexia** | **58 (52.73)** | **29 (28.16)** | **<0.001** |
| **Vomiting** | **58 (52.73)** | **31 (30.10)** | **0.001** |
| **Weight loss** | **81 (73.64)** | **55 (53.40)** | **0.002** |
| Fever | 45 (40.91) | 36 (34.95) | 0.37 |
| Oral ulcers | 4 (3.64) | 7 (6.80) | 0.30 |
| **Joint symptoms** | **2 (1.82)** | **17 (16.50)** | **<0.001** |
| Mass abdomen | 9 (8.18) | 6 (4.85) | 0.37 |
| **Perianal disease** | **2 (1.82)** | **14 (13.59)** | **0.001** |

Univariate analysis showed that blood in stools (P=<0.001), diarrhea (P=0.001), joint symptoms (P=<0.001) and perianal disease (P=0.001) were more common in Crohn's disease while abdominal pain (P=0.007), anorexia (P=<0.001), vomiting (P=0.001) and weight loss (P=0.002) were more often seen in intestinal tuberculosis .

The mean duration of symptoms in patients with intestinal tuberculosis [29.5 months (range 1-240 ) ] was similar to those with Crohn's disease [29.37 months (range 1-240 ) ] (p= 0.975).

**Blood tests**

ESR, CRP and serum albumin in patients with intestinal tuberculosis and Crohn's disease are shown in Table 2.

**Table 2: Blood investigations**

| Test | TB | CD | P value |
|---|---|---|---|
| Hb | 11.4 ± 0.9 (n=110) | 10.3 ± 0.2 (n=98) | 0.29 |
| ESR | 69.5 ± 11.8 (n=94) | 59.9 ± 3.3 (n=95) | 0.43 |
| CRP | 32.8 ± 4.7 (n=45) | 37.5 ± 4.8 (n=70) | 0.50 |
| Albumin | 3.19 ± 0.08 (n=99) | 3.21 ± 0.1 (n=94) | 0.85 |

Blood investigations revealed anemia, high ESR, high CRP and low albumin (< 3.5 g/dL) in most patients of both groups; there was no significant difference between the two groups.

**Radiology**

**Barium Meal Follow Through (BMFT)**

A total of 35 patients with intestinal tuberculosis and 61 with Crohn's disease had BMFT. Table 3 shows the comparison of BMFT findings between the two groups.

**Table 3: BMFT findings**

| **Parameter** | **TB (n=35)** | **CD(n=61)** | **P value** |
|---|---|---|---|
| Segmentation | 0 (0) | 1 (1.64) | 0.45 |
| Flocculation | 0 (0) | 1 (1.64) | 0.45 |
| Retraction of mesenteric border | 0 (0) | 6 (9.84) | 0.06 |
| Antimesenteric sacculations | 0 (0) | 6 (9.84) | 0.06 |
| Patulous IC valve | 1 (2.86) | 1 (1.64) | 0.69 |
| **Contracted cecum** | **17 (48.57)** | **15 (24.59)** | **0.016** |
| Cobblestone appearence | 0 (0) | 6 (9.84) | 0.06 |
| Narrowed IC junction | 7 (20.00) | 6 (9.84) | 0.16 |
| Short segment stricture | 10 (27.78) | 9 (14.75) | 0.12 |
| Long segment stricture | 0 (0) | 5 (8.20) | 0.08 |
| Ulcer | 5 (14.29) | 11 (17.74) | 0.66 |
| Fistula | 1 (2.86) | 1 (1.64) | 0.69 |
| **Pulled up IC junction** | **8 (22.86)** | **4 (6.67)** | **0.022** |
| Separated small bowel loops | 1 (2.86) | 7 (11.67) | 0.14 |

.

After univariate analysis, contracted cecum (P= 0.016) and a pulled up IC junction (P= 0.022) were significantly more common in intestinal tuberculosis as compared to Crohn's disease.

Retraction of mesenteric border, antimesenteric sacculations, cobblestone appearance and long segment stricture were more often seen in Crohn's disease but did not reach

statistical significance probably because of the small number of patients in whom the study was performed.

**CT abdomen**

CT abdomen was performed on 42 patients with intestinal tuberculosis and 35 patients with Crohn's disease. The CT abdomen findings are shown in Table 4.

**Table 4: CT findings**

| **Parameter** | **TB(n=42)** | **CD(n=35)** | **P value** |
|---|---|---|---|
| Short segment stricture | 11 (26.19) | 8 (22.86) | 0.74 |
| Ascites | 7 (16.67) | 2 (5.71) | 0.14 |
| Omega sign | 1 (2.38) | 1 (2.86) | 0.90 |
| Fistulae | 3 (7.14) | 5 (14.29) | 0.31 |
| Mesenteric fat proliferation | 2 (4.76) | 4 (11.43) | 0.28 |
| Contracted cecum | 3 (7.14) | 0 (0) | 0.11 |
| **Mesenteric hypervascularity (Comb sign)** | **0 (0)** | **5 (14.29)** | **0.011** |
| **Abdominal nodes** | **31 (73.81)** | **9 (25.71)** | **<0.001** |
| Mural thickening | 33 (78.57) | 26 (74.29) | 0.66 |

Abdominal nodes were found more often in patients with intestinal tuberculosis (P= < 0.001) while mesenteric hypervascularity was more common in Crohn's disease (P= 0.011). Other parameters evaluated were similar in the two groups of patients.

**Colonoscopy**

Colonoscopy was performed in all patients included in the study . The colonoscopy findings in patients with intestinal tuberculosis and Crohn's disease are shown in Table 5.

**Table 5: Colonoscopy findings.**

| Parameter | TB(n=110) | CD(n=103) | P value |
|---|---|---|---|
| **Pseudopolyps** | **4 (3.64)** | **17 (16.50)** | **0.002** |
| Skip lesions | 0 (0) | 3 (2.91) | 0.07 |
| Cobble stone appearence | 1 (0.91) | 5 (4.85) | 0.08 |
| **Nonulcerated stenosis** | **21 (19.09)** | **8 (7.77)** | **0.016** |
| **Ulcerated stenosis** | **21 (19.09)** | **4 (3.88)** | **0.001** |
| **Aphthous ulcer** | **3 (2.73)** | **29 (28.16)** | **<0.001** |
| **Linear/Serpiginous ulcer** | **1 (0.91)** | **12 (11.65)** | **0.001** |
| Transverse ulcer | 2 (1.82) | 1 (0.97) | 0.60 |
| **Narrowed IC valve** | **18 (16.36)** | **4 (3.88)** | **0.003** |
| Patulous IC valve | 15 (13.64) | 9 (8.74) | 0.26 |

Pseudopolyps (p=0.002), aphthous ulcers (p= <0.001) and linear/ serpiginous ulcers (p=0.001) were more common in Crohn's disease than intestinal tuberculosis while nonulcerated stenosis (P= 0.016) , ulcerated stenosis (P= 0.001) and narrowed IC valve (P= 0.003 ) were more often seen in patients with intestinal tuberculosis.

## Histopathology

### Colonoscopy biopsy

Table 6 shows the histological features on colonoscopy biopsy in the patients studied.

**Table 6: Histological features on colonoscopy biopsy**

| Parameter | TB (n=110) | CD(n=103) | P value |
|---|---|---|---|
| Chronic inflammation | 92 (83.64) | 76 (73.79) | 0.08 |
| **Ulceration** | **52 (47.27)** | **26 (25.24)** | **0.001** |
| **Granulomas** | **57 (51.82)** | **31 (30.1.)** | **0.001** |
| **Confluent granulomas** | **27 (24.55)** | **2 (1.94)** | **<0.001** |
| Cryptitis | 39 (35.45) | 46 (44.66) | 0.17 |
| Crypt abscess | 28 (25.45) | 29 (28.16) | 0.66 |
| Architectural alteration | 19 (17.27) | 19 (18.45) | 0.82 |

Table 6 shows that ulceration (P= 0.001), granulomas (P= 0.001) and confluent granulomas (p= <0.001) were more common in intestinal tuberculosis than Crohn's disease.

## Development of the scoring system

Table 7 shows the clinical, colonoscopy and histopathology parameters that were significantly different in intestinal tuberculosis and Crohn's disease after univariate analysis.

**Table 7:Parameters that were significantly different in intestinal tuberculosis and Crohn's disease after univariate analysis.**

| Parameter | TB | CD | P value |
|---|---|---|---|
| Blood in stools | 17 (15.5) | 38 (36.89) | <0.001 |
| Diarrhea | 34 (30.91) | 55 (53.40) | 0.001 |
| Abdominal pain | 97 (88.18) | 76 (73.79) | 0.007 |
| Anorexia | 58 (52.73) | 29 (28.16) | <0.001 |
| Vomiting | 58 (52.73) | 31 (30.10) | 0.001 |
| Weight loss | 81 (73.64) | 55 (53.40) | 0.002 |
| Joint symptoms | 2 (1.82) | 17 (16.50) | <0.001 |
| Perianal disease | 2 (1.82) | 14 (13.59) | 0.001 |
| Pseudopolyps | 4 (3.64) | 17 (16.50) | 0.002 |
| Nonulcerated stenosis | 21 (19.09) | 8 (7.77) | 0.016 |
| Ulcerated stenosis | 21 (19.09) | 4 (3.88) | 0.001 |
| Aphthous ulcer | 3 (2.73) | 29 (28.16) | <0.001 |
| Linear/Serpiginous ulcer | 1 (0.91) | 12 (11.65) | 0.001 |
| Narrowed IC valve | 18 (16.36) | 4 (3.88) | 0.003 |
| Ulceration | 52 (47.27) | 26 (25.24) | 0.001 |
| Granulomas | 57 (51.82) | 31 (30.1.) | 0.001 |
| Confluent granulomas | 27 (24.55) | 2 (1.94) | <0.001 |

After univariate analysis the parameters that were significantly more common in intestinal tuberculosis were:

(a) Clinical : abdominal pain, anorexia, vomiting, weight loss.

(b) Colonoscopy: nonulcerated / ulcerated stenosis, narrowed IC valve.

(c) Histology: ulceration, granulomas, confluent granulomas.

Parameters significantly more common in Crohn's disease were:

(a) Clinical: blood in stools, diarrhea, joint symptoms, perianal disease

(b) Colonoscopy: pseudopolyps, aphthous ulcers and linear/ serpiginous ulcers.

The blood tests and radiology parameters were not included in multivariate analysis since the data was incomplete for those parameters.

Logistic regression was then performed using the parameters that were significant on univariate analysis. The results of logistic regression analysis is shown in Table 8.

**Table 8: Parameters that were significantly different in intestinal tuberculosis and Crohn's disease after logistic regression analysis.**

| Parameter | Coefficient | P value |
|---|---|---|
| Anorexia | 1.104188 | 0.020 |
| Vomiting | 0.8633479 | 0.042 |
| Pseudopolyps | -1.869838 | 0.023 |
| Aphthous ulcer | -2.456286 | 0.003 |
| Linear/Serpiginous ulcer | -3.522889 | 0.031 |
| Ulceration | 1.426832 | 0.002 |
| Confluent granulomas | 4.272531 | <0.001 |

After logistic regression analysis the parameters that favoured intestinal tuberculosis were :

Clinical : Anorexia ,vomiting.

Histology: Ulceration ,confluent granulomas.

The parameters that favoured Crohn's disease were :

Colonoscopy: pseudopolyps, aphthous ulcers, linear / serpiginous ulcers

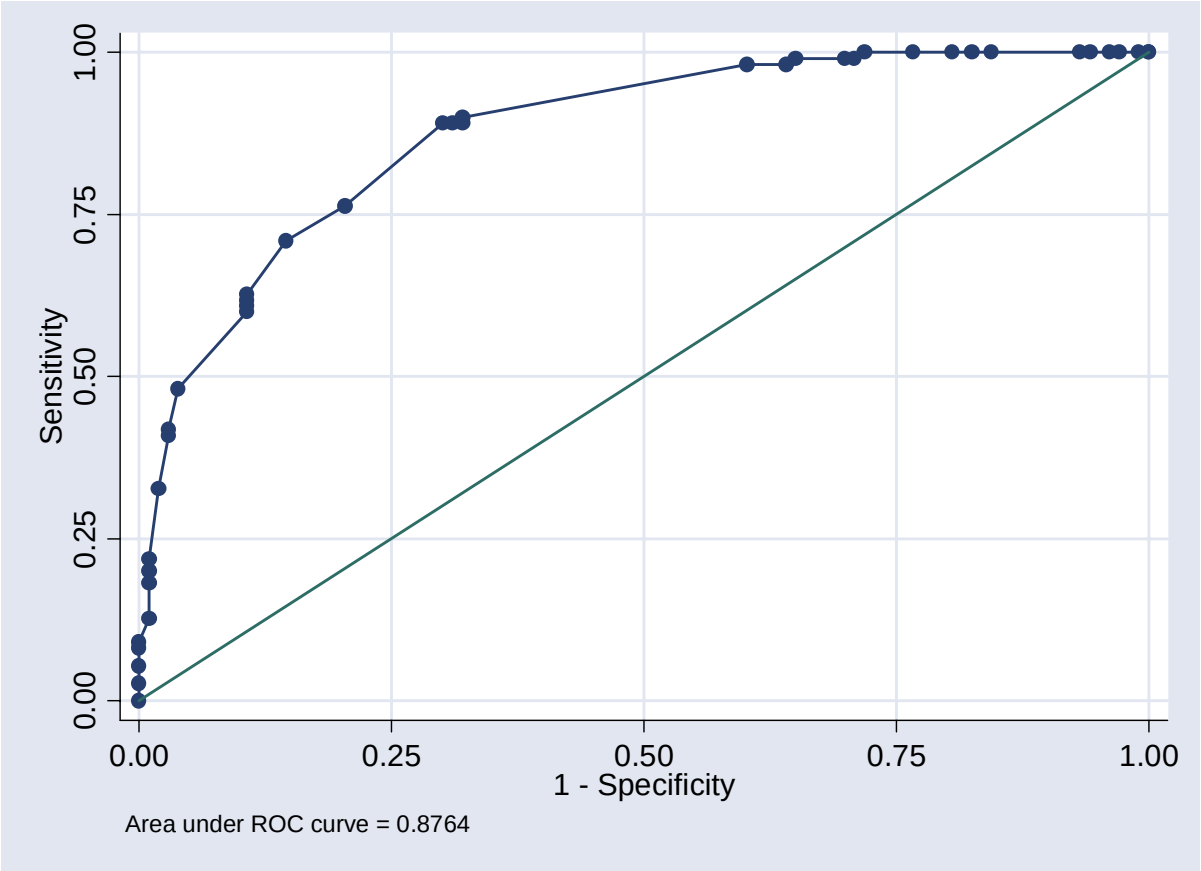
Each of the coefficients of the significant parameters after logistic regression analysis was multiplied by 10 and rounded off to the nearest integer to obtain a score for each parameter- (Table 9)

**Table 9: Score of individual parameter**

| **Parameter** | **Coefficient** | **Score** |
|---|---|---|
| Anorexia | 1.104188 | +11 |
| Vomiting | 0.8633479 | +9 |
| Pseudopolyps | -1.869838 | -19 |
| Aphthous ulcer | -2.456286 | -25 |
| Linear/Serpiginous ulcer | -3.522889 | -35 |
| Ulceration | 1.426832 | +14 |
| Confluent granulomas | 4.272531 | +43 |

A total score was calculated for each patient by summing up the individual coefficients expressed in integers. The total score was plotted on ROC curve to derive the cut-points. (Figure 1).

**Figure 1: ROC curve**



The detailed report of sensitivity and specificity is shown in Table 10.

**Table 10.**

Detailed report of Sensitivity and Specificity

| Cutpoint | Sensitivity | Specificity | Correctly Classified | LR+ | LR- |
|---|---|---|---|---|---|
| ( >= -65 ) | 100.00% | 0.00% | 51.64% | 1.0000 | |
| ( >= -54 ) | 100.00% | 0.97% | 52.11% | 1.0098 | 0.0000 |
| ( >= -49 ) | 100.00% | 2.91% | 53.05% | 1.0300 | 0.0000 |
| ( >= -46 ) | 100.00% | 3.88% | 53.52% | 1.0404 | 0.0000 |
| ( >= -37 ) | 100.00% | 5.83% | 54.46% | 1.0619 | 0.0000 |
| ( >= -25 ) | 100.00% | 6.80% | 54.93% | 1.0729 | 0.0000 |
| ( >= -24 ) | 100.00% | 15.53% | 59.15% | 1.1839 | 0.0000 |
| ( >= -21 ) | 100.00% | 17.48% | 60.09% | 1.2118 | 0.0000 |
| ( >= -19 ) | 100.00% | 19.42% | 61.03% | 1.2410 | 0.0000 |
| ( >= -16 ) | 100.00% | 23.30% | 62.91% | 1.3038 | 0.0000 |
| ( >= -14 ) | 100.00% | 28.16% | 65.26% | 1.3919 | 0.0000 |
| ( >= -11 ) | 99.09% | 29.13% | 65.26% | 1.3981 | 0.0312 |
| ( >= -10 ) | 99.09% | 30.10% | 65.73% | 1.4176 | 0.0302 |
| ( >= -8 ) | 99.09% | 34.95% | 68.08% | 1.5233 | 0.0260 |
| ( >= -5 ) | 98.18% | 35.92% | 68.08% | 1.5322 | 0.0506 |
| ( >= 0 ) | 98.18% | 39.81% | 69.95% | 1.6311 | 0.0457 |
| ( >= 1 ) | 90.00% | 67.96% | 79.34% | 2.8091 | 0.1471 |
| ( >= 6 ) | 89.09% | 67.96% | 78.87% | 2.7807 | 0.1605 |
| ( >= 8 ) | 89.09% | 68.93% | 79.34% | 2.8676 | 0.1583 |
| ( >= 9 ) | 89.09% | 69.90% | 79.81% | 2.9601 | 0.1561 |
| ( >= 11 ) | 76.36% | 79.61% | 77.93% | 3.7455 | 0.2969 |
| ( >= 14 ) | 70.91% | 85.44% | 77.93% | 4.8691 | 0.3405 |
| ( >= 15 ) | 62.73% | 89.32% | 75.59% | 5.8736 | 0.4173 |
| ( >= 17 ) | 61.82% | 89.32% | 75.12% | 5.7884 | 0.4275 |
| ( >= 18 ) | 60.91% | 89.32% | 74.65% | 5.7033 | 0.4376 |
| ( >= 20 ) | 60.00% | 89.32% | 74.18% | 5.6182 | 0.4478 |
| ( >= 23 ) | 48.18% | 96.12% | 71.36% | 12.4068 | 0.5391 |
| ( >= 24 ) | 41.82% | 97.09% | 68.54% | 14.3576 | 0.5993 |
| ( >= 25 ) | 40.91% | 97.09% | 68.08% | 14.0455 | 0.6086 |
| ( >= 34 ) | 32.73% | 98.06% | 64.32% | 16.8545 | 0.6860 |
| ( >= 43 ) | 21.82% | 99.03% | 59.15% | 22.4726 | 0.7895 |
| ( >= 52 ) | 20.00% | 99.03% | 58.22% | 20.5999 | 0.8078 |
| ( >= 54 ) | 18.18% | 99.03% | 57.28% | 18.7272 | 0.8262 |
| ( >= 57 ) | 12.73% | 99.03% | 54.46% | 13.1090 | 0.8813 |
| ( >= 63 ) | 9.09% | 100.00% | 53.05% | | 0.9091 |
| ( >= 66 ) | 8.18% | 100.00% | 52.58% | | 0.9182 |
| ( >= 68 ) | 5.45% | 100.00% | 51.17% | | 0.9455 |
| ( >= 77 ) | 2.73% | 100.00% | 49.77% | | 0.9727 |
| ( > 77 ) | 0.00% | 100.00% | 48.36% | | 1.0000 |

| Obs | ROC Area | Std. Err. | -Asymptotic Normal- [95% Conf. | Interval] |
|---|---|---|---|---|
| 213 | 0.8764 | 0.0229 | 0.83163 | 0.92124 |

number of observations = 213
Hosmer-Lemeshow chi2(3) = 2.06
Prob > chi2 = 0.5610

Table 10 shows that a 'cut off score' of +11 ( >/= +11 favours intestinal tuberculosis and < +11 favours Crohn's disease) has a sensitivity of 76.36% and a specificity of 79.61% in differentiating intestinal tuberculosis from Crohn's disease. The model was validated using bootstrap analysis. The result of boot strap analysis is shown in Table 11. All variables selected after logistic regression analysis occurred in > 50% of the bootstrap samples confirming the validity of the variables.

**Table 11: Number of times each variable was selected on bootstrapping.**

| **Parameter** | **No: of times each variable was selected** |
|---|---|
| Anorexia | 810 |
| Vomiting | 700 |
| Pseudopolyps | 750 |
| Aphthous ulcer | 870 |
| Linear/Serpiginous ulcer | 530 |
| Ulceration | 930 |
| Confluent granulomas | 760 |

# Discussion

Differentiating Crohn's disease from intestinal tuberculosis is of utmost importance because treatment for the two diseases are different and wrong treatment may result in disastrous consequences. Earlier studies have attempted to identify parameters on clinical , radiologic or endoscopic / histological evaluation to differentiate the two diseases. Unfortunately , the dilemma of differentiating the two diseases which have similar presentations still continues. The present study was therefore aimed at comprehensively studying the problem, identifying parameters that differentiate intestinal tuberculosis from Crohn's disease and develop a scoring system to make a positive diagnosis.

Previous studies have identified clinical features that are more common either in intestinal tuberculosis or Crohn's disease. Amarapurkar et al have reported absence of fever, presence of hematochezia, presence of diarrhoea and long duration of symptoms to be more common in Crohn's disease than intestinal tuberculosis [69]. Another study by Makharia et al found blood in stools to be more common in Crohn's disease and weight loss more common in intestinal tuberculosis[68]. A study from China did not find any significant difference in the clinical features between the two diseases [58]. In the present study there was no difference between the two groups with respect to age or sex of the individual or the duration of the disease.

Univariate analysis of clinical features showed that blood in stools, diarrhea, joint symptoms and perianal disease were more common among the patients with Crohn's

disease whereas abdominal pain, anorexia, vomiting and weight loss were found to be more common among the patients with intestinal tuberculosis. After logistic regression analysis anorexia and vomiting were significant and both favoured intestinal tuberculosis.

Blood investigations have not been helpful in differentiating the two diseases in previous studies though anemia has been found to be more prevalent in Crohn's disease than intestinal tuberculosis [69]. In our study , the results of Hb, ESR, CRP and albumin between the two groups were comparable.

Barium studies have not been found to be helpful in differentiating the two diseases. In a study of 36 patients by Makanjuola et al, none of the BMFT findings could differentiate between intestinal tuberculosis and Crohn's disease [81]. In the present study, 35 patients with intestinal tuberculosis and 61 patients with Crohn's disease had BMFT done. Contracted cecum and pulled up ic junction were found to be more common in intestinal tuberculosis than Crohn's disease . However these parameters were not included in logistic regression analysis since the data was not available for all the patients.

Boudiaf et al have shown that CT parameters which help differentiate between the two diseases are abdominal nodes and bowel wall thickening which favour intestinal tuberculosis and mesenteric hypervascularity which favours Crohn's disease [83]. In the present study, where 42 patients with intestinal tuberculosis and 35 patients with Crohn's disease had CT abdomen done, mesenteric hypervascularity ( comb sign) was noted to favour Crohn's disease and abdominal nodes were noted to be more common in intestinal

tuerculosis. . Bowel wall thickening was however comparable between the two groups. Logistic regression analysis could not be done on these variables since the data was incomplete.

Attempts have been made in the past to identify colonoscopic features which will help to differentiate between the two diseases. A study by Lee et al showed anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone appearance to be significantly more common in patients with Crohn's disease and a patulous ileocecal valve, transverse ulcers, and pseudopolyps to be more frequent in patients with intestinal tuberculosis[6]. Amarapurkar et al showed linear / serpiginous ulcers and cobble stone appearance to be more common in Crohn's disease compared to intestinal tuberculosis [69]. Aphthous ulcers, linear ulcers and cobble stone appearance were the features favouring Crohn's disease in a study by Makharia et al [68]. In our study, colonoscopy showed pseudopolyps, aphthous ulcers, linear/ serpigenous ulcers to be more common in Crohn's disease where as ulcerated stenosis, nonulcerated stenosis and narrowed ic valve were more common in intestinal tuberculosis. Cobble stone appearance was more common in Crohn's disease but the difference was not statistically significant. On multivariate analysis the significant parameters which favoured Crohn's disease were pseudo polyps, aphthous ulcers and serpigenous / linear ulcers. Colonoscopy findings in the present study was grossly similar to the previous studies.

Previous studies have shown that histopathologic findings are helpful in differentiating Crohn's disease from intestinal tuberculosis. Pulimood et al have reported that on

mucosal biopsy, in addition to AFB detection, large granuloma, greater than four sites of granulomatous inflammation, caseation, band of epitheloid histiocytes in ulcer base and granulomatous inflammation in cecum favour diagnosis of tuberculosis; whereas non-caseating granuloma, mucosal changes distant to sites with granuloma, focal crypt-related inflammation and granuloma in sigmoid or rectum favour diagnosis of Crohn's disease [9]. Amarapurkar et al found confluent granulomas to be more prevalent in intestinal tuberculosis. A South African study and a Chinese study have also noted confluent granulomas to be more common in intestinal tuberculosis[10, 59] . However in the Chinese study it was also reported that apart from caseation and confluent granulomas, no other features were helpful in differentiating between the two diseases [59]. Focally enhanced colitis was found to be a histological hallmark in making a diagnosis of Crohn's disease in the study by Makharia et al [68]. In our study, ulceration, granulomas and confluent granulomas were more common in intestinal tuberculosis where as the other parameters were comparable between the two groups. After logistic regression analysis, ulceration and confluent granulomas were still found to be significant. Limitations of this study were retrospective design and incomplete radiological data. This study shows that there are clinical , colonoscopic and histological parameters that are different in the two diseases. Further, all parameters donot have the same weightage. In order to include all parameters and apportion appropriate weightage to each parameter we developed a scoring system and hoped that this would help in better differentiating intestinal tuberculosis from Crohn's disease. For the development of the scoring system, the clinical features, colonoscopy findings and the histopathologic findings significant after univariate analysis were included in logistic regression analysis. After logistic

regression analysis a scoring system was developed as described in the results section. A score of +11 was derived as the 'cut off score' to differentiate between the two diseases. A score >/= +11 suggested intestinal tuberculosis and a score of < +11 suggested Crohn's disease. The scoring system was validated using boot strapping method. A prospective study using the scoring system will help confirm and validate its usefulness in differentiating intestinal tuberculosis from Crohn's disease.

# Conclusion

Evaluation of clinical, radiological, colonoscopic and histological parmeters were performed to differentiate intestinal tuberculosis from Crohn's disease.

1) On univariate analysis-

*Parameters favouring intestinal tuberculosis were --

- Clinical: abdominal pain, anorexia, vomiting and weight loss.
- Radiology: contracted cecum, pulled up IC junction in BMFT and abdominal nodes in CT abdomen.
- Colonoscopy: Nonulcerated / ulcerated stenosis, narrowed IC valve.
- Histology: ulceration, granulomas and confluent granuloma.

*Parameters favouring Crohn's disease were

- Clinical: blood in stools, diarrhea, joint symptoms and perianal disease.
- Radiology: mesenteric hypervascularity in CT abdomen.
- Colonoscopy: Pseudopolyps, aphthous ulcer, linear/ serpiginous ulcer.
- Histology: none

2) On multivariate analysis (logistic regression)-

* Parameters favouring intestinal tuberculosis were anorexia, vomiting and ulceration and confluent granulomas in histology.

*Parameters favouring Crohn's disease were pseudopolyps ,aphthous ulcers and linear/ serpiginous ulcers in colonoscopy.

3) A scoring system was devised to differentiate intestinal tuberculosis from Crohn's disease. A cut off score >/= +11 was suggestive of intestinal tuberculosis while a score < +11 was suggestive of Crohn's disease. The model was validated using bootstrapping method

# Bibliography

[1] Das K, Ghoshal UC, Dhali GK, Benjamin J, Ahuja V, Makharia GK. Crohn's disease in India: a multicenter study from a country where tuberculosis is endemic. Digestive diseases and sciences. 2009 May;54(5):1099-107.
[2] Patel N, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, et al. Gastrointestinal luminal tuberculosis: establishing the diagnosis. Journal of gastroenterology and hepatology. 2004 Nov;19(11):1240-6.
[3] Ghoshal UC, Ghoshal U, Singh H, Tiwari S. Anti-Saccharomyces cerevisiae antibody is not useful to differentiate between Crohn's disease and intestinal tuberculosis in India. J Postgrad Med. 2007 Jul-Sep;53(3):166-70.
[4] Makharia GK, Sachdev V, Gupta R, Lal S, Pandey RM. Anti-Saccharomyces cerevisiae antibody does not differentiate between Crohn's disease and intestinal tuberculosis. Digestive diseases and sciences. 2007 Jan;52(1):33-9.
[5] Amarapurkar DN, Patel ND, Amarapurkar AD, Agal S, Baigal R, Gupte P. Tissue polymerase chain reaction in diagnosis of intestinal tuberculosis and Crohn's disease. J Assoc Physicians India. 2004 Nov;52:863-7.
[6] Lee YJ, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, et al. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy. 2006 Jun;38(6):592-7.
[7] Tandon HD, Prakash A. Pathology of intestinal tuberculosis and its distinction from Crohn's disease. Gut. 1972 Apr;13(4):260-9.
[8] Pulimood AB, Ramakrishna BS, Kurian G, Peter S, Patra S, Mathan VI, et al. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. Gut. 1999 Oct;45(4):537-41.
[9] Pulimood AB, Peter S, Ramakrishna B, Chacko A, Jeyamani R, Jeyaseelan L, et al. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. Journal of gastroenterology and hepatology. 2005 May;20(5):688-96.
[10] Kirsch R, Pentecost M, Hall Pde M, Epstein DP, Watermeyer G, Friederich PW. Role of colonoscopic biopsy in distinguishing between Crohn's disease and intestinal tuberculosis. J Clin Pathol. 2006 Aug;59(8):840-4.
[11] Pai CG, Khandige GK. Is Crohn's disease rare in India? Indian J Gastroenterol. 2000 Jan-Mar;19(1):17-20.
[12] Ouyang. Inflammatory bowel disease in China. J Gastroenterol Hepato. 2000; 15 (Suppl.):S25 (Abstract).
[13] Snider DE, Jr., Roper WL. The new tuberculosis. N Engl J Med. 1992 Mar 5;326(10):703-5.
[14] Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. The American journal of gastroenterology. 1998 May;93(5):692-6.
[15] Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. The American journal of gastroenterology. 1993 Jul;88(7):989-99.
[16] Al-Ghamdi AS, Al-Mofleh IA, Al-Rashed RS, Al-Amri SM, Aljebreen AM, Isnani AC, et al. Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh. World J Gastroenterol. 2004 May 1;10(9):1341-4.

[17] El Mouzan MI, Abdullah AM, Al Habbal MT. Epidemiology of juvenile-onset inflammatory bowel disease in central Saudi Arabia. Journal of tropical pediatrics. 2006 Feb;52(1):69-71.
[18] Abdul-Baki H, ElHajj I, El-Zahabi LM, Azar C, Aoun E, Zantout H, et al. Clinical epidemiology of inflammatory bowel disease in Lebanon. Inflammatory bowel diseases. 2007 Apr;13(4):475-80.
[19] Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firouzi F. Inflammatory bowel disease in Iran: a review of 457 cases. Journal of gastroenterology and hepatology. 2005 Nov;20(11):1691-5.
[20] Wright JP, Froggatt J, O'Keefe EA, Ackerman S, Watermeyer S, Louw J, et al. The epidemiology of inflammatory bowel disease in Cape Town 1980-1984. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 1986 Jul 5;70(1):10-5.
[21] MacDonald TT. Effector and regulatory lymphoid cells and cytokines in mucosal sites. Curr Top Microbiol Immunol. 1999;236:113-35.
[22] Duchmann R, May E, Heike M, Knolle P, Neurath M, Meyer zum Buschenfelde KH. T cell specificity and cross reactivity towards enterobacteria, bacteroides, bifidobacterium, and antigens from resident intestinal flora in humans. Gut. 1999 Jun;44(6):812-8.
[23] D'Inca R, Di Leo V, Corrao G, Martines D, D'Odorico A, Mestriner C, et al. Intestinal permeability test as a predictor of clinical course in Crohn's disease. The American journal of gastroenterology. 1999 Oct;94(10):2956-60.
[24] Binder V. Genetic epidemiology in inflammatory bowel disease. Dig Dis. 1998 Nov-Dec;16(6):351-5.
[25] Peeters M, Nevens H, Baert F, Hiele M, de Meyer AM, Vlietinck R, et al. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. Gastroenterology. 1996 Sep;111(3):597-603.
[26] Satsangi J, Grootscholten C, Holt H, Jewell DP. Clinical patterns of familial inflammatory bowel disease. Gut. 1996 May;38(5):738-41.
[27] Bayless TM, Tokayer AZ, Polito JM, 2nd, Quaskey SA, Mellits ED, Harris ML. Crohn's disease: concordance for site and clinical type in affected family members--potential hereditary influences. Gastroenterology. 1996 Sep;111(3):573-9.
[28] Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature. 2001 May 31;411(6837):603-6.
[29] Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001 May 31;411(6837):599-603.
[30] Zhou Z, Lin XY, Akolkar PN, Gulwani-Akolkar B, Levine J, Katz S, et al. Variation at NOD2/CARD15 in familial and sporadic cases of Crohn's disease in the Ashkenazi Jewish population. The American journal of gastroenterology. 2002 Dec;97(12):3095-101.
[31] Rioux JD, Daly MJ, Silverberg MS, Lindblad K, Steinhart H, Cohen Z, et al. Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. Nat Genet. 2001 Oct;29(2):223-8.

[32] Peltekova VD, Wintle RF, Rubin LA, Amos CI, Huang Q, Gu X, et al. Functional variants of OCTN cation transporter genes are associated with Crohn disease. Nat Genet. 2004 May;36(5):471-5.
[33] Okada M, Maeda K, Yao T, Iwashita A, Nomiyama Y, Kitahara K. Minute lesions of the rectum and sigmoid colon in patients with Crohn's disease. Gastrointest Endosc. 1991 May-Jun;37(3):319-24.
[34] Chambers TJ, Morson BC. The granuloma in Crohn's disease. Gut. 1979 Apr;20(4):269-74.
[35] Shaikh MS DK, Jalbani MA, et al. Prevalence of intestinal tuberculosis in cases of acute abdomen; 2007.
[36] Munkholm P. Crohn's disease--occurrence, course and prognosis. An epidemiologic cohort-study. Dan Med Bull. 1997 Jun;44(3):287-302.
[37] Baker WN, Milton-Thompson GJ. The anal lesion as the sole presenting symptom of intestinal Crohn's disease. Gut. 1971 Oct;12(10):865.
[38] Buchmann P, Alexander-Williams J. Classification of perianal Crohn's disease. Clin Gastroenterol. 1980 May;9(2):323-30.
[39] Wagtmans MJ, Verspaget HW, Lamers CB, van Hogezand RA. Clinical aspects of Crohn's disease of the upper gastrointestinal tract: a comparison with distal Crohn's disease. The American journal of gastroenterology. 1997 Sep;92(9):1467-71.
[40] D'Haens G, Rutgeerts P, Geboes K, Vantrappen G. The natural history of esophageal Crohn's disease: three patterns of evolution. Gastrointest Endosc. 1994 May-Jun;40(3):296-300.
[41] Greenstein AJ, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD, et al. Perforating and non-perforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. Gut. 1988 May;29(5):588-92.
[42] Heuschkel RB, MacDonald TT, Monteleone G, Bajaj-Elliott M, Smith JA, Pender SL. Imbalance of stromelysin-1 and TIMP-1 in the mucosal lesions of children with inflammatory bowel disease. Gut. 2000 Jul;47(1):57-62.
[43] Ribeiro MB, Greenstein AJ, Yamazaki Y, Aufses AH, Jr. Intra-abdominal abscess in regional enteritis. Ann Surg. 1991 Jan;213(1):32-6.
[44] Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol. 1996 Jul;23(1):29-34.
[45] Shah S, Thomas V, Mathan M, Chacko A, Chandy G, Ramakrishna BS, et al. Colonoscopic study of 50 patients with colonic tuberculosis. Gut. 1992 Mar;33(3):347-51.
[46] Donoghue HD, Holton J. Intestinal tuberculosis. Current opinion in infectious diseases. 2009 Oct;22(5):490-6.
[47] Basu S, Ganguly S, Chandra PK, Basu S. Clinical profile and outcome of abdominal tuberculosis in Indian children. Singapore medical journal. 2007 Oct;48(10):900-5.
[48] Dinler G, Sensoy G, Helek D, Kalayci AG. Tuberculous peritonitis in children: report of nine patients and review of the literature. World J Gastroenterol. 2008 Dec 21;14(47):7235-9.

[49] Stange EF, Travis SP, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. Gut. 2006 Mar;55 Suppl 1:i1-15.
[50] Farmer RG, Hawk WA, Turnbull RB, Jr. Clinical patterns in Crohn's disease: a statistical study of 615 cases. Gastroenterology. 1975 Apr;68(4 Pt 1):627-35.
[51] Schwartz DA, Loftus EV, Jr., Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology. 2002 Apr;122(4):875-80.
[52] Jones JH, Lennard-Jones JE, Morson BC, Chapman M, Sackin MJ, Sneath PH, et al. Numerical taxonomy and discriminant analysis applied to non-specific colitis. The Quarterly journal of medicine. 1973 Oct;42(168):715-32.
[53] Lennard-Jones JE, Shivananda S. Clinical uniformity of inflammatory bowel disease a presentation and during the first year of disease in the north and south of Europe. EC-IBD Study Group. European journal of gastroenterology & hepatology. 1997 Apr;9(4):353-9.
[54] Scotiniotis I, Rubesin SE, Ginsberg GG. Imaging modalities in inflammatory bowel disease. Gastroenterol Clin North Am. 1999 Jun;28(2):391-421, ix.
[55] Pera A, Bellando P, Caldera D, Ponti V, Astegiano M, Barletti C, et al. Colonoscopy in inflammatory bowel disease. Diagnostic accuracy and proposal of an endoscopic score. Gastroenterology. 1987 Jan;92(1):181-5.
[56] Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. Gastroenterology. 1990 Apr;98(4):811-8.
[57] Riedel L, Segal I, Mohamed AE, Hale M, Mannell A. The prolonged course of gastrointestinal tuberculosis. J Clin Gastroenterol. 1989 Dec;11(6):671-4.
[58] Zhou ZY, Luo HS. Differential diagnosis between Crohn's disease and intestinal tuberculosis in China. International journal of clinical practice. 2006 Feb;60(2):212-4.
[59] Gan HT, Chen YQ, Ouyang Q, Bu H, Yang XY. Differentiation between intestinal tuberculosis and Crohn's disease in endoscopic biopsy specimens by polymerase chain reaction. The American journal of gastroenterology. 2002 Jun;97(6):1446-51.
[60] Johnson CA, Hill ID, Bowie MD. Abdominal tuberculosis in children. A survey of cases at the Red Cross War Memorial Children's Hospital, 1976-1985. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 1987 Jul 4;72(1):20-2.
[61] Nakamura S, Yanagihara K, Izumikawa K, Seki M, Kakeya H, Yamamoto Y, et al. Severe pulmonary tuberculosis complicating Ileocecal intussusception due to intestinal tuberculosis: a case report. Ann Clin Microbiol Antimicrob. 2008;7:16.
[62] Cello JP. Capsule endoscopy features of human immunodeficiency virus and geographical diseases. Gastrointest Endosc Clin N Am. 2004 Jan;14(1):169-77.
[63] Segal I, Tim LO, Mirwis J, Hamilton DG, Mannell A. Pitfalls in the diagnosis of gastrointestinal tuberculosis. The American journal of gastroenterology. 1981 Jan;75(1):30-5.
[64] Sato S, Yao K, Yao T, Schlemper RJ, Matsui T, Sakurai T, et al. Colonoscopy in the diagnosis of intestinal tuberculosis in asymptomatic patients. Gastrointest Endosc. 2004 Mar;59(3):362-8.

[65] Jayanthi V, Robinson RJ, Malathi S, Rani B, Balambal R, Chari S, et al. Does Crohn's disease need differentiation from tuberculosis? Journal of gastroenterology and hepatology. 1996 Feb;11(2):183-6.
[66] Franco-Paredes C, Diaz-Borjon A, Senger MA, Barragan L, Leonard M. The ever-expanding association between rheumatologic diseases and tuberculosis. Am J Med. 2006 Jun;119(6):470-7.
[67] Umapathy KC, Begum R, Ravichandran G, Rahman F, Paramasivan CN, Ramanathan VD. Comprehensive findings on clinical, bacteriological, histopathological and therapeutic aspects of cutaneous tuberculosis. Trop Med Int Health. 2006 Oct;11(10):1521-8.
[68] Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, et al. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. The American journal of gastroenterology. Mar;105(3):642-51.
[69] Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. World J Gastroenterol. 2008 Feb 7;14(5):741-6.
[70] Epstein D WG, Kirsch R . Review article: The diagnosis and management of Crohn’s disease in populations with high-risk rates for tuberculosis Aliment Pharmacol - er. 2007;25:1373 – 88

[71] Pulimood AB, Peter S, Rook GW, Donoghue HD. In situ PCR for Mycobacterium tuberculosis in endoscopic mucosal biopsy specimens of intestinal tuberculosis and Crohn disease. American journal of clinical pathology. 2008 Jun;129(6):846-51.
[72] Li JY, Lo ST, Ng CS. Molecular detection of Mycobacterium tuberculosis in tissues showing granulomatous inflammation without demonstrable acid-fast bacilli. Diagn Mol Pathol. 2000 Jun;9(2):67-74.
[73] Al-Jahdali H, Memish ZA, Menzies D. The utility and interpretation of tuberculin skin tests in the Middle East. Am J Infect Control. 2005 Apr;33(3):151-6.
[74] Rangaka MX WK, Seldon R et al. . Effect of HIV-1 infection on T-Cell-based and skin test detection of tuberculosis infection. 2007;175:514-20.
[75] Manuel O, Kumar D. QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. Expert Rev Mol Diagn. 2008 May;8(3):247-56.
[76] Franken WP, Timmermans JF, Prins C, Slootman EJ, Dreverman J, Bruins H, et al. Comparison of Mantoux and QuantiFERON TB Gold tests for diagnosis of latent tuberculosis infection in Army personnel. Clin Vaccine Immunol. 2007 Apr;14(4):477-80.
[77] Nsutebu E MCea. Use of QuantiFERON-TB Gold test in the investigation of unexplained positive tuberculin skin tests . Public Health 2008;122:1284-7.
[78] Carvalho AC, Pezzoli MC, El-Hamad I, Arce P, Bigoni S, Scarcella C, et al. QuantiFERON-TB Gold test in the identification of latent tuberculosis infection in immigrants. J Infect. 2007 Aug;55(2):164-8.
[79] Caputo D AR, Garberini A et al. Experience with two cases of intestinal tuberculosis: utility of the QuantiFERON-TB Gold test for diagnosis Surg Infect (Larchmt). 2008;9:407-10.
[80] Ibrahim M, Osoba AO. Abdominal tuberculosis. On-going challenge to gastroenterologists. Saudi Med J. 2005 Feb;26(2):274-80.

[81] Makanjuola. Is it Crohn's disease or intestinal tuberculosis? European journal of radiology. 1998;28:55 – 61.
[82] Balthazar EJ, Gordon R, Hulnick D. Ileocecal tuberculosis: CT and radiologic evaluation. AJR Am J Roentgenol. 1990 Mar;154(3):499-503.
[83] Boudiaf M, Zidi SH, Soyer P, Lavergne-Slove A, Kardache M, Logeay O, et al. Tuberculous colitis mimicking Crohn's disease: utility of computed tomography in the differentiation. Eur Radiol. 1998;8(7):1221-3.
[84] Sinan T, Sheikh M, Ramadan S, Sahwney S, Behbehani A. CT features in abdominal tuberculosis: 20 years experience. BMC Med Imaging. 2002 Nov 12;2(1):3.
[85] Papadakis KA, Tabibzadeh S. Diagnosis and misdiagnosis of inflammatory bowel disease. Gastrointest Endosc Clin N Am. 2002 Jul;12(3):433-49.
[86] Singh V, Kumar P, Kamal J, Prakash V, Vaiphei K, Singh K. Clinicocolonoscopic profile of colonic tuberculosis. The American journal of gastroenterology. 1996 Mar;91(3):565-8.
[87] Bhargava DK, Tandon HD, Chawla TC, Shriniwas, Tandon BN, Kapur BM. Diagnosis of ileocecal and colonic tuberculosis by colonoscopy. Gastrointest Endosc. 1985 Apr;31(2):68-70.
[88] Naga MI, Okasha HH, Ismail Z, El-Fatatry M, Hassan S, Monir BE. Endoscopic diagnosis of colonic tuberculosis. Gastrointest Endosc. 2001 Jun;53(7):789-93.
[89] Leung VK, Tang WL, Cheung CH, Lai MS. Importance of ileoscopy during colonoscopy for the early diagnosis of ileal tuberculosis: report of two cases. Gastrointest Endosc. 2001 Jun;53(7):813-5.
[90] Alvares JF, Devarbhavi H, Makhija P, Rao S, Kottoor R. Clinical, colonoscopic, and histological profile of colonic tuberculosis in a tertiary hospital. Endoscopy. 2005 Apr;37(4):351-6.
[91] Kalvaria I, Kottler RE, Marks IN. The role of colonoscopy in the diagnosis of tuberculosis. J Clin Gastroenterol. 1988 Oct;10(5):516-23.
[92] Pettengell KE, Pirie D, Simjee AE. Colonoscopic features of early intestinal tuberculosis. Report of 11 cases. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 1991 Mar 2;79(5):279-80.
[93] Ferentzi CV, Sieck JO, Ali MA. Colonoscopic diagnosis and medical treatment of ten patients with colonic tuberculosis. Endoscopy. 1988 Mar;20(2):62-5.
[94] Pepe MS. Receiver Operating Characteristic Methodology. Journal of the American Statistical Association. 2000;95:308-11.
[95] Efron BaGG. A Leisurely Look at the Bootstrap, the Jackknife, and Cross-Validation. The American Statistician. 1983;37:36-48.

# Proforma

- **Serial number**
- DIAGNOSIS: TB / CD
- Name
- Age
- Hospital number
- Sex
- Religion
- Occupation
- Address
- E mail
- Phone number

**History of illness**

- Duration of symptoms

- Blood in the stools -yes / no / not recorded
- Large volume bleed y / n / nr
  - Transfusions y / n / nr
  - Hospital admission y / n / nr
  - Surgery y / n / nr

- Diarrhoea -y / n / nr
  -Number of times a day
  -Day
  -Night

- Abdominal pain -y / n / nr
  -constant / colicky / other type (description)
- Subac obstrn y / n / nr
- Anorexia y / n / nr
- Vomiting y / n / nr
- Wt loss y / n / nr
  -in kgs
  -as %
- Abdominal lump y / n / nr
- Surgery y / n / nr

  Indication -For bleeding / obstruction / abscess / perforation / mass / diagnostic lap
  -Other indications (description)

- Appendicectomy y / n / nr
- Fever y / n / nr
  Character -Chills / rigors / nr
  -Continuous / remittent / intermittent / nr
  - Low grade < 101 F / high grade 101 F or more
  - Evening rise y / n / nr (pt feels more fever b/w 4pm and MN)
  - Is the fever > 101 F, in the absence of an intra abdominal abscess y / n / nr
- Hypercoagulable state
  Venous thrombosis y / n / nr
  (if yes, description of vessels involved)
- Red eye y / n / nr
- Skin lesions y / n / nr
- Oral ulcers y / n / nr
- Joint pains y / n / nr
- Joint swellings y / n / nr
  -Which joint

## Past history

- Of TB -y / n / nr
  -(if yes, details)
- Treatment with ATT y / n / nr
  Details
- Of BCG y / n / nr

**Family history**

- TB y / n / nr (details)
- CD y / n / nr (details)

**Physical findings**

- Clubbing y / n / nr
- Icterus y / n / nr
- Growth retardation y / n / nr
- Delayed secondary sexual characteristics y / n / nr
- Height in kgs
- Weight in cms
- BMI
- Hepatomegaly y / n / nr
- Splenomegaly y / n / nr
- Mass -y / n / nr
  -If yes, location
- Peristalsis y / n / nr
- Ascites y / n / nr
- Nodes -y / n / nr

-site
-size
-character

- Perianal disease -y / n / nr (current or evidence of past disease)
  -Fissure y / n / nr
  -Fistula y / n / nr
  -Abscess y / n / nr
- Extraintestinal manifestations
  -Pyoderma y / n / nr
  -E nodosum y / n / nr
  -Vasculitis y / n / nr
  -Oral ulcers y / n / nr
  -A spondylitis y / n / nr
  -Arthritis y / n / nr
  Which joint:
  -Episcleritis y / n / nr
  -Uveitis y / n / nr

**BMFT**

- Not done
- Normal y / n / nr
- Stricture y / n / nr
- Ulcer y / n / nr
- Fistula y / n / nr
- mucosal fold thickening y / n / nr
- intermediary segments y / n / nr
- segmentation
- flocculation
- skip lesions
- retraction of mesenteric border
- antmesenteric sacculations
- Patulous ic valve
- Narrowed ic junction
- contracted cecum
- cobble stoning
- pulled up cecum
- separated small bowel loops
-

**CT**

- not done y / n / nr
- Normal y / n / nr
- Stricture y / n / nr
- inflammatory mass y / n / nr
- Ascites y / n / nr
- Ascites when albumin > 2.5 y / n / nr

- Peritoneal thickening y / n / nr
- Mesenteric thickening y / n / nr
- Mesenteric fat proliferation y / n / nr
- Contracted cecum y / n / nr
- mural thickening y / n / nr
- Omega sign y / n / nr
- Internal fistulae y / n / nr
- Omental cake y / n / nr
- Cocoon y / n / nr
- Creeping fat y / n / nr
- Comb sign y / n / nr
- Tuberculoma in liver / spleen y / n / nr
- Abdominal nodes -y / n / nr
  -Size of nodes / largest
  -Character y / n / nr
  -Matting y / n / nr
  -Calcification y / n / nr
  -Other descriptions

**Upper GI Scopy:**

- Notdone
- Normal
- superficial/deep ulcer y / n / nr
- aphthous ulcer y / n / nr
- Stenosis y / n / nr
- gastric erythema y / n / nr
- edematous gastric mucosa y / n / nr
- erosions y / n / nr

**Lower GI Scopy:**

- not done
- Normal
- Ulcerated stenosis y / n / nr
- Non-ulcerated stenosis, y / n / nr
- Aphthous ulcers y / n / nr
- Pseudopolyps y / n / nr
- Linear ulcers/serpigenous y / n / nr
- Transverse ulcer y / n / nr
- Circumferential ulcers y / n / nr
- only ileal ulcers y / n / nr
- ileo-colonic ulcers y / n / nr
- Cobblestoning y / n / nr
- Fistula y / n / nr
- Skip lesions y / n / nr
- Neoplasm like appearance y / n / nr

- Contracted cecum y / n / nr
- Narrowed IC valve y / n / nr
- Patulous IC valve y / n / nr

**Capsule**

- not done
- Normal
- SB Ulcers y / n / nr
- Stricture y / n / nr
- Strictures + Ulcer) y / n / nr

**Surgical findings**

- Skip lesions y / n / nr
- Stricutre -y / n / nr
  -Number of strictures
  -Stricture sites
  -Length of longest stricture (actual length)

- Bowel wall induration y / n / nr
- Creeping fat y / n / nr
- Mesenteric lymphadenopathy y / n / nr

**Other Investigations**

- Quantiferon gold y / n / nr

  Result pos / neg / equivocal / nr

  Value

- Mantoux pos / neg / equivocal / not done

  Size of the induration

- CXR normal / abnormal

  (if abnormal, description)

- Antibodies

  ASCA pos / neg / equivocal / not done

  ANCA pos / neg / equivocal / not done

  AFB c/s pos / neg / not done

TB at extraintestinal site y /n /nr ---- Details

**Histology**

Upper GI

- Chronic inflammation
- Ulceration
- Granulomas
- Confluent granulomas
- Caseation

- Presence of AFB
- Architectural alteration

LowerGI

- Chronic inflammation
- Ulceration
- Granulomas
- Confluent granulomas
- Caseation
- Presence of AFB
- Cryptitis
- Cyypt abscess
- Architectural alteration

Resection specimen histopathology

- not done
- Normal
- chronic inflammation with architecture changes
- granulomatous inflammation
- transmural inflammation

**Site of disease**

**Course**

- Treatment given ATT / ASA / steroids / immunosuppressants (details)
- If ATT was given
  - -Drugs used
  - -Duration of treatment
  - -? DOTS
- Reassessment at _____ months

# Abstract


| | |
|---|---|
| TITLE OF ABSTRACT: | Identification of parameters that help in differentiating Crohn's disease from intestinal tuberculosis. |
| DEPARTMENT: | Gastrointestinal Sciences |
| NAME OF THE CANDIDATE: | Dr Anoop K Koshy |
| DEGREE AND SUBJECT: | DM; Gastroenterology |
| NAME OF THE GUIDE: | Dr Ashok Chacko |



OBJECTIVES: (1)To analyze clinical, laboratory, radiologic, endoscopic and histological characteristics of intestinal tuberculosis and Crohn's disease and identify the parameters that differentiate the two diseases. (2) To devise and validate a scoring system to help differentiate Crohn's disease from intestinal tuberculosis

METHODS: Case records of patients with definite diagnosis of intestinal tuberculosis and Crohn's disease were analysed using uniform structured data forms with respect to clinical, laboratory, radiologic, endoscopic and histological parameters. Univariate analysis to identify the significant differences between the two diseases was initially performed followed by logistic regression analysis to identify the final significant parameters. Using the final significant parameters a scoring system was developed to differentiate Crohn's disease from intestinal tuberculosis. The scoring system was validated using bootstrapping method.

RESULTS: Parameters favouring intestinal tuberculosis were anorexia, vomiting and ulceration and confluent granulomas in histology. Parameters favouring Crohn's disease

were pseudopolyps ,aphthous ulcers and linear/ serpiginous ulcers in colonoscopy. A scoring system was devised to differentiate intestinal tuberculosis from Crohn's disease. A cut off score >/= +11 was suggestive of intestinal tuberculosis while a score < +11 was suggestive of Crohn's disease. The model was validated using bootstrapping method